Assessment of Cognitive Impairment among Multiple Sclerosis Patients in Ismailia

Abdelrahman M. Ali*, Osama M. Shehab, Mohamed A. Elsamahy, Ehab A. Hashish*

Neurology and Psychiatry Department, Faculty of Medicine, Suez Canal University

Abstract

Background and aim: **Multiple sclerosis (MS) has shown an increasing prevalence over last decade. Cognitive impairment is a crucial implication of MS affecting patients' quality of life in different aspects. The current study is designed aiming to evaluate the cognitive impairment among multiple sclerosis patients and its association with multiple disease related factors.** ***Patients and Methods:*** **A total of 34 patients and another 34 age and sex matched healthy controls have been included into the study. Patients were included based on McDonald Criteria 2017. Cognitive function was evaluated among the studied participants of the study and control groups using Symbol Digit Modalities (SDM) test.** ***Results:*** **MS patients demonstrated significantly lower cognitive scores compared to controls ($p < 0.001$). Mean score was 29.9 versus 57.1 among the control participants. Median value was 57.5 in the control group and 30 in cases group. Multiple regression analysis showed that number of T2 MRI lesions and age are the most independent factors affecting the cognition of the patients .**

Conclusion: **MS has significant effect on cognitive function of MS patients. This impact is significantly correlated with multiple personal and disease features including patients' age duration of disease, number of relapsed, physical disability, progressive phenotype and number of brain lesions.**

Keywords: Cognition, multiple sclerosis, Symbol digit modalities, cognitive impairment.

Introduction

Multiple sclerosis (MS) is a condition that involves inflammation of the immune system, affecting the central nervous system. The pathology of MS encompasses various factors, including inflammation, demyelination of neural tissue, and degeneration of axons, ultimately leading to neurological disabilities in young adults [1, 2].

Since 2013, the worldwide prevalence of MS has been on the rise. By 2020, it was estimated that approximately 2.8 million people globally were diagnosed with MS, reflecting a prevalence of around 35.9 per 100,000 individuals [3]. Concerning the prevalence of MS in Egypt, current and precise data is lacking [4], and various limited studies have reported estimates ranging from 3.376 per 100,000 [5] to 13.7 per 100,000 [6].

A significant aspect of MS is its effect on the cognitive abilities of patients, which was recognized as a manifestation of the disease as early as 1877 by Charcot [7]. He remarked, "conceptions are formed slowly and the intellectual and emotional faculties are blunted in their totality [8]." Cognitive dysfunction affects approximately 43-70% of individuals with MS [9]. Clinically, it can be identified early in the progression of

**Corresponding Author: ehab83hashish@yahoo.com*

the disease [10] and serves as a crucial prognostic indicator [11]. Several cognitive domains are impacted, with the most frequently affected being information processing speed along with memory, attention, and executive functions [12]. Cognitive impairment is thought to arise from atrophy of gray matter and degeneration of white matter [13].

Research has previously explored factors related to cognitive impairment in MS patients. It has been noted that disease subtype, duration, the patient's gender, and educational level correlate with increased cognitive decline. Furthermore, those with progressive MS tend to experience more severe cognitive deficits. Studies have indicated that immunomodulatory drugs may offer protective benefits against cognitive deterioration [14].

The Symbol Digit Modalities Test (SDMT) is a vital and clinically endorsed tool for assessing cognitive impairment in MS and other neurological disorders [15]. It provides a brief evaluation of information processing speed. As the standard measure for screening cognitive impairment in MS, SDMT is administered in a short time frame (less than 5 minutes), is straightforward to carry out [12, 16], and is recognized for its high sensitivity in detecting even minor cognitive declines [7, 17, 18].

Given the clinical significance of MS and the shortage of studies examining cognitive impairment among MS patients, the present study was initiated to assess cognitive deficits in multiple sclerosis patients and their association with various disease-related factors.

Patients and methods:

Following the ethics committee's approval at Suez Canal University-Faculty of Medicine, we carried out this case-control study involving MS patients presenting to the outpatient clinic of the Neurology department at Suez Canal University Hospital and Ismailia Medical Complex Hospital with simple random sampling. The Age range from 20-50 years with median 31 year and age matched for control group. The study period spanned from January 2023 to August 2024. It comprised two groups: the cases group and the healthy controls group. The cases group consisted of patients with a confirmed diagnosis of MS based on the McDonald Criteria 2017 [20]. Patients with other organic or psychiatric conditions that could influence cognitive function, such as anxiety and depression, were excluded from the study. Patient was receiving medications that affect cognitive function was excluded. Illiterate patient was excluded. A control group was comprised of age, educational level and sex-matched healthy individuals collected from attendees with the patient. In total, 34 patients and 34 matched healthy participants were included in the study. The sample size was calculated using an alpha error of 5% and study power of 80% [21].

To evaluate anxiety, the Hamilton Anxiety Rating Scale was administered to all patients involved [22], and depression was assessed using the Beck Depression Inventory scale [23].

An interview questionnaire captured data on patient demographics including age, gender, special habits, educational background, illness duration, and clinical course, which

could be relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), or progressive relapsing (PR).

Cognitive function assessment for both study and control groups was conducted using the Symbol Digit Modalities (SDM) test [15]. This test involved nine digits (ranging from 1 to 9) paired with corresponding symbols. Participants were instructed to write the matching symbol for each digit as quickly as possible in the empty space provided beneath each digit, with the total number of correct symbols recorded within a specified time (90 seconds) [7].

For statistical analysis, data were processed and evaluated using the SPSS statistical software Version 20. Quantitative data were presented as mean ± SD, while qualitative data were represented as numbers and percentages. The Shapiro-Wilk test was utilized to assess data normality. Unpaired t-tests were applied to normally distributed quantitative variables, while the Mann-Whitney test was utilized for non-normally distributed quantitative variables. Chi-square and Fisher's exact tests were employed for qualitative variables. A p-value of <0.05 was deemed statistically significant.

Results:

Table 1 showed that both cases (No 34) and control (No 34) groups were matched as regarding age and sex. Mean age was 31.2 years old among control group and 31.6 years old among cases group. Most of the participants were females. P-value regarding age and sex is 0.8 and 1 respectively.

Table 1: Personal characteristics among cases and control groups:

		Control group	Cases group	p-value
Age in years	Mean ± SD	31.2 ± 9.07	31.6 ± 1.7	0.8 (NS)
Sex	Male	8 (23.5%)	8 (23.5%)	1 (NS)
	Female	26 (76.5%)	26 (76.5%)	

NS: no statistically significant difference

As presented in **Figure 1**, cases with MS were found to have lower cognitive function as evaluated by SDM test score with statistically significant difference. Mean score was 29.9 versus 57.1 among the control participants. Median value was 57.5 in the control group and 30 in cases group.

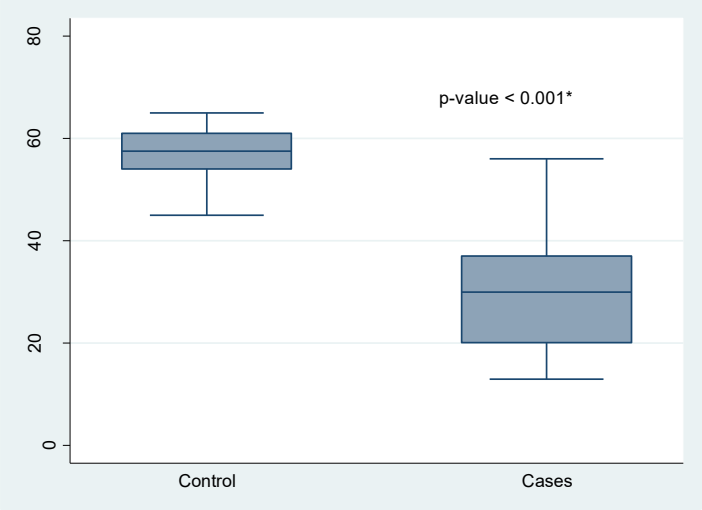

Figure 1: SDM test among cases and control groups**:**

Table 2 showed that mean duration of disease since diagnosis was 4.79 years with range from 1 to 4.4 years. The most common type of first relapse was optic neuritis (41.18%). Mean disability status as evaluated by expanded disability status scale was 2.78 with range from 1 – 5.5. Most of patients have periventricular brain lesions as reported by T2 MRI (94.12%).

Table 2: Diseases characteristics among MS patients:		
Duration since diagnosis (years)	Mean ± SD	4.79 ± 4.4
	Range	1 – 15
Latency (years)	Mean ± SD	1.38 ± 2.12
	Range	0 – 8
Number of relapses	Mean ± SD	2.67 ± 1.34
	Range	1 – 5
Type of first relapse	Optic neuritis	14 (41.18%)
	Motor	7 (20.59%)
	Sensory	6 (17.65%)
	Cerebellar	6 (17.65%)
	Brain stem	1 (2.94%)
EDSS	Mean ± SD	2.78 ± 1.12
	Range	1 – 5.5
MS phenotype	RR MS	25 (73.53%)
	SP MS	9 (26.47%)
Number of T2 MRI lesions	Mean ± SD	12.6 ± 5.03
	Range	4 – 22
Site of MRI lesions	Cortical/Juxta cortical lesions	23 (67.65%)
	Periventricular	32 (94.12%)
	Infratentorial	15 (44.12%)
RR: relapsing remitting, SP: secondary progressive *EDSS: Expanded Disability Status Scale*		

Table 3 showed that older age patients were found to have more impaired cognition (lower SDM test score) with significant difference P-value 0.03. The longer the duration of the disease the lower the SDM score as there was significant negative correlation between duration of the disease and SDM test score (P-value 0.01). Secondary progressive phenotypes have lower SDM test mean compared to relapsing remitting phenotype patients (17.33 versus 34.44; p-value < 0.001). The number of relapses and number of T2 MRI brain lesions was found to be negatively correlated with SDM score P value 0.001 (patients with more relapses and more lesions have lower score and worse cognition). However, the site of these lesions and the type of these relapses were not found to affect the cognition of the patient and their SDM score)

Table 3: Association between patient and diseases characteristics and cognitive function assessment according to SDM test:

		SDM test	p-value
Age	14 – <25a	40.38 ± 13.16a	0.03*
	25 – <40b	28.9 ± 8.5b	
	40 – 50c	22.4 ± 6.7b	
	r	-0.6	0.001*
Sex	Male	27 ± 9.7	0.3 (NS)
	Female	30.8 ±11.6	
Duration since diagnosis	r	-0.4	0.01*
Latency	r	-0.2	0.3 (NS)
Number of relapses	r	-0.5	0.01*
Type of first relapse	Optic neuritis	33.57 ± 10.7	0.5 (NS)
	Motor	25.7 ± 14.3	
	Sensory	30.8 ± 10.9	
	Cerebellar	26.5 ± 8.4	
	Brain stem	23 ± 0	
EDSS	r	-0.7	0.001*
MS phenotype	RR MS	34.44 ± 9.36	<0.001*
	SP MS	17.33 ± 3.16	
Number of T2 MRI lesions	r	-0.7	0.001*
Site of MRI lesions	Cortical/Juxta cortical lesions	29 ± 10.8	0.8 (NS)
	Periventricular	29.8 ± 11.3	
	Infratentorial	28.3 ± 10.9	

RR: relapsing remitting, SP: secondary progressive
**Statistically significant* *NS: not statistically significant*
EDSS: Expanded Disability Status Scale

Multiple regression analysis showed that number of T2 MRI lesions and age are the most significant independent factors affecting the cognition of the patients P-Value 0.005 and 0.001 respectively **(Table 4).**

Table 4: Multiple regression analysis of factors affecting cognitive function as evaluated by SDM test:				
	Coefficient	t-statistic	p-value	95% CI
MS phenotype	-6.4	-1.73	0.09 (NS)	-13.9 – 1.14
Number of T2 MRI lesions	-1.03	-3.02	0.005*	-1.7 - -0.3
Age	-6.02	-4.06	0.001*	-9.05 - -2.9
*Statistically significant		NS: not statistically significant		

Discussion:

Cognitive impairment (CI) and MS are high co-incident among patients, and CI has been reported among 34–65% of patients during the course of the disease. Surprisingly, CI has been reported along the course of MS and can even be detected before the onset of clinical symptoms [24, 25].

Cognition can be affected by other neurological or psychological disorders [26]. That's why we have excluded patients having depression or anxiety. Depression can affect cognition via negative influence on processing speed, memory, executive functioning or attention [27], meanwhile the effect of anxiety is related to changes in processing speed, working memory, visuo-spatial memory and/or verbal learning abilities [28].

As there is no validated normal range of SDM test we have included a control group for comparative purposes. We have found that cases have significantly lower results of SDM test indicating worse cognition among MS patients. This was similar to results reported by earlier studies [17]. The observation of lower cognition among MS patients even by different neuro-cognitive assessment scales has been reported by different various previous reports. SDMT has been administered by Johnen et al., [29] as well as Osman and Mohamed [30], Bartosz et al., [31] and reported decreased processing speed and impaired executive functions. Similar findings were also published by Zeng and colleagues [32] but using another scale that is the MMSE and also found impaired cognition among MS compared to controls. This result was also consistent with Potagas and associates [33].

We have found association between cognitive impairment among MS patients and disease duration. Also we have found that patients with secondary progressive MS have more severe cognitive impairment than those with relapsing remittent disease and this may be due to more neuronal loss. The difference in prevalence of CI in different phenotypes of MS has been previously reported. It has been reported that prevalence of CI is more among patients with secondary progressive MS (50 -75%) versus 30 - 45% in patients with PR MS and 20 -25% in patients with RR MS [24, 25] .

Consistently a recent meta-analysis has reported that observed that patients with primary progressive MS are more severely cognitively impaired than relapsing remittent MS patients [34] and this was also supported by Patti et al., [35]. Their observation that patients having secondary progressive multiple sclerosis (SP MS) have lower SDMT scores compared to those with relapsing-remitting multiple sclerosis (RRMS), as well as a positive correlation with the Expanded Disability Status Scale (EDSS),

supports the influence of accumulated disability and white matter damage on cognitive function. The association between physical disability and cognitive impairment among patients with MS have also been previously proven. As well as our study, previous report has emphasized the association between older patients' age and longer disease duration [36].

At the brain level, our study has shown that lesions load as indicated by number of brain lesions on MRI is significantly correlated with cognitive impairment. We have found that the more the number of lesions is, the lower the SDM test score is. This is consistently reported by Rocca and colleagues [37].

Conclusion:

Based on current study, we concluded that MS has significant effect on cognitive function of MS patients. This impact is significantly correlated with multiple personal and disease features including patients' age duration of disease, number of relapsed, physical disability, progressive phenotype and number of brain lesions.

There are a number of limitations in this study that should be acknowledged. Because the study follows a case-control design, it is unclear how stable the identified groups remain over time. We chose to analyze data from only one point in time to capture a snapshot of cognitive patterns in individuals with MS. However, future longitudinal studies that track cognitive phenotypes over time may provide more accurate and informative models for predicting cognitive decline in MS. This is especially relevant given that, as MS progresses, the factors influencing each identified group may change.

References

1. Hauser SL and Cree BA. Treatment of multiple sclerosis: a review. The American journal of medicine. 2020; 133: 1380-1390.
2. Jakimovski D, Bittner S, Zivadinov R, Morrow SA, Benedict RH, Zipp F, et al. Multiple sclerosis. Lancet. 2024;403:183–202.
3. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising Prevalence Of Multiple Sclerosis Worldwide: Insights from the Atlas Of Ms, Third Edition. Mult Scler. 2020; 26: 1816-1821.
4. Hashem S, El-Tamawy M, Mohamed H, Elmasry T. Epidemiology of multiple sclerosis in Egypt. Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 20101; 47: 625-632.
5. Ramadan BM, Fahmi RM, Soliman AM, Sadik MA, Elmotayam A, Sarhan N. Multiple Sclerosis in Sharkia Governorate through Patients Attending Zagazig University Multiple Sclerosis Unit. ZUMJ. 2023; 29(4): 1044 – 1050.
6. El-Tallawy HN, Farghaly WM, Badry R, Metwally NA, Shehata GA, Rageh TA, et al. Prevalence of multiple sclerosis in Al Quseir city, Red Sea Governorate, Egypt. Neuropsychiatr Dis Treat. 2016; 12:155-8.
7. Benedict RH, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R, et al.. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler. 2017; 23(5):721-733.
8. Charcot JM. Lectures on the Diseases of the Nervous System. London: New Sydenham Society, 1877.
9. Edgar R. Alejandra M, Teresita V, Mario A, Fernando C, Miguel A. Validation of the Brief International

Cognitive Assessment for Multiple Sclerosis (BICAMS) in individuals with multiple sclerosis from Mexico, Multiple Sclerosis and Related Disorders. 2024; 83.
10. Brummer T, Muthuraman M, Steffen F, Uphaus T, Minch L, Person M, et al. Improved prediction of early cognitive impairment in multiple sclerosis combining blood and imaging biomarkers. Brain Commun. 2022; 4(4): fcac153.
11. Diker S, Has AC, Kurne A, Göçmen R, Oğuz KK, Karabudak R. The association of cognitive impairment with gray matter atrophy and cortical lesion load in clinically isolated syndrome. Mult Scler Relat Disord. 2016 Nov;10:14-21.
12. Gajewski B, Karlińska I, Stasiołek M. Symbol Digit Modalities Test in progressive multiple sclerosis. Polish Journal of Neurology and Neurosurgery. 2024; 58 (3): 221 – 232.
13. West K, Sivakolundu D, Maruthy G, Zuppichini M, Liu P, Thomas B, et al. Baseline cerebral metabolism predicts fatigue and cognition in Multiple Sclerosis patients. Neuroimage Clin. 2020;27:102281.
14. Elshebawy H, Fahmy EM, Elfayoumy NM, Abdelalim AM, Ismail RS. Clinical predictors to cognitive impairment in multiple sclerosis patients. Egypt J Neurol Psychiatry Neurosurg. 2021; 57: 38.
15. Smith A. Symbol digit modalities test. Los Angeles, CA: Western Psychological Services, 1982.
16. Pogoda-Wesołowska A, Dziedzic A, Maciak K, Stępień A, Dziaduch M, Saluk J. Neurodegeneration and its potential markers in the diagnosing of secondary progressive multiple sclerosis. A review. Front Mol Neurosci. 2023 Sep 12;16:1210091.
17. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RH. Screening for cognitive impairment in multiple sclerosis using the symbol digit modalities test. Mult Scler 2007; 13: 52–57.
18. Charvet LE, Beekman R, Amadiume N, Belman AL, Krupp LB. The symbol digit modalities test is an effective cognitive screen in pediatric onset multiple sclerosis (MS). J Neurol Sci 2014; 341: 79–84.
19. Benedict RH, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R, et al. Validity of the symbol digit modalities test as a cognition performance outcome measure for multiple sclerosis. Mult Scler 2017; 23: 721–733.s
20. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–173.
21. Dawson B and Trapp RG. Basic and clinical biostatistics, ALANGE medical book, 2004.
22. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55
23. Beck AT, Ward CH, Mendelson M, Mock J, & Erbauch J. Beck Depression Inventory (BDI), 1961 [Database record]
24. DeLuca J. Chiaravalloti ND, Sandroff BM. Treatment and management of cognitive dysfunction in patients with multiple sclerosis. Nat. Rev. Neurol. 2020, 16, 319–332.
25. Benedict R, Amato M, DeLuca J, Geurts J. Cognitive impairment in multiple sclerosis: Clinical management, MRI, and therapeutic avenues. Lancet Neurol. 2020, 19, 860–871. S
26. Kalron A, Aloni R, & Allali G. The relationship between depression, anxiety and cognition and its paradoxical impact on falls in multiple sclerosis patients. Multiple Sclerosis and Related Disorders. 2018; 25: 167–172.
27. Diamond B, Johnson S, Kaufman M, & Graves L. Relationships between

information processing, depression, fatigue and cognition in multiple sclerosis. Archives of Clinical Neuropsychology. 2008; 23(2): 189–199.
28. DiGiuseppe G, Blair M, & Morrow SA. Short Report: Prevalence of Cognitive Impairment in Newly Diagnosed Relapsing-Remitting Multiple Sclerosis. International Journal of MS Care. 2018; 20(4): 153–157.
29. Johnen A, Landmeyer NC, Bürkner PC, Wiendl H, Meuth SG, Holling H. Distinct cognitive impairments in diferent disease courses of multiple sclerosis-a systematic review and meta-analysis. Neurosci Biobehav Rev. 2017; 83:568–578.
30. Osman DF and Mohamed AK. Effect of Multiple Sclerosis Disability Status on Cognitive Functions. EJENTAS. 2025; 336238.1794
31. Bartosz G, Iwona K, Mariusz S. Neurol Neurochir Pol 2024; 58(3):221-232.
32. Zeng Q, Dong X, Ruan C, Hu B, Zhou B, Xue Y, et al. Cognitive impairment in Chines e IIDDs revealed by MoCA and P300. Mult Scler Relat Disord. 2017;16:1–7.
33. Potagas C, Giogkaraki E, Koutsis G, Mandellos D, Tsirempolou E, Sfagos C, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. J. Neurol. Sci. 2008; 267: 100–106
34. Penner IK and Paul F. Fatigue as a symptom or comorbidity of neurological diseases. Nature Reviews Neurology. 2017; 13(11): 662–675
35. Patti F, De Stefano M, Lavorgna L, Messina S, Chisari CG, Ippolito D, et al. Lesion load may predict long-term cognitive dysfunction in multiple sclerosis patients. PloS one. 2015; 10: e0120754.
36. Ruano L, Portaccio E, Goretti B, Niccolai C, Severo M, Patti F, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. Mult. Scler. J. 2016; 23: 1258–1267.
37. Rocca MA, Riccitelli GC, Meani A, Pagani E, Del Sette P, Martinelli V, et al. Cognitive reserve, cognition, and regional brain damage in MS: A 2 - year longitudinal study. Multiple Sclerosis Journal. 2018; 25(3): 372–381.