Original Article

Prevalence and Odds of Cognitive Impairment in Multiple Sclerosis Subtypes and Neuromyelitis Optica Spectrum Disorder: A Case–Control Study

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Abstract

Background: Autoimmune demyelinating disorders, such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), are caused by persistent inflammation and damage to the central nervous system. Cognitive impairment (CI) is a growing challenge in these diseases, underscoring the need for a thorough exploration of its prevalence and risk across various subtypes. This study aimed to assess the prevalence and odds of CI using the Symbol Digit Modalities Test (SDMT) in various MS subtypes and NMOSD.

Materials and Methods: A case–control study involving 616 participants, including healthy controls (HC) and individuals with different MS subtypes (Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), Primary Progressive MS (PPMS)), clinically isolated syndrome (CIS), and NMOSD, was conducted. CI was defined as SDMT z-scores 1.5 standard deviations below the HC average. The chi-square test was used to assess the risk of CI.

Results: The prevalence of CI varied across different groups: HC (10.7%), RRMS (33.8%), SPMS (71.3%), PPMS (62.8%), CIS (19.2%), and NMOSD (32.8%). Odds ratios (OR) for CI were significantly increased in RRMS (OR: 4.23, confidence interval (CI): 2.18-8.22, $P < 0.001$), SPMS (OR: 20.58, CI: 10.36-40.88, $P < 0.001$), PPMS (OR: 14.02, CI: 5.80-33.86, $P < 0.001$), and NMOSD (OR: 4.04, CI: 2.07-7.87, $P < 0.001$) compared to HC.

Conclusion: This study emphasizes a significantly increased risk of CI in MS subtypes and NMOSD compared to HC. Although no significant difference in CI risk was found between individuals with RRMS and NMOSD, those with progressive forms of MS exhibited notably higher risks of CI.

Keywords: Cognitive impairment, multiple sclerosis, neuromyelitis optica spectrum disorder, prevalence

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Introduction

Autoimmune demyelinating disorders include a range of disorders, such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), which are caused by the degeneration of astrocytes and neurons by auto-aggressive lymphocytes.[1] In these patients, the location of the inflammatory lesions in the brain, spinal cord, or optic nerve leads to a wide range of symptoms.[2] Many of these symptoms, such as imbalance and, motor and sensory disturbances, are easily diagnosable by physicians.[3] However, other symptoms in these patients, including cognitive impairment (CI), are difficult to distinguish and may be ignored in the early stages of CI.[2] Determining the risk of CI in each MS subtype can help physicians diagnose CI early, improve treatment outcomes

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in these patients, and prevent its development.[4] Moreover, the risk of CI in people with clinically isolated syndrome (PwCIS) may be lower because they are in the pre-MS stages. However, when CI occurs, it can serve as a significant marker for potential conversion to MS.[5]

Information processing speed (IPS) is one of the main domains for examining cognitive function.[6] It is often used for CI screening due to its high diagnostic sensitivity[7] and the ease of performing the test.[7,8] In this regard, the study by Charvet *et al*.[8] showed that IPS measured by Symbol Digit Modalities Test (SDMT) has the highest sensitivity and specificity for detecting CI compared to other measured domains. Similarly, the study by Moghadasi *et al*.[9] demonstrated that IPS in both people with MS (PwMS) and NMOSD (PwNMOSD) was more sensitive than other measured domains in diagnosing CI.

Various tests have been developed to measure IPS, with the most common for PwMS being the SDMT[10] and the Paced Auditory Serial Addition Test (PASAT).[11] According to previous studies, the SDMT has a higher effect size than the PASAT for CI measurement.[12-14] Additionally, the SDMT offers the advantages of easier administration and faster measurement speed compared to the other tests.[13]

Although previous studies have investigated the prevalence of CI in PwMS and PwNMOSD,[9,14] the odds of CI in MS subtypes, CIS, and NMOSD compared to healthy controls (HC) and with each other remains unclear. This study aims to determine the odds of CI in different MS subtypes and NMOSD using the SDMT test.

Materials and Methods

This case–control study was conducted from April 1, 2023, to April 1, 2024, at the MS department of Kashani Hospital and the Hakim MS Clinic[15] in Isfahan.

Inclusion criteria include definite diagnosis of MS and CIS, with subtype identification using McDonald's criteria,[16,17] and definite diagnosis of NMOSD using the 2015 IPND criteria,[18] confirmed by an expert neurologist; 2: a minimum of 9 years of literacy education; 3: visual acuity of 20 / 40 or higher; and 4: age range of 18–65 years. The HC group was selected from individuals visiting Kashani Clinic for nonmedical reasons or accompanying patients. These individuals were screened based on the study's inclusion criteria, and upon approval by the physician, they participated in the study in exchange for an incentive fee.

Exclusion criteria include 1: diagnoses such as Alzheimer's disease and non-MS or NMOSD-related types of dementia, as confirmed by a neurologist, and 2: participant dissatisfaction with continued cooperation or inability to perform cognitive tests due to high disability (EDSS 7.0 and above.[19]

This study randomly selected eligible participants according to predefined study criteria and invited them to the study. Demographic and clinical data, including age, sex, education (measured in years), disease duration, and disease-modifying therapy (DMT) usage, were collected through interviews, while the EDSS was assessed during neurological examinations. In addition, PwNMOSD were categorized into two groups based on the presence or absence of the AQP-4 antibody, as documented in their medical records.

All study participants took the SDMT to measure CI. The SDMT involves matching symbols with numbers within a 90-second timeframe, with scores ranging from 0 to 110.[20,21] Based on previous studies, participants whose SDMT z-scores were 1.5 standard deviations lower than the average of the HC group were classified as the CI group.[22-24]

For statistical analysis, the study data were analyzed using IBM SPSS Statistics (version 18; IBM Corporation, Armonk, NY, USA).[25] Descriptive statistics were used to summarize demographic and clinical characteristics, with frequencies (percentages) used for categorical variables and measures of central tendency (mean or median) and dispersion (standard deviation or interquartile range) for continuous variables. The Kolmogorov–Smirnov test was used to evaluate the normal distribution of the variables. Analysis of variance (ANOVA) was used to compare quantitative data between groups, while the chi-square test was used to compare qualitative data and assess the odds of CI. A P value of less than 0.05 was considered statistically significant.

Results

This study included 616 participants. Among them were 130 HC, 130 with RRMS, 128 with NMOSD, 115 with SPMS, 78 with CIS, and 35 with PMS.

Based on the results obtained from the participants, the average age (SD) in the HC, RRMS, SPMS, PPMS, CIS, and NMOSD groups was 37.3 (9.9), 36.2 (8.8), 39.2 (7.8), 37.5 (7.7), 36.8 (9.3), and 38.1 (9.6), respectively. No significant difference was observed among the age, gender ratio, and level of education of the groups. Refer to Table 1 for more demographic and clinical data.

According to the cut-off of the study, the prevalence of CI in the total MS, HC, RRMS, SPMS, PPMS, CIS, and NMOSD groups was 42.18%, 10.7%, 33.8%, 71.3%, 62.8%, 19.2%, and 32.8%, respectively. Refer Table 2 for more information.

The study's results showed that the odds of CI occurring in total MS, RRMS, SPMS, PPMS, and NMOSD groups compared to HC were significantly higher, with respective odds ratios (OR) and 95% confidence intervals (CI) as follows: total MS (OR: 6.04, CI: 3.37-10.82, $P < 0.001$), RRMS (OR: 4.23, CI: 2.18-8.22, $P < 0.001$), SPMS (OR: 20.58, CI: 10.36-40.88, $P < 0.001$), PPMS (OR: 14.02, CI: 5.80-33.86, $P < 0.001$), and NMOSD (OR: 4.04, CI: 2.07-7.87, $P < 0.001$). However, the odds of CI occurrence in the PwCIS compared to HC did not reach statistical significance (OR: 1.97, CI: 0.89-4.34, P: 0.092).

Table 1: Demographic and clinical information of study participants. Analyzes were performed by Chi-square and ANOVA

		HC	RRMS	SPMS	PPMS	CIS	NMOSD	*P*
N. of participants		130	130	115	35	78	128	
Age; mean (SD)		37.3 (9.9)	36.2 (8.8)	39.2 (7.8)	37.5 (7.7)	36.8 (9.3)	38.1 (9.6)	0.247
Gender (female); *n* (%)		108 (83.0)	109 (83.8)	91 (79.1)	27 (0.77)	64 (82.0)	102 (79.6)	0.456
Years of education; mean (SD)		14.1 (2.8)	14.1 (2.9)	13.8 (3.3)	13.7 (3.6)	14.2 (2.6)	13.9 (2.7)	0.173
EDSS; median (IQR)		-	1.0 (2.0)	3.5 (1.5)	3.0 (2.0)	0.0 (0.5)	1.5 (2.0)	<0.001
Disease duration; mean (SD)		-	8.5 (6.1)	13.3 (6.4)	4.7 (5.0)	5.1 (3.2)	6.6 (4.3)	<0.001
AQP-4 antibody positive; *n* (%)		-	-	-	-	-	51 (39.8)	-
DMT; *n* (%)	AZA	-	0	0	0	0	15 (11.7)	-
	DMF	-	16 (12.3)	0	0	15 (19.2)	0	
	FGL	-	4 (3.0)	1 (0.9)	0	1 (1.3)	0	
	Interferon	-	26 (20.0)	0	0	30 (38.4)	0	
	NAZ	-	3 (2.3)	0	1 (2.8)	0	0	
	GA		2 (1.6)	0	0	1 (1.3)	0	
	OCR	-	6 (4.6)	25 (21.7)	20 (57.2)	0	0	
	RTX	-	45 (34.6)	85 (73.9)	14 (40.0)	0	113 (88.3)	
	TFM	-	28 (21.6)	0	0	22 (28.3)	0	
	None		0	4 (3.5)	0	9 (11.5)	0	

HC: healthy control, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive MS, PPMS: primary progressive MS, CIS: clinical isolate syndrome, NMOSD: neuromyelitis optica spectrum disorder, SD: standard deviation, AQP-4: Aquaporin-4, AZA: azathioprine, DMF: dimethyl fumarate, FGL: fingolimod, NAZ: natalizumab, GA: glatiramer acetate, OCR: ocrelizumab, RTX: rituximab

Table 2: SDMT scores and CI prevalence comparison between groups. Analyzes were performed by Chi-square and ANOVA

	HC	RRMS	SPMS	PPMS	CIS	NMOSD	*P*
N. of participants	130	130	115	35	78	128	
SDMT; mean (SD)	51.9 (8.1)	42.4 (9.7)	33.7 (10.5)	32.0 (13.1)	47.0 (10.7)	42.5 (9.5)	<0.001
SDMT z-score; mean (SD)	0.0 (1.0)	-1.1 (1.2)	-2.2 (1.3)	-2.4 (1.6)	-0.6 (1.3)	-1.1 (1.1)	<0.001
N. of cognitive impairment; *n* (%)	14 (10.7)	44 (33.8)	82 (71.3)	22 (62.8)	15 (19.2)	42 (32.8)	<0.001

HC: healthy control, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive MS, PPMS: primary progressive MS, CIS: clinical isolate syndrome, NMOSD: neuromyelitis optica spectrum disorder, SD: standard deviation. SDMT: Symbol Digit Modalities Test

The comparison of CI among different groups showed that the risk of CI in SPMS and PPMS was significantly higher than in other study groups. Although the risk of CI in SPMS was 1.5 times that of PPMS, this difference was not statistically significant. This study also indicated that the CI risk was higher in all MS subgroups compared to NMOSD. However, this difference was insignificant in PwRRMS (P: 0.860). Furthermore, the risk of CI in the CIS group was significantly lower than in all groups except HC. For detailed comparisons among other groups, refer Table 3.

Discussion

This study aimed to determine the odds of CI among different MS subtypes and NMOSD. The findings contribute critical insights that could help refine future treatment protocols for these conditions. Our results indicate that the risk of CI is notably higher in PwPMS compared to other subtypes studied. In this study, by selecting homogeneous populations, we effectively controlled confounding factors such as age, gender, and educational level, allowing for a more accurate assessment of the relationship between MS subtype and cognitive function.

According to our study's findings, the risk of CI was higher in all studied groups than in HC. However, this increase in PwCIS was not statistically significant. The reason for this slight difference between CIS and HC, as well as the lower risk of CI in PwCIS compared to other groups, is probably due to the pathogenesis of CIS itself. In the CIS group, the risk of CI occurrence was much lower than in other patients due to the smaller volume of lesions, less brain atrophy,[26] and, subsequently, less destruction of neural pathways.[27] In addition, the prevalence of 19.2% for PwCIS reported in this study is consistent with the results of previous studies.[27-29] Additionally, the study by Hynčicová *et al*.[30] demonstrated that while CI was observed similarly in PwCIS and PwRRMS, the patterns of CI often differed. Furthermore, in PwCIS, there was frequently no correlation between CI and structural changes in the brain, which may account for the reduced severity of CI in PwCIS.

Another significant result of this study was the risk of CI in PwNMOSD. This study showed that although the risk of CI in PwNMOSD was higher than in HC and PwCIS, it was slightly less than in PwRRMS. Additionally, the risk of CI was significantly higher in people with progressive MS (PwPMS) than in PwNMOSD. In this regard, the study by Cho *et al*.[31] indicated that the risk of CI in PwMS was equal to HR (hazard ratio): 2.34, and in PwNMOSD, it was equal to

Table 3: Odds of CI among different study groups. Analyzes were performed by Chi-square

	Odds of CI compared to HC OR (CI) (95%)	*P*	Odds of CI compared to RRMS OR (CI) (95%)	*P*	Odds of CI compared to SPMS OR (CI) (95%)	*P*
HC (*n*=130)	-	-	0.23 (0.12-0.45)	<0.001	0.04 (0.02-0.09)	<0.001
RRMS (*n*=130)	4.23 (2.18-8.22)	<0.001	-	-	0.20 (0.11-0.35)	<0.001
SPMS (*n*=115)	20.58 (10.36-40.88)	<0.001	4.85 (2.82-8.36)	<0.001	-	-
PPMS (*n*=35)	14.02 (5.80-33.86)	<0.001	3.30 (1.52-7.18)	0.002	0.68 (0.30-1.50)	0.344
NMOSD (*n*=128)	4.04 (2.07-7.87)	<0.001	0.95 (0.56-1.60)	0.860	0.19 (0.11-0.33)	<0.001
CIS (*n*=78)	1.97 (0.89-4.34)	0.092	0.46 (0.23-0.90)	0.025	0.09 (0.04-0.19)	<0.001
	Odds of CI compared to PPMS OR (CI) (95%)	***P***	**Odds of CI compared to NMOSD OR (CI) (95%)**	***P***	**Odds of CI compared to CIS OR (CI) (95%)**	***P***
HC (*n*=130)	0.07 (0.03-0.17)	<0.001	0.24 (0.12-0.48)	<0.001	0.50 (0.23-1.11)	0.092
RRMS (*n*=130)	0.30 (0.13-0.65)	0.006	1.04 (0.62-1.75)	0.860	2.14 (1.09-4.19)	0.025
SPMS (*n*=115)	1.46 (0.66-3.25)	0.344	5.08 (2.94-8.79)	<0.001	10.43 (5.21-20.78)	<0.001
PPMS (*n*=35)	-	-	3.46 (1.59-7.54)	0.002	7.10 (2.92-17.26)	<0.001
NMOSD (*n*=128)	0.28 (0.13-0.62)	0.002	-	-	2.05 (1.04-4.02)	0.036
CIS (*n*=78)	0.14 (0.05-0.34)	<0.001	0.48 (0.24-0.95)	0.036	-	-

HC: healthy control, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive MS, PPMS: primary progressive MS, CIS: clinical isolate syndrome, NMOSD: neuromyelitis optica spectrum disorder, SD: standard deviation. CI: cognitive impairment. (CI): confidence interval

HR: 2.19. Although there were no significant differences, the HR was slightly higher in PwMS. The results of the studies by Czarnecka *et al*.[32] and Saji *et al*.[33] were in the same direction. Considering that the number and volume of brain T2-enhanced lesions in PwNMOSD are less than in PwMS,[34,35] the destruction of effective information transmission pathways in the IPS process probably occurs at a slower rate, subsequently decreasing the risk of CI in PwNMOSD.[10] However, a conclusion still needs to be revised due to the inconsistent findings on the risk and prevalence of CI in PwNMOSD. Previous studies reported the prevalence of CI in PwNMOSD to range from 30% to 70%.[36,37] This wide heterogeneity in CI findings in PwNMOSD is likely due to the lack of a specially developed tool to measure NMOSD cognitive functions.

The results also revealed that the risk of CI in PwPMS was significantly greater than that in the other groups studied, including RRMS, CIS, NMOSD, and HC. The primary reason for the increased risk of CI in PMS can be related to the higher lesion load,[38] the higher rate of neurodegeneration, and subsequent brain atrophy and destruction of the pathways involved in IPS.[38,39] This study also showed that the risk and prevalence of CI in SPMS were slightly higher than in the PPMS group, although these results were not statistically significant. The significant difference in disease duration of these two groups is probably one of the primary reasons for clarifying this difference between SPMS and PPMS. According to previous studies, increased disease duration can lead to increased brain atrophy and, subsequently, the destruction of effective pathways in IPS function.[40] In line with this point of view, in the study of Brochet *et al*.,[41] when SPMS and PPMS were compared, a significant difference in the risk of CI was observed, and this difference lost its significance after adjusting parameters such as disease duration.

According to previous studies, age is one of the primary confounding variables in measuring the risk of CI. For example, the study by Branco *et al*.[42] showed that the prevalence of CI in PwMS over 50 years old is 77.4%, while the reported prevalence in patients under 50 years old was only 42.8%. In addition, in the study by Jakimovski *et al*.,[43] aging was recognized as an effective parameter in increasing the risk of CI.

Gender differences are another parameter affecting CI. According to the study by Donaldson *et al*.,[44] the progression of MS and the risk of CI are higher in men than women with MS. However, the results of the study by Tedone *et al*.[45] showed that although men with MS achieved weaker in some cognitive domains compared to women with MS, no significant overall gender difference was seen.

Education level is another critical parameter in measuring CI. According to Estrada-López *et al*.'s[46] study findings, an increase in education level may be the probable preventing factor for the risk of CI in PwMS. Similarly, the study by de Medeiros Rimkus *et al*.[47] showed that the risk of CI was significantly lower in patients with a higher education level, suggesting that new cut-offs should be determined according to the education level of the patients.

In the present study, no significant difference was observed between the three main variables among the studied groups. The homogeneity of the populations can control the effect of these three confounding variables, allowing the comparison of the populations based solely on the stage of the disease in each group.

One of the key strengths of this study was comparing different subtypes of MS and NMOSD in terms of CI occurrence while controlling for the effects of age, gender, and education by selecting nearly homogeneous samples. However, the primary limitation of this study is the lack of examination of additional cognitive domains across the groups, along with the use of

crude odds ratios. Additionally, the cross-sectional design and the limited sample size represent further limitations. Future studies with larger sample sizes and exploring additional cognitive domains are recommended.

Conclusion

In conclusion, this study demonstrated that the odds of CI are significantly higher in MS subtypes and NMOSD compared to HC. While no significant difference was observed in the risk of CI between PwRRMS and PwNMOSD, the risk of CI was significantly higher in the PwPMS. Additionally, the findings indicated no significant difference in the risk of CI between CIS and HC, as well as between PPMS and SPMS.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR. MUI.MED. REC.1402.459).

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Conflicts of interest

There are no conflicts of interest.

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