E-ISSN: 2791-7851

Journal of MULTIPLE SCLEROSIS Research

VOLUME 2 ISSUE 3 December 2022

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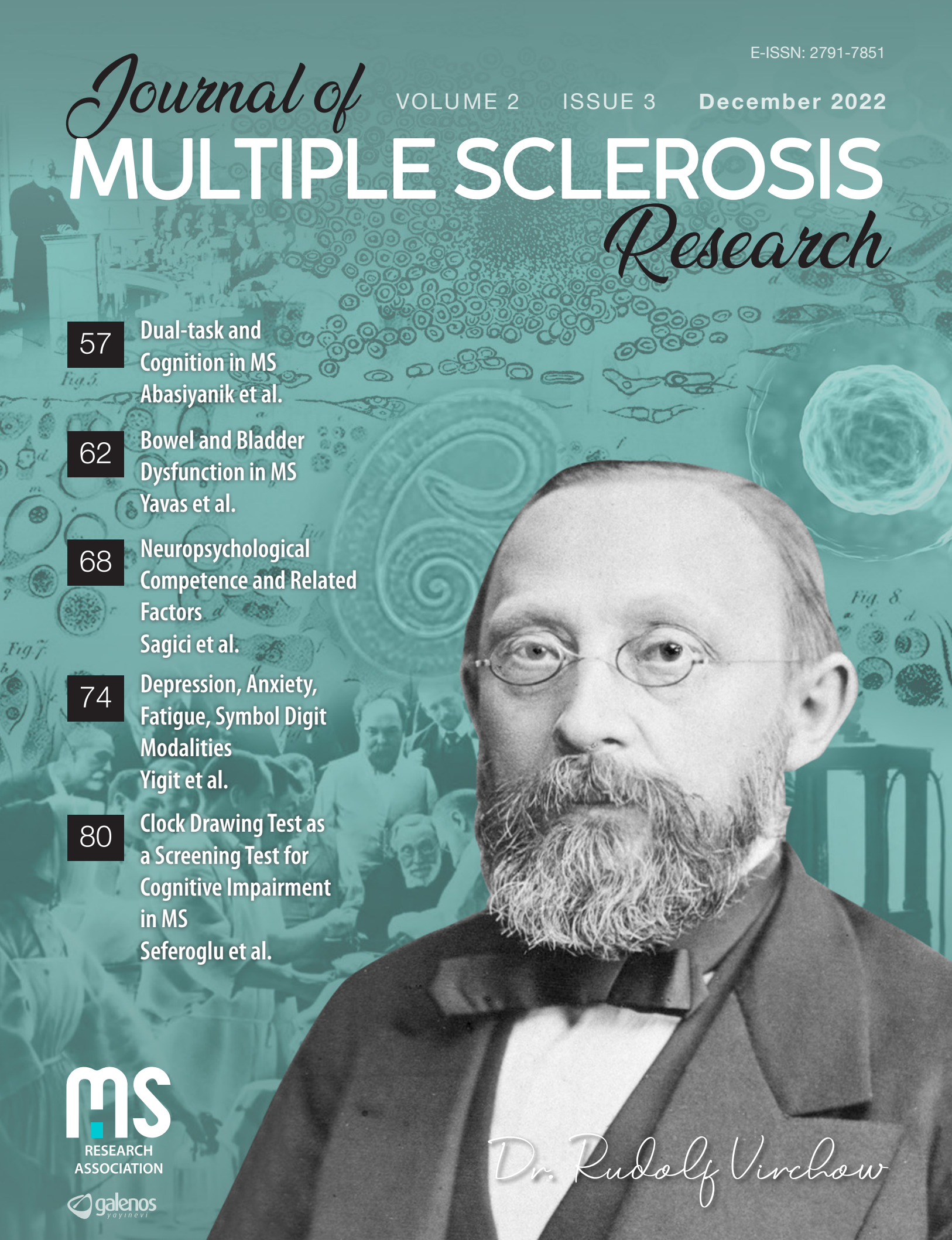

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Online Yayınlanma Tarihi/Online Publication Date: Aralık 2022/December 2022

E-ISSN: 2791-7851

Üç ayda bir yayımlanan süreli yayındır.
International scientific journal published quarterly.

Journal of MULTIPLE SCLEROSIS Research

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ABOUT US

Journal of Multiple Sclerosis Research is the official open access scientific publication of the Multiple Sclerosis Research Association. This double-blind peer-reviewed journal is published quarterly in April, August, and December.

The target audience of the *Journal of Multiple Sclerosis Research* includes all health professionals working in the fields of multiple sclerosis, neuromyelitis optica and spectrum diseases, and other related diseases of the central nervous system.

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Manuscripts should be prepared according to ICMJE guidelines (http://www.icmje.org).

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Technical and other assistance should be provided on the title page.

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CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-1991) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(7):e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Toward complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-44.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

Meta-analysis of observational Studies in Epidemiology (MOOSE) guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting MOOSE group. JAMA 2000;283:2008-2012).

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Manuscript Format and Style

Writing rules

The submission should be split into separate files in the following order:

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b. Main Document (English abstract and keywords-Turkish abstract and keywords, main text, references, tables and figure explanations should be included).

c. Figures, pictures and graphics files in .jpeg or .gif formats should be uploaded separately.

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e. Ethics committee approval form should be available for research articles.

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Title: The title should provide important information regarding the manuscript's content. The title page should include the authors' names, degrees, and institutional/professional affiliations, a short title, abbreviations, keywords, financial disclosure statement, and conflict of interest statement. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number corresponding to their institution, which is listed separately. The contact information for the corresponding author should also be provided, including name, e-mail address, telephone, and fax numbers.

Running Head: The running head should not be more than 40 characters, including spaces, and should be located at the bottom of the title.

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The journal expects that data supporting the results in the paper will be archived in an appropriate public repository. Authors are required to provide a data availability statement to describe the availability or the absence of shared data. When data have been shared, authors are required to include a link to the used repository in their data availability statement and to cite their shared data. Journal of Multiple Sclerosis Research requests detailed information from the authors regarding the data sharing policy.

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Abstract and Keywords: The second page should include an abstract not exceeding 250 words. Moreover, as various electronic databases integrate only abstracts into their index, important findings should be presented in the abstract.

Abstract

The abstract should be short and factual. It should state the purpose of the research briefly and should be structured according to the following subheadings: Objective, Materials and Methods, Results, and Conclusion. Abbreviations should be avoided and reference citations are not permitted. References should be avoided, and nonstandard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself. The clinical trial number should be provided at the end of the abstract.

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Materials and Methods: Important methods should be written respectively.

Results: Important findings and results should be provided here.

Conclusion: The study's new and important findings should be highlighted and interpreted.

Other types of manuscripts, such as case reports, reviews, and others, will be published according to uniform requirements.

Keywords: Provide at least three keywords below the abstract to assist indexers. Use terms from the Index Medicus Medical Subject Headings List (for randomized studies, a CONSORT abstract should be provided (http://www.consort-statement.org).

1. Original Articles:

An article is considered original research if;

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- The researchers describe their hypothesis or research question and the purpose of the study.
- The researchers detail their research methods.
- The results of the research are reported.
- The researchers interpret their results and discuss possible implications.

This is the most common type of journal manuscript used to publish full data reports from research. It may be called an Original Article, Research Article, Research, or just Article, depending on the journal.

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Materials and Methods: The selection of observational or experimental participants, such as patients, laboratory animals, and controls, must be clearly described, including inclusion and exclusion criteria and a description of the source population. Sufficiently detailed methods and procedures must be identified to allow other researchers to reproduce the results. References to established methods (including statistical methods) and to brief modified methods and the rationale for using them and evaluation of their limitations must be provided. All drugs and chemicals used, including generic names, doses, and routes of administration, must be identified. The section should include only information that was available at the time the plan or protocol for the study was devised on STROBE (http://www.strobe-statement.org).

Statistics: The statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported results must be described. Statistically important data should be provided in the text, tables, and figures. Details about randomization and the number of observations must be provided as well, the treatment complications must be described, and all computer programs used must be specified.

Results: Your results should be presented in logical sequence in the text, tables, and figures. Not all the data provided in the tables and/or figures in the text must be presented; Only important findings, results, and observations should be emphasized and/or summarized. For clinical studies, the number of samples, cases, and controls included in the study should be provided. Discrepancies between the planned number and the obtained number of participants should be explained. Comparisons and statistically important values (i.e., p-value and confidence interval) should be provided.

Discussion: This section should include a discussion of the data. New and important findings/results and the conclusions they lead to should be emphasized. The conclusions should be linked with the goals of the study, but unqualified statements and conclusions not entirely supported by the data should be avoided. The detailed findings/results should not be repeated; important findings/results should be compared with those of similar studies in the literature, along with a summary. In other words, similarities or differences in the obtained findings/results with those previously reported should be discussed.

Study Limitations: Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

2. Case Reports: A case report is a detailed report of the symptoms, signs, diagnosis, treatment, and follow-up of an individual patient. It usually describes an unusual or novel occurrence and remains one of the cornerstones of medical progress and provides many new ideas in medicine. Case reports should be structured as follows:

> **Abstract:** an unstructured abstract that summarizes the case
>
> **Introduction:** a brief introduction (recommended length: 1–2 paragraphs)
>
> **Case Presentation:** describes the case in detail, including the initial diagnosis and outcome
>
> **Discussion:** should include a brief review of the relevant literature and how the presented case furthers our understanding to the disease process

3. Review Articles: Review articles provide a comprehensive summary of research on a certain topic and a perspective on the state of the field and where it is heading. They are often written by leaders in a particular discipline after an invitation from the editors of a journal.

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7. Editorial Comment: Editorial comments are a brief remark on an article published in the journal by the viewer of their article or by a relevant authority. Most comments are invited by the editor in chief, but spontaneous comments are welcome. An abstract is not required with this type of manuscripts.

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https://www.nlm.nih.gov/bsd/uniform_requirements.html

Examples of References

1. List All Authors

Bonanni E, Tognoni G, Maestri M, Salvati N, Fabbrini M, Borghetti D, DiCoscio E, Choub A, Sposito R, Pagni C, Iudice A, Murri L.

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Sleep disturbancesin elderly subjects: an epidemiological survey in an Italian district. ActaNeurol Scand 2010;122:389-397.

2. Organization as Author

American Geriatrics Society 2015 Updated Beers Criteria Expert panel. American geriatrics society 2015 updated Beer criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63: 2227-2246.

3. Complete Book

Ham RJ, Sloane PD, Warshaw GA, Potter JF, Flaherty E. Ham's primary care geriatrics : a case-based approach, 6th ed. Philadelphia, Elsevier/Saunders, 2014.

4. Chapter in Book

BG Katzung. Special Aspects of Geriatric Pharmacology, In:Bertram G. Katzung,Susan B. Masters, Anthony J. Trevor (Eds). Basic and Clinical Pharmacology. 10th edition, Lange, Mc Graw Hill, USA 2007, pp 983-90.

5. Abstract

Reichenbach S, Dieppe P, Nuesch E, Williams S, Villiger PM, Juni P. Association of bone attrition with knee pain, stiffness and disability; a cross sectional study. Ann Rheum Dis 2011;70:293-8. (abstract).

6. Letter to the Editor

Rovner B. The Role of the Annals of Geriatric Medicine and Research as a Platform for Validating Smart Healthcare Devices for Older Adults. Ann Geriatr. 2017;21:215-216.

7. Supplement

Garfinkel D. The tsunami in 21st century healthcare: The age-related vicious circle of co-morbidity - multiple symptoms - over-diagnosis - over treatment - polypharmacy [abstract]. J Nutr Health Aging 2013;17(Suppl 1):224-227.

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Type of Article	Abstract	Word Count*	Number of References	Tables/ Figures
Original Articles	250	3000	50	5
Review Articles	250	3500	100	5
Invited Review Article	250	3500	75	5
Case Reports	100	1000	15	2
Images	None	500	10	2
Letters to the Editor	None	600	10	1
Editorial Comment	None	1500	20	2

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All authors participated in the study concept and design, analysis and interpretation of the data, and drafting or revising of the manuscript and have approved the manuscript as submitted.

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Approval of the Ethics Committee and a statement on the adherence of the study protocol to international guidelines (Declaration of Helsinki revised in 2013 [www.wma.net/e/policy/b3.html]) are required for experimental and clinical studies as well as studies on drug–human interactions. In experimental animal studies, the authors should indicate that the procedures were followed in accordance with animal rights (Guide for the Care and Use of Laboratory Animals [https://www.nap.edu/catalog/5140/]) and should obtain approval from the Animal Ethics Committee.

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DOI: 10.4274/jmsr.galenos.2022.2022-7-3
Journal of Multiple Sclerosis Research 2022;2(3):57-61

RESEARCH ARTICLE

Relationship Between Dual-task Walking and Cognitive Functions in Persons with Multiple Sclerosis

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Abstract

Objective: Dual-task performance assessment is a holistic approach that incorporates both motor and cognitive assessment. However, there is scarce data on the relationship between dual-task walking and cognitive functions in persons with multiple sclerosis (pwMS). The aim was to investigate the relationship between dual-task walking and cognitive functions in pwMS.

Materials and Methods: This study analyzed 156 patients (median age 35 years, 73.1% female). Timed Up and Go tests (TUG), with and without cognitive task (TUG), were performed to assess dual-task performance. Dual-task cost (DTC) was calculated. Cognitive information processing speed, visuospatial memory, and verbal memory were assessed using a Brief International Cognitive Assessment for MS (BICAMS).

Results: The DTC was 11.8%. The TUG-cog tests were moderately correlated with all subtests of BICAMS (r=-0.322 to -0.440). However, DTC has a significant but small correlation with cognitive tests (r=0.227-0.254). Disability level was the significant predictor of dual-task performance.

Conclusion: Our findings confirm that higher dual-task performance is significantly associated with better cognitive processing speed, visuospatial memory, and verbal memory in pwMS. This result may facilitate the use of dual-tasking paradigms in studies on cognitive impairment screening methods. However, such research undertakings should be supported by longitudinal studies.

Keywords: Multiple sclerosis, cognition, dual-task, cognitive-motor interference, walking

Introduction

Multiple sclerosis (MS) is a neurodegenerative condition of the central nervous system, mainly characterized by walking and cognitive impairment that begin in the early stages of the disease (1). Traditionally, these symptoms are evaluated and treated separately. However, when persons with MS (pwMS) are subjected to simultaneous evaluation for motor and cognitive performance, they often experience worsening in one or both tasks (2,3). This deterioration has been termed cognitive-motor interference (CMI), which can be quantified by calculating the percentage change between single-task and dual-task performance (4,5).

In recent years, there has been increasing interest in the clinical characteristics of CMI, its neural correlates and associated factors in pwMS, given that it has been considered a marker of daily life impairment. Although some neuroimaging studies suggest that there is increased activation in the prefrontal cortex and premotor cortex during dual tasking in pwMS, findings on whether pwMS have higher CMI than age-matched healthy controls are inconsistent (6-8). This may be due to the fact that varied dual-task paradigms have been used in studies or different baseline conditions of patients associated with diseases. Recently, Rooney et al. (9) summarized the findings in the literature on related clinical factors of dual-task in pwMS. They found that there were few studies on the relationship between dual-task and cognition, and that of these limited studies, majority focused on the correlation between processing speed and dual-task performance. Furthermore, the results arrived at in the studies were inconsistent (9).

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Received: 30.07.2022 **Accepted:** 18.09.2022

In this study, we aimed to investigate the association between cognitive-motor dual-task performance, cognitive functions and falls in pwMS using a larger sample than in the studies found in the literature. In addition, we aimed to explore the relationship between different domains of cognitive functions using an extensive cognitive battery.

Materials and Methods

The Dokuz Eylul University Ethics Board approved the study protocol (approval number: 2016/27-08, date: 20.10.2016). All participants provided their written consent after being fully informed.

Participants

The data were secondary outcomes of our previously published study (10). The inclusion criteria were diagnosis of MS according to the 2017 McDonald criteria (11), Expanded Disability Status Scale (EDSS) range was between 0 and 6.5, and age was between 18 and 65 years. Exclusion criteria were the following: relapse occurring within 30 days, neurological disease diagnosis other than MS, and severe cognitive impairment according to clinician judgments as to hindered understanding of test instructions.

Outcome Measures

Primary Outcome Measures

Dual-task Performance

The Timed Up and Go (TUG) test was performed with and without a cognitive task. The subject was instructed to stand up, walk three meters to a particular spot on the ground, turn around, and go back to the chair and sit (12). The activity, timed using a stopwatch, was ended when the participant was already sitting in the chair, with the total duration was noted. Each participant underwent the TUG test in the same standardized order, and they were instructed to use their regular mobility device and walk quickly but as safely as possible. Secondly, participants performed another TUG, this time with a cognitive task (i.e., TUG-cog). The cognitive task was serial subtraction by threes from a given starting number (between 20 and 100). Participants were instructed to execute both tasks at their best without prioritization. We reported single-task performance (TUG), absolute dual-task performance (TUG-cog), and dual-task cost (DTC). DTC was calculated by this formula:

DTC (%)=[(single-task performance - dual-task performance)/(single-task performance)]x100

The larger the minus value of the DTC, the higher is the DTC, meaning, worse dual-task performance.

Cognitive Functions

The Turkish version of the Brief International Cognitive Assessment for MS (BICAMS) was administered to measure cognitive functions. It includes three subtests: the oral version of the Symbol Digit Modalities Test (SDMT) that measures cognitive processing speed and sustained attention; the Brief Visuospatial Memory Test-Revised (BVMT-R) that assesses visuospatial memory; and the California Verbal Learning Test (CVLT-II) that assesses verbal memory (13).

Secondary Outcome Measures

Demographic and clinical information such as age, sex, disease duration, course of the disease and neurological disability level rated by EDSS were noted.

Timed-25 Foot Walking (T25FW) was used to assess gait speed on 7.62 m pathway (14). The perceived walking performance was evaluated using the 12-item MS Walking Scale (MSWS-12) (15).

Statistical Analysis

In order to analyze the data, IBM SPSS Statistics for Windows was used (Version 25.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test and evaluation of the histogram and plots were utilized to determine the distribution of the data. The use of descriptive statistics yielded median and interquartile ranges since data did not show normal distribution. Spearman's rank correlation was calculated to determine the association between absolute dual-task performance, DTC and cognitive functions, and falls. Correlation coefficients between 0.1 and 0.29 were considered to be small, 0.3-0.49 to be moderate, and 0.5-1.0 to be strong (16). Hierarchical binary regression models were conducted to explain the relationship between cognitive functions and dual-task performance.

Results

Study Participants

In total, data from 156 subjects were analyzed in this study. The median EDSS score was 1.5. For majority of the subjects, the course of the disease was relapsing-remitting. The baseline demographics, clinical characteristics, and descriptives of outcome measures of participants are summarized in Table 1.

When the TUG was applied with the cognitive task, the duration increased from 6.78 to 7.69. The median DTC was 11.82%.

Correlations of Dual-task Performance with Cognitive Functions

Based on Spearman correlation analysis, absolute dual-task performance (i.e., TUG-cog) moderately correlated with all subtests of BICAMS (r=-0.322 to -0.440). However, DTC has a significant but small correlation with cognitive tests (r=0.227-0.254). Age and EDSS were strongly correlated with both TUG and TUG-cog. Age was weakly correlated with DTC but EDSS was found not to be correlated with DTC. Correlation coefficients are shown in Table 2.

Regression Analysis

Table 3 presents the hierarchical binary regression models to show the impact of age, disability level, and cognitive functions on absolute dual-task performance and DTC. In step 1, age and EDSS were entered, showing EDSS (β=0.58) to be significantly correlated with the TUG-cog (R2 =0.41). Step 2 included cognitive test outcomes in addition to age and EDSS, which yielded EDSS as the only variable significantly correlating with the TUG-cog that, in turn, explained 43% of the variance. The addition of cognitive tests explained an additional 2% of variance over age and disability level assessed by EDSS. For the DTC, no variable was found significant based on step 1 and step 2.

Table 1. Demographic and clinical characteristics of the participants

	Total (n=156)
Age (years)	35 (28.0-44.0)
Gender, n (%)	
Female	114 (73.1%)
Male	42 (26.9%)
EDSS (0-10)	1.5 (0-2.0)
Disease duration (years)	2 (2.0-11.37)
Clinical course of MS, n (%)	
Relapsing-remitting	144 (92.3%)
Secondary-progressive	9 (5.8%)
Primary-progressive	3 (1.9%)
TUG	6.78 (6.15-8.41)
TUG-cog	7.69 (6.64-10.55)
DTC	-11.82 [(-23.61)-(-4.74)]
T25FW	4.75 (4.34-5.65)
MSWS-12	17.0 (12.0-29.0)
SDMT	49.0 (41.0-56.0)
CVLT-II	53.0 (42.0-61.0)
BVMT-R	28.0 (22.0-31.0)

EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis, TUG: Timed Up and Go test, TUG-cog: TUG cognitive, DTC: Dual-task cost, T25FW: Timed 25 Foot Walk, MSWS-12: Multiple Sclerosis Walking Scale-12, SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-Second Edition, BVMT-R: Brief visuospatial memory test-revised

Discussion

This study aimed to investigate the relationship between cognitive functions and dual-task walking performance in pwMS. Our findings suggest that (i) pwMS showed significant CMI (DTC: -11.8%); (ii) there was a statistically significant correlation between cognitive tests and dual-task performance; and (iii) disability level assessed by EDSS was the only significant determinant factor on absolute dual-task performance in pwMS.

Previous studies that investigated the relationship between dual-task performance and cognitive functions the mechanism underlying CMI in pwMS (9,17). Our study found that absolute dual-task performance was moderately correlated, while motor DTC was insignificantly correlated, with cognitive functions. Our results are consistent with the findings of Prosperini et al. (18) who assessed dual-task performance during static postural control task with Stroop task. Prosperini et al. (18) also found a higher correlation between SDMT and absolute dual-task performance than DTC (r=-0.481 and -0.242, respectively). In another study, Motl et al. (19) did not find a correlation with all parameters of gait but they found a significant correlation between SDMT and DTC of speed (r=-0.32). In their study, verbal fluency task was applied during a short walking distance test (19). Recently, Veldkamp et al. (20) assessed the relationship between cognition and dual-task performance with different cognitive and motor task combinations. They observed that SDMT was a factor associated with dual-task performance in less challenging walking conditions (20). Some studies do not support findings of a significant relationship between SDMT and dual-task performance, though (21,22). However, none of these studies employed a motor test containing functional mobility tasks (i.e., TUG) as we used in this study. Despite the methodological heterogeneity in the literature, the association of better processing speed with higher dual-task performance is increasingly supported by investigations on the relationship between dual-task performance and cognitive functioning. However, further studies are needed to confirm these findings.

Our findings show significant association between disability level and absolute dual-task performance but not DTC. In the systematic review of Rooney et al. (9), no correlation between

Table 2. Correlation coefficients between variables

	TUG	TUG-cog	DTC
SDMT	-0.407**	-0.440**	0.254*
CVLT-II	-0.266*	-0.322**	0.233*
BVMT-R	-0.337**	-0.343**	0.227*
Age	0.533**	0.529**	-0.194*
EDSS	0.603**	0.535**	-0.057

*p<0.05, **p<0.001

TUG: Timed Up and Go test, DTC: Dual-task cost, SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-Second Edition, BVMT-R: Brief visuospatial memory test-revised, EDSS: Expanded Disability Status Scale, TUG-cog: TUG cognitive

Table 3. Regression analysis

		B	SEB	β	R^2	ΔR^2	p
Absolute dual-task performance (TUG-cog)	Step 1				0.41	0.41	0.794
	Age	0.12	0.08	0.12			
	EDSS	3.77	0.48	0.58*			
	Step 2				0.43	0.02	0.083
	Age	0.08	0.08	0.08			
	EDSS	3.64	0.50	0.56*			
	SDMT	-0.12	0.08	-0.12			
	CVLT-II	-0.06	0.08	-0.07			
	BVMT-R	0.06	0.14	0.04			
DTC	Step 1				0.001	0.001	0.386
	Age	-0.19	0.61	-0.03			
	EDSS	0.83	3.79	0.02			
	Step 2				0.043	0.042	0.207
	Age	0.04	0.64	0.006			
	EDSS	-0.10	3.94	-0.003			
	SDMT	0.49	0.65	0.09			
	CVLT-II	1.09	0.59	0.19			
	BVMT-R	-1.89	1.13	-0.18			

*p<0.05, TUG: Timed Up and Go test, DTC: Dual-task cost, SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-Second Edition, BVMT-R: Brief visuospatial memory test-revised, EDSS: Expanded Disability Status Scale, TUG-cog: TUG cognitive

DTC and EDSS was found in most of the studies. However, due to the methodological heterogeneity of the studies, no firm conclusions could be drawn about the relationship between disability level and dual-task performance in pwMS. Nonetheless, some studies show that a higher disability level is associated with lower dual-task performance (19,23) but such findings should be confirmed by future studies involving participants having different disability levels and the use of different motor-cognitive tasks.

We found a correlation between dual-task performance in different domains of cognition with similar magnitude. To the best of our knowledge, there is no other study that examined this relationship using the BICAMS battery, which is valid for pwMS and includes different cognitive domains. This study showed that in addition to cognitive processing speed, verbal memory and visuospatial memory are also associated with dual-task performance in pwMS.

Study Limitations

Although our study includes a relatively larger sample size compared to studies found in the literature, some limitations should be noted. Firstly, we mostly included patients with mild disability, which affects the generalizability of our results to persons with moderate and severe disability. Secondly, we evaluated dual-task performance using the TUG test with a cognitive task. Although the evaluation is reflective of daily life functionality as it includes many activities that are undertaken in everyday living, such as sitting, walking, and turning, the limitation is that it is a short-term test. Additionally, there is no test-retest reliability study on TUG with the cognitive task in pwMS. Furthermore, since its reliability is low, we did not assess cognitive DTC. Lastly, we also did not assess gait parameters by instrumented gait analysis methods. In future studies, we recommend measuring the dual-task performance during different TUG tasks with the use of wearable sensors.

Conclusion

Our results confirm that higher dual-task performance is significantly associated with better cognitive processing speed, visuospatial memory, and verbal memory in pwMS. This finding may facilitate the use of dual-tasking paradigms in research on cognitive impairment screening methods. However, such investigations should be supported by longitudinal studies.

Ethics

Ethics Committee Approval: The Dokuz Eylul University Ethics Board approved the study protocol (approval number: 2016/27-08, date: 20.10.2016).

Informed Consent: All participants provided their written consent after being fully informed.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., Concept: Z.A., P.Y., H.K., S.O., Design: Z.A., P.Y., H.K., S.O., Data Collection or Processing: Z.A., P.Y., H.K., S.O., Analysis or Interpretation: Z.A., P.Y., H.K., S.O., Literature Search: Z.A., P.Y., H.K., S.O., Writing: Z.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/jmsr.galenos.2022.2022-7-4
Journal of Multiple Sclerosis Research 2022;2(3):62-67

RESEARCH ARTICLE

Determining the Prognostic Characteristics of People with Multiple Sclerosis with Bowel and Bladder Dysfunction as the Initial Presentation: A Cohort Study

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Abstract

Objective: This study's first aim is to assess the prognostic characteristics of people with multiple sclerosis (pwMS) who initially had bowel-bladder dysfunction and to present their relationship with the transition to secondary progressive MS (SPMS). The second aim of the study is to show the frequency of relapses that affect bowel-bladder functions as one of the first reasons for hospital admission among pwMS. The third aim is to present the frequency of relapses affecting bowel-bladder functions in pwMS throughout the disease process.

Materials and Methods: Study data of this retrospective cohort study were obtained from longitudinal follow-up data of pwMS who were followed up since 1996 in an Dokuz Eylul University Hospital MS Unit. A total of 3448 pwMS were assessed for eligibility, and those who met the eligibility criteria were included in the study. Included pwMS were assessed for relapse affecting bowel and bladder functions and transition from the Relapsing-Remitting MS (RRMS) course to the SPMS course.

Results: A total of 459 (13.3%) pwMS experienced at least one relapse affecting their bowel-bladder functions at any point in their disease process, and these bowel-bladder functions were affected in 129 of 3,448 (3.7%) patients during their first relapse. Affected bowel and bladder functions during the first relapse were ineffective in predicting the transition to the SPMS course ($p>0.05$). The initial Expanded Disability Status Scale score ($p=0.001$), age of disease onset ($p<0.001$), age at the start of progression ($p=0.035$), and spinal cord involvement in the functional systems affected at first admission ($p=0.013$) effectively predicted the transition to the SPMS course.

Conclusion: Bowel and bladder dysfunction is a common but poorly-addressed clinical presentation. It is observed even at the onset of the disease. Although the affected bowel and bladder function at first relapse is not effective in predicting the transition from the RRMS course to the SPMS course, the onset of the disease at a young age, severe disability at the beginning, and the spinal origin of the first symptom are promising predictors. Bowel and bladder dysfunction and factors predicting the transition to the SPMS course should be addressed in many ways.

Keywords: Multiple sclerosis, bowel, bladder, relapse, prognostic, progression

Introduction

Multiple sclerosis (MS) is a chronic, neurodegenerative disease characterized by its autoimmune origin and transected inflammatory demyelination affecting the central nervous system (CNS) (1). Around 2.8 million people worldwide and 58,401 people in our country live with MS (2,3). Although the exact cause of MS is still unknown, it is thought that various genetic, environmental, and immunological factors play a role in the etiology of this complex disease (4).

The clinical course of MS is defined under three main headings: clinically isolated syndrome (CIS), relapsing MS, and progressive MS (5). CIS is the first neurological picture in which inflammation and demyelination are observed in the CNS. CIS is used to describe the first clinical event of acute or subacute onset, which peaks quickly, in which a patient has symptoms and signs

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Received: 08.08.2022 **Accepted:** 02.12.2022

suggestive of an inflammatory demyelinating disorder of the CNS (6). Relapsing-Remitting MS (RRMS) is the most common course of MS. It progresses with recurrent relapses of varying severity and frequency (relapse, exacerbation), followed by a period of complete or nearly-complete recovery (remission) (5). Studies have shown that most untreated RRMS patients eventually progress to secondary progressive MS (SPMS) (7). It has been reported that 62% of RRMS patients switch to the SPMS course by the age of 75 years (8). SPMS is a course of MS in which exacerbations are seen in addition to progressive clinical worsening (5). The mean age of onset of progression has been reported as 45 years (8). Advancing age and the longer duration of MS are the most important risk factors for progressive disease. Other clinical risk factors for the early onset of SPMS include incomplete recovery from the first MS relapse, multifocal clinical manifestations of relapses, and the presence of brainstem and/or infratentorial lesions (9). Oh et al. (7) identified early symptom recognition as a key step in the transition from the RRMS course to the SPMS course.

Among the most important signs and symptoms of MS are fatigue, impaired balance and decreased mobility, neuropathic pain, bowel and bladder dysfunction, cognitive impairment, and mood disorders (4). Bowel and bladder dysfunctions are common in MS, affecting the bowel in 39-73% of the population and urinary function in more than 80% of the population (10,11).

Nortvedt et al. (12) reported that bowel and bladder involvement is present at an early stage of MS (within 2-5 years after diagnosis). Given that these symptoms worsen with disease progression in MS and those treatments and preventive strategies are available, they recommended focusing on these aspects of MS in patient interviews from the early stages of the disease (12).

This study has three aims; the first is to assess the prognostic characteristic of people with MS (pwMS) who initially had bowel-bladder dysfunction and to present their relationship with the transition from the RRMS course to the SPMS course. The second aim of this study is to determine the frequency of relapses that affect bowel-bladder functions as one of the first reasons for admission among pwMS. The third aim of this study is to determine the frequency of relapses affecting bowel-bladder functions among pwMS throughout the disease process.

Materials and Methods

Study Design

This is a retrospective cohort study. Ethical approval was obtained from the Non-Invasive Clinical Research Ethics Board of Dokuz Eylul University (decision no: 2022/31-04, date: 28.09.2022). The strengthening the reporting of observational studies in epidemiology statement was followed for this retrospective cohort study (13).

Participants and Procedures

Data collection was done in July 2022. Study data were obtained from longitudinal follow-up data of pwMS since 1996 in the MS Unit of the Dokuz Eylul University Hospital Neurology Department. A total of 3,448 pwMS followed in our MS unit were assessed for eligibility, and those who met the eligibility criteria were included in the study. Inclusion criteria were: (i) being over the age of 18 years, (ii) being definitively diagnosed with MS per the Poser or the McDonald diagnostic criteria (14-18). We excluded pwMS with missing data from the study. For the first aim, the whole cohort was screened, and people with the SPMS course were included in the study. For the second and third aims, the whole cohort was screened for relapse affecting bowel and bladder functions, and those identified were included. The first relapse was defined as an episode of worsening reported at disease onset, lasting at least 24 hours, and presenting with one or more clinical signs in the absence of fever or infection, without any clinical features of encephalopathy. A standardized form was applied for data records.

Outcome Measures

Demographic and Clinical Measurement

Age, sex, MS course, disease duration, first and last Expanded Disability Status Scale (EDSS) (19) scores, first MS treatments, age at the start of disease progression, age at the onset of the disease, disease duration from the RRMS course to the SPSS course, functional systems affected at first admission (by the first clinical event), functional systems involved during the first relapse, and medical history were obtained from the related medical records.

EDSS

It is the most commonly used scale to assess the disability of pwMS, and it was developed by Kurtzke (19,20). Scoring based on neurological examination findings takes a value between 0-10. Normal neurological findings are represented by 0 and death due to MS is represented by 10. In this scale, in which pyramidal, cerebral, cerebellar, visual, sensory, brainstem, bladder, and bowel functions are scored, the best performance is evaluated without the patient making any special effort. Scores of 1-4.5 indicate full ambulation, scores of 5-6.5 indicate ambulation with assistance, and scores ≥7 indicate the need for a wheelchair for mobilization. EDSS scoring of the patients was done by a specialist neurologist.

Statistical Analysis

The Kolmogorov-Smirnov test and histograms were used to assess the normal distribution of data. Descriptive analyses were presented using the mean and standard deviation for

continuous variables and frequencies and percentages for categorical variables. Linear logistic regression models were structured to understand the factors affecting the duration transition from the RRMS course to the SPMS course. The first and last EDSS scores, age at the start of disease progression, age at the onset of the disease, sex, functional systems affected at first admission, relapse involving bowel and bladder functions during the first admission, and first MS treatment were included in the model. The threshold for statistical significance was set at $p<0.05$. Data were analyzed using IBM SPSS (Version 25.0. Armonk, NY: IBM Corp).

Results

In this study, 3,448 pwMS followed up at the MS Unit of Dokuz Eylul University were screened in terms of having the SPMS course and having a relapse that affects their bowel-bladder functions. It was determined that 459 (13.3%) pwMS experienced at least one relapse involving their bowel-bladder functions at any point in their disease course and that bowel-bladder functions were affected in 129 (3.7%) of these people during their first relapse. As a result of the screening, it was determined that 358 pwMS had the SPMS course, and 17 of these individuals had their bowel-bladder function affected during their first relapse. Twelve participants were excluded due to missing data and could not be included in the analysis. (Figure 1). Demographic and clinical characteristics of pwMS included in the study are presented in Table 1.

The linear logistic regression model is presented in Table 2. The first EDSS score and the age at the onset of the disease were found to have a negative correlation with the duration of the transition from the RRMS course to the SPMS course (respectively, $p=0.001$; $p<0.001$). Moreover, while the increase in the age at the start of disease progression increases the duration of the transition from the RRMS course to the SPMS course ($p=0.035$), spinal cord involvement among the functional systems affected during the first admission decreases this duration ($p=0.013$).

Discussion

The predictors of SPMS remain uncertain and heterogeneous. In addition, there are no clear clinical, imaging, immunological, or pathological criteria to define the transition to the SPMS course (5). Although the risk of conversion to SPMS is challenging to determine, older age, longer disease duration, and cumulative CNS lesions are the most significant clinical risk factors (9). Information on potential biomarkers of progression is promising but limited (21). The detection of transition to the SPMS course is a complex and challenging process for patients, caregivers, and healthcare professionals, and its detection is important for clinical care (7). Determining the predictors of the transition to the SPMS course is crucial. Therefore, this study aimed to evaluate the prognostic features of pwMS who initially had bowel and bladder dysfunction and their relationship with the transition to the SPMS course. We identified the young age of disease onset,

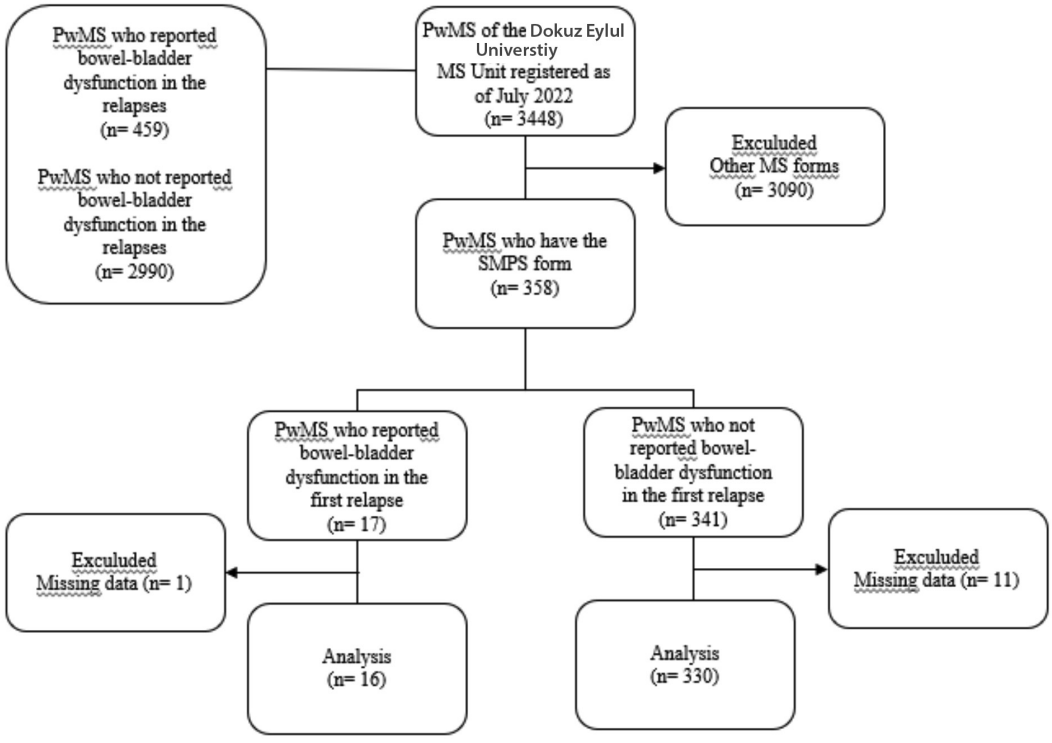

Figure 1. Flow chart

MS: Multiple sclerosis, PwMS: People with MS

severe disability at the beginning, and the spinal origin of the first symptom as effective predictors of the transition time from the RRMS course to the SPMS course. However, sex, first MS treatment, and bowel and bladder function involved in the first relapse were ineffective predictors. The other aims of this study were to demonstrate that the frequency of relapses affecting bowel and bladder function throughout the disease process was one of the first reasons for referral among pwMS. Relapse involving bowel and bladder functions was identified as one of the first reasons for admission in 3.7% of pwMS and at any time point in 13.3% of pwMS.

Bowel (39-73%) and bladder (>80%) functions are frequently affected in pwMS (10,11). However, in this study, we found that bowel and bladder functions were involved in the first relapse (3.7%) or subsequent relapses (13.3%) of a small number of patients. The low frequency of relapses affecting bowel and bladder functions suggests that dysfunctions in these systems occur due to progression and was independent of relapses. Although the first relapse involving bowel and bladder functions fails to predict the transition to the SPMS course, the involvement in these functions may suggest the transition to the SPMS course. This should be taken into account in the clinic. Future studies focused on this point will illuminate the situation.

Similar to our results, it has been reported in the literature that the onset of the disease at a young age and the presence of an initial severe disability may increase the risk of developing the SPMS course. It has been stated that this can be explained by the fact that the inflammation or CNS destruction accumulated in the early period may lead to an irreversible point when it reaches a certain level (9).

Disease-modifying drugs (DMDs) used in MS are associated with a slight delay in conversion to SPMS by preventing the additional disability burden due to relapses; however, they do not seem very effective in delaying the transition to SPMS course (8,9). Similarly, in this study, we found that any DMD used

Table 1. Demographic and clinical characteristics of pwMS (n=346)

Variables	mean (SD)/n (%)
First EDSS score	4.9 (1.9)
Last EDSS score	6.3 (1.2)
Age of start of progression	42.7 (10.6)
Disease onset age	30.3 (9.9)
Transition time to SPMS	14.7 (49)
Sex	
Female	225 (65%)
Male	121 (35%)
Functional systems affected at first admission-supratentorial	
Yes	99 (28.6%)
Functional systems affected at first admission-optic pathways	
Yes	71 (20.5%)
Functional systems affected at first admission-brainstem and cerebellum	
Yes	124 (35.8%)
No	
Functional systems affected at first admission-spinal cord	
Yes	139 (40.2%)
Relapse affecting bowel and bladder functions in the first admission	
Yes	16 (4.6%)
First MS treatment	
None	69 (19.9%)
First line treatments	277 (80.1%)

EDSS: Expanded Disability Status Scale, SD: Standard deviation, SPMS: Secondary progressive multiple sclerosis, pwMS: People with MS

Table 2. Risk factors on the duration transition from the RRMS course to the SPMS course

Risk factors	OR	95% CI	p-value
First EDSS score	-3.215	(-1.086)-(-0.262)	**0.001**
Last EDSS score	0.293	-0.598-0.807	0.770
Age of start of progression	2.119	0.001-0.032	**0.035**
Disease onset age	-5.478	(-0.294)-(-0.139)	**<0.001**
Sex			
Female (references)			
Male	-0.927	-2.352-0.845	0.355
Functional systems affected at first admission-supratentorial			
Yes (references)			
No	1.129	-0.777-2.870	0.260
Functional systems affected at first admission-optic pathways			
Yes (references)			
No	0.560	-1.522-2.732	0.576
Functional systems affected at first admission-brainstem and cerebellum			
Yes (references)			
No	1.714	-0.230-3.344	0.088
Functional systems affected at first admission-spinal cord			
Yes (references)			
No	2.498	0.521-4.381	**0.013**
Relapse affecting bowel and bladder functions in the first admission			
Yes (references)			
No	-0.310	-4.292-3.125	0.757
First MS treatment			
None (references)			
First line treatments	0.412	-1.524-2.330	0.681

Significant p-values are presented in bold.

EDSS: Expanded Disability Status Scale, CI: Confidence interval, OR: Odds ratio

at the onset of the disease did not affect the transition time to the SPMS course. In addition, we found that the male sex was not an additional risk factor for the transition to the SPMS course, a finding that aligns with those of Tutuncu et al. (8).

Sexual dysfunction is also a common and very stressful problem in MS. The prevalence of sexual dysfunction among pwMS is higher than that in the general population and among people with other neurological diseases (22,23). In addition, Nortvedt et al. (12) reported that sexual dysfunction, such as bladder and bowel dysfunction, was present within 2-5 years after the diagnosis of MS. Drulovic et al. (24) emphasized that although the importance of sexual function problems is known, it has not been adequately addressed, and more focus should be placed on this aspect of the disease during follow-up. Since bowel and bladder function is a component of EDSS and their bowel and bladder dysfunctions are recorded in the relapse, they are relatively easier symptoms to follow up than sexual dysfunction. We found that we could not adequately address sexual dysfunction during our study period. We recommend that sexual dysfunction be handled in detail and followed up in clinical practice from the moment of the initial diagnosis. This issue could be investigated in future studies.

Study Limitations

Our study has some strengths and limitations. The main strength of this study is that it is a cohort study. Data were obtained from the longitudinal follow-up of a large cohort of patients. In addition, these data were collected in a standardized single center. The major limitation of this study is that a few patients could not be included in the study due to missing data. Another rule is that current bowel and bladder function conditions are not presented. Considering these limitations, we think that studies on this topic that consider different functions, such as sexual function, will contribute significantly to the literature in the future.

Conclusion

We found that the onset of the disease at a young age, severe disability at the beginning, and the spinal origin of the first symptom were effective determinants of the transition time from the RRMS course to the SPMS course. However, sex, initial MS treatment, and affected bowel and bladder functions at the first relapse were ineffective predictors of the transition to the SPMS course. Bowel and bladder dysfunction is a common condition that is often overlooked but is also indicated at the onset of the disease.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Invasive Clinical Research Ethics Board of Dokuz Eylul University (decision no: 2022/31-04, date: 28.09.2022).

Informed Consent: This is a retrospective cohort study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: I.Y., Design: I.Y., A.T.O., Data Collection or Processing: I.Y., E.K., A.T.O., Analysis or Interpretation: I.Y., A.T.O., Literature Search: I.Y., E.K., Writing: I.Y., A.T.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/jmsr.galenos.2022.2022-11-1
Journal of Multiple Sclerosis Research 2022;2(3):68-73

RESEARCH ARTICLE

Determination of the Factors Related to Neuropsychological Competence in People with Multiple Sclerosis

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Abstract

Objective: Cognitive impairment occurs in 34-65% of persons with multiple sclerosis (pwMS). MS Neuropsychological Screening Questionnaire (MSNQ) is a self-report scale that measures neuropsychological competence and has the power to detect cognitive impairment. However, there are many other objective tests that can measure cognitive impairment. The aim of this study is to examine the relationship between neuropsychological competence and anxiety, depression, cognitive functions, fatigue, quality of life, disease duration and disability level in pwMS.

Materials and Methods: Six hundred and forty-eight pwMS (n=479 female) were enrolled in this study. PwMS with a score of 23 and above on the MSNQ were considered positive for neuropsychological competence impairment test, while pwMS with a score below 23 in MSNQ were considered negative. Disability was assessed using the Expanded Disability Status Scale (EDSS), quality of life with EuroQol 5-Dimensions (EQ-5-D), cognitive functions with the Brief International Cognitive Assessment in Multiple Sclerosis, fatigue with the brief Modified Fatigue Impact Scale, and anxiety and depression levels with The Hospital Anxiety and Depression Scale.

Results: Positive MSNQ was detected in 264 (41%) pwMS, which means worse neuropsychological competence. A statistically significant difference was found between pwMS with positive MSNQ and pwMS with negative MSNQ in terms of age, education, gender, EDSS, fatigue, quality of life, anxiety and depression levels, and cognitive functions. While increasing anxiety level was considered a risk factor for positive MSNQ, each additional increase in the usual activities subscore of the EQ-5D was found to be related to the decrease in the odds of having positive MSNQ.

Conclusion: In this study, it was found that pwMS with positive MSNQ had worse cognitive functions, had higher fatigue levels, were unemployed, and had higher levels of depression and anxiety. Also, the dependence and anxiety level of the pwMS should be considered during cognitive rehabilitation.

Keywords: Depression, multiple sclerosis, neuropsychological competence, quality of life

Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (CNS), affecting more than 2 million people worldwide (1). The condition is characterized by effects on the brain and the spinal cord. Since MS can affect any part of the CNS, its symptoms may be associated with motor, gait, sensory, visual, bowel/bladder, and/or cognitive impairments. However, cognitive impairment is more insidious and can be destructive if not assessed (2). Cognitive impairment could range from 34% to 65%, depending on the research design in people with MS (pwMS) (3). Cognitive impairment leads to problems such as vocational disability and deterioration in the quality of life (4). Early diagnosis and follow-up on cognitive impairments in MS are also important in helping patients' psychosocial adjustment. Neuropsychological tests were developed to identify neuropsychological disorders and their severity. These tests are also used to assess decline in neuropsychological competence, which is defined as the efficacy of brain functioning after brain injury.

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Received: 05.12.2022 **Accepted:** 22.12.2022

Neuropsychological testing can be used to monitor patients during treatment (5). The availability of neuropsychological tests has increased significantly over the past decade. Cognitive impairment is measured in pwMS based on a broad range of tests. However, these measurement methods can take time. For this reason, the MS Neuropsychological Screening Questionnaire (MSNQ) has been recommended as a rapid screening test for neuropsychological evaluation (4,6). A score of 23 and above on pwMS is considered positive for this test, an indication of impaired neuropsychological function, while a pwMS score of below 23 indicates negative results (4). With 23 as the cut-off value in pwMS for the MSNQ, 74% of patients were correctly classified as affected compared to the healthy population.

To improve patients' functionality and quality of life in daily and vocational life, it is important not only to determine their neuropsychological competence, but also to determine the factors associated with the neuropsychological competence. Therefore, this study aims to examine the relationship between neuropsychological competence and anxiety, depression, cognitive functions, fatigue, quality of life, disease duration, and disability level in pwMS.

Materials and Methods

Study Design

This cross-sectional study was conducted at the MS Clinic of Dokuz Eylul University, Izmir, Turkey. This study was approved by the Non-Invasive Research Ethics Board of Dokuz Eylul University (protocol number: 7368-GOA and approval number 2022/39-04). All participants were required to complete the informed consent form.

Participants

Participants with a confirmed diagnosis of MS according to 2017 McDonald criteria and aged between 18 and 65 were included in the study. Patients having neurological disorders other than MS and those with cognitive impairments that made them unable to engage in tests and/or complete questionnaires were excluded.

Outcome Measures

Demographic (gender, age, education level, marital status) and clinical data (disease course, disease duration) of pwMS were obtained by interviewing and based on medical records.

The Kurtzke Expanded Disability Status Scale (EDSS) is used widely to evaluate disability levels in pwMS (7). It consists of seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, mental) and the ambulatory system (8). Based on the patient's neurologic examination, each of these functional systems is scored between 0 and 10. 0 indicates routine neurological examination, and 10 indicates MS-related death.

MSNQ-Patient Version (MSNQ-P) is a self-report scale consisting of 15 questions reflecting neuropsychological competence in the performance of activities of daily living. Responses are scored between 0 and 4 (5). A maximum of 60 points can be obtained from this scale, and higher scores mean deteriorated neuropsychological competence. MSNQ scores were considered positive if self-report scores were greater than 23 (9).

The Hospital Anxiety and Depression Scale (HAD) was developed by Zigmond and Snaith (10) in 1983 to assess clinical anxiety and depression. This scale has also been shown to be a valid measure of the severity of mood disorders. It consists of 14 questions, seven of which measure anxiety while the other seven measure depression (10). The Turkish version of the scale was validated (11).

EuroQol 5-Dimensions (EQ-5D) developed by the European Quality of Life Group to measure health-related quality of life. The EQ-5D scale consists of five sub-dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (12).

The brief MFIS is a fatigue scale frequently used in clinical and experimental studies (13). The scale consists of a total of 5 questions aimed at evaluating the cognitive, physical and psychosocial aspect of the perceived fatigue. Each item is scored between 0 and 4, and a low score indicates a low degree of fatigue (14).

The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) is a time-consuming measurement method developed for cognitive assessment in MS that does not require special evaluator training or equipment. BICAMS consists of Symbol Digit Modalities Test, California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Tests (BVMT) (15). The validation study on Turkish pwMS was performed by Ozakbas et al. (16).

Sample Size

In a study examining the relationship between factors such as depression, pain, age, gender, disability level, and neuropsychological competence, the adjusted R-square value of the regression model was reported to be 0.13 (17). With these data, the effect size of the model in the study was calculated to be 0.15. In this context, the smallest sample size for the study was calculated as 107 with effect size =0.15, power =95%, while the error probability was determined to be 0.05 using G*Power (version 3.1) software.

Statistical Analysis

The normal data distribution was checked using the Kolmogorov-Smirnov test and histograms. Descriptive analyses were presented namely, the median and interquartile range for continuous variables and percentages for categorical variables.

The difference between pwMS with positive MSNQ and pwMS with negative MSNQ was measured by the Mann-Whitney U test. Binary logistic regression was used to determine the related factors with positive MSNQ. Statistical significance was set at $p<0.05$. Data were analyzed using IBM SPSS Statistics software (Version 25.0. Armonk, NY: IBM Corp.).

Results

Six hundred and forty-eight pwMS (n=479 female) were enrolled in this study. Positive MSNQ was detected in 264 (41%) pwMS. PwMS with positive MSNQ were older in age and had higher disability levels compared with pwMS with negative MSNQ. Between-group differences were also observed to be influenced by gender, education level, employment status, and marital status. The demographic and clinical differences between pwMS with positive MSNQ and pwMS with negative MSNQ are given in Table 1.

Table 2 shows differences between pwMS with positive MSNQ and pwMS with negative MSNQ in terms of EQ-5D subscales, MFIS subscales, BICAMS subscales, and HAD anxiety and depression subscales. There was a statistically significant difference between these two groups across all the variables. PwMS with positive MSNQ has worse cognitive performance and quality of life and higher fatigue, anxiety, and depression score than pwMS with negative MSNQ.

Table 3 presents the results of the binary logistic regression models to determine the contribution of fatigue, quality of life, depression and anxiety, and cognitive function on affected neuropsychological competence in pwMS. From binary logistic regression, increasing anxiety level was found to be a risk factor for positive MSNQ. However, each additional increase in the usual activities subscore of the EQ-5D is related to a decrease in the odds of having positive MSNQ.

Discussion

The primary finding of this study is that neuropsychological competence could be related to anxiety level and the usual activities subscore of the quality of life. Moreover, except for disease course and duration, all variables were found to be different between groups. PwMS with positive MSNQ have a worse score in patient-reported outcomes, worse cognitive functions, and a higher disability level than pwMS with negative MSNQ.

Table 1. Demographic and clinical characteristics of the participants

		pwMS with positive MSNQ (n=264)	pwMS with negative MSNQ (n=384)	p-value
Age (years) median (IR)		36.00 (30.0; 45.0)	34.00 (27.0; 42.0)	0.002*
Gender (n, %)	**Female**	208, 78.8%	271, 70.6%	0.019*
	Male	56, %21.2	113, 29.4%	
Disease duration (years) median (IR)		5.68 (1.82; 11.40)	4.84 (1.02; 10.13)	0.055
Disease course (n, %)	**Relapsing-remitting MS**	260, 98.5%	379, 98.7%	0.667
	Secondary progressive MS	3, 1.1%	5, 1.3%	
	Primary progressive MS	1, 0.4%	0, 0.0%	
EDSS median (IR) (range between 0-10)		1.50 (0.0; 2.0)	1.0 (0.0; 1.50)	<0.001*
Education level (n, %)	**Elementary school**	72, 27.3%	63, 16.4%	0.001*
	High school	82, 31.1%	117, 30.5%	
	University	107, 40.5%	204, 53.1%	
Employment status (n, %)	**Employment**	108, 41.2%	200, 52.2%	0.003*
	Unemployment	115, 43.9%	118, 30.8%	
	Retired	20, 7.6%	24, 6.3%	
	Student	19, %7.3	41, 10.7%	
Marital status (n, %)	**Single**	66, 25.0%	148, 38.6%	0.001*
	Married	180, 68.2%	213, 55.6%	
	Divorced	18, 6.8%	22, 5.7%	

*p<0.05, IR: Interquartile range, pwMS: People with multiple sclerosis, MSNQ: Multiple Sclerosis Neuropsychological Questionnaire, EDSS: Expanded Disability Status Scale

Table 2. Differences in pwMS with positive MSNQ and pwMS with negative MSNQ in terms of EQ-5D subscales, MFIS subscales, BICAMS subscales, and HAD anxiety and depression subscales

	pwMS with positive MSNQ (n=264)	pwMS with negative MSNQ (n=384)	p-value
Brief-MFIS total	11.0 (7.0; 14.0)	3 (1.0; 6.0)	<0.001*
Brief-MFIS physical score	4.0 (3.0; 6.0)	1.0 (0.0; 3.0)	<0.001*
Brief-MFIS cognitive score	4.0 (3.0; 6.0)	1.0 (0.0; 3.0)	<0.001*
Brief-MFIS psychosocial score	2.0 (1.0; 3.0)	0.0 (0.0; 1.0)	<0.001*
EQ-5D-mobility	15.0 (6.9; 93.1)	93.1 (79.1; 93.4)	<0.001*
EQ-5D-self care	98.7 (6.8; 98.8)	98.7 (98.0; 98.8)	<0.001*
EQ-5D-usual activities	10.9 (6.6; 91.2)	91.2 (84.1; 92.8)	<0.001*
EQ-5D-pain-discomfort	22.0 (15.4; 64.3)	68.3 (22.0; 83.4)	<0.001*
EQ-5D-anxiety-depression	19.0 (12.6; 22.8)	72.2 (17.3; 82.0)	<0.001*
EQ-5D-visual analog scale	70.0 (60.0; 80.0)	90.0 (70.0; 90.0)	<0.001*
HADS-A	9.0 (6.0; 13.0)	5.0 (2.0; 7.0)	<0.001*
HADS-D	8.0 (5.0; 10.0)	3.0 (1.0; 6.0)	<0.001*
SDMT	45.0 (35.0; 54.0)	51.5 (42.0; 60.0)	<0.001*
CVLT-II	49.0 (39.0; 57.0)	51.0 (43.0; 61.0)	<0.001*
BVMT	24.0 (19.0; 28.0)	26.0 (22.0; 31.0)	<0.001*

*p<0.05, MSNQ: Multiple Sclerosis Neuropsychological Questionnaire, MFIS: Modified Fatigue Impact Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, SDMT: Symbol Digit Modalities Test, CVLT: California Verbal Learning Test, BVMT: Brief Visuospatial Memory Tests, pwMS: People with multiple sclerosis, BICAMS: Brief International Cognitive Assessment farms

Table 3. Estimates of binary logistic regression for having positive MSNQ

Risk factors	OR	95% CI	p-value
Brief-MFIS total	1.202	0.951-1.520	0.124
Brief-MFIS physical score	0.842	0.622-1.142	0.269
Brief-MFIS cognitive score	1.183	0.891-1.572	0.245
Brief-MFIS psychosocial score	1.014	0.846-1.215	0.881
EQ-5D-mobility	0.999	0.992-1.005	0.731
EQ-5D-self care	0.995	0.987-1.003	0.237
EQ-5D-usual activities	0.992	0.986-0.999	0.017*
EQ-5D-pain-discomfort	1.000	0.992-1.008	0.947
EQ-5D-anxiety-depression	0.996	0.988-1.004	0.289
EQ-5D-visual analog scale	0.992	0.977-1.007	0.288
HADS-D	1.053	0.975-1.137	0.191
HADS-A	1.098	1.027-1.175	0.006*
SDMT	0.979	0.957-1.002	0.074
CVLT II	0.999	0.977-1.023	0.955
BVMT	0.992	0.946-1.041	0.793
Hosmer and Lemeshow test		11.547	
Sig.		0.173	
Nagelkerke R2		0.531 (53.1%)	

*p<0.05, MSNQ: Multiple Sclerosis Neuropsychological Questionnaire, MFIS: Modified Fatigue Impact Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, SDMT: Symbol Digit Modalities Test, CVLT: California Verbal Learning Test, BVMT: Brief Visuospatial Memory Tests, CI: Confidence interval, OR: Odds ratio

Fenu et al. (18) investigated the relationship between cognitive functions and daily activities in pwMS from both the patient and the caregivers' perspective. The authors showed a significant correlation between the performance of daily activities and cognitive impairment. It should be highlighted that the correlation coefficient was higher in caregiver perception (18). Similarly, we found that increasing independence in usual activities decreased the risk of neuropsychological competence. However, there is an informant report version of the MSNQ questionnaire that was not applied in the present study. For future studies, using the two versions of the MSNQ could be more informative.

Akbar et al. (19) examined the role of anxiety on self-reported measures of cognitive functions in pwMS. They reported that the anxiety level negatively affects perceptions reported in self-cognitive assessment of the pwMS (19). Our study showed that increased anxiety level is one of the risk factors for positive MSNQ. Therefore, the cognitive rehabilitation process for pwMS should consider the dependence and anxiety levels.

Although it is accepted that an increase in MSNQ score can be due to depression, many studies show that perceived cognitive difficulties are correlated with decreased employment and job performance, decreased health-related quality of life and increased subjective cognitive complaints (20,21). Likewise, the results of this study show that unemployment is higher among pwMS with positive MSNQ than among pwMS with negative MSNQ. Also, the quality of life and depression levels are shown to be worse among the pwMS with positive MSNQ than among those with negative MSNQ negative.

While there is no difference between the two groups in terms of disease duration and disease course, the higher EDSS in MSNQ-positive patients was statistically significant and was not consistent with the lack of a relationship between EDSS and MSNQ in a few studies (20,21). The difference between these findings and our study is that in the present study, the EDSS interval is relatively narrow and any slight increase has significant impacts on the measurement.

Our study found that pwMS with MSNQ positive had worse cognitive functions, had higher fatigue levels, were more likely to be unemployed, and had higher levels of depression and anxiety. This finding is consistent with studies showing that working capacity in pwMS is affected by the combination of these factors (22).

Study Limitations

The most important limitation of this study is the low EDSS level. However, it has been shown that pwMS have low neuropsychological competence even in cases where the EDSS is low.

Conclusion

This study showed that worse neuropsychological competence could be seen even at low EDSS levels. It has been shown that there is a correlation between employment statuses, quality of life, fatigue, depression, anxiety, and cognitive impairment affect neuropsychological competence in pwMS, affecting daily life functionality negatively. Also, the dependence and anxiety level of the pwMS should be considered during cognitive rehabilitation.

Ethics

Ethics Committee Approval: This study was approved by the Non-Invasive Research Ethics Board of Dokuz Eylul University (protocol number: 7368-GOA and approval number 2022/39-04).

Informed Consent: All participants were required to complete the informed consent form.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., Concept: O.S., H.K., S.O., Design: O.S., H.K., S.O., Data Collection or Processing: O.S., H.K., S.O., Analysis or Interpretation: O.S., H.K., S.O., Literature Search: O.S., H.K., S.O., Writing: O.S., H.K., S.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/jmsr.galenos.2022.2022-11-3
Journal of Multiple Sclerosis Research 2022;2(3):74-79

RESEARCH ARTICLE

The Relationship between Depression, Anxiety, Fatigue, and the Symbol Digit Modalities Test in Persons with Multiple Sclerosis

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Abstract

Objective: Cognitive impairment, fatigue, and neuropsychiatric symptoms are commonly intertwined in multiple sclerosis. The multifactorial etiology of these disease-related symptoms has not been delineated clearly. This study aimed to investigate the relationship between fatigue, anxiety, depression, and cognitive function, as assessed by Symbol Digit Modalities Test (SDMT), in people with multiple sclerosis (pwMS).

Materials and Methods: The oral version of the SDMT was used to measure cognitive function, the Hospital Anxiety and Depression Scale (HADS) for depression and anxiety, and the shortened version of the Modified Fatigue Impact Scale in MS (MFIS-5) for fatigue.

Results: This single-center study included 269 pwMS (206 female, mean age: 33.66±9.57, mean education years: 11.97±3.5). The demographic and clinical outcomes were collected retrospectively. The hierarchical regression analyses demonstrated that the model was significant and explained the 44% of the variance (R^2=0.44). The SDMT scores were not associated with fatigue, depression, and anxiety symptoms. Longer disease duration, fewer education years, and younger age were also independently associated with lower SDMT scores. PwMS with cognitive impairment (CI) (15.6%) and without CI differ significantly in disability level, age, HADS-depression score, and subscores and overall score of MFIS-5 ($p<0.05$).

Conclusion: In conclusion, lower education level, longer disease duration, and older age were associated with lower information processing speed in pwMS. No associations were found between SDMT and fatigue, anxiety, or depression levels.

Keywords: Multiple sclerosis, information processing, fatigue, anxiety, depression

Introduction

Cognitive impairment (CI) is a common symptom at all stages of multiple sclerosis (MS), present in 43-70% of patients (1). Previous research has shown the relationship between the disability level and CI (2). CI is often correlated to disability progression, decreased brain volume, and cortical thinning in persons with MS (pwMS) (3,4). A preliminary study showed that total lesion area is a strong predictor of impairment in memory, executive functions, language, and visuospatial functions (5). Meanwhile, risk of CI was associated with normal-appearing white matter and gray matter (6). One study evaluated 240 pwMS and 60 healthy controls in terms of cognitive functions for five years and found that occurrence of CI can be predicted by evaluating the volume of the anterior thalamus, superior longitudinal fasciculus, and temporal cortex (7).

Although studies continue to elucidate the complex relationship between brain structure and CI, this is not replicable in daily practice. Nevertheless, CI negatively affects the quality of life of pwMS, independent of physical deficiency (8). Information processing speed is the most most common cognitive deficit in pwMS, which is frequently measured in clinical practice with the Symbol Digit Modalities Test (SDMT) (9).

PwMS face difficulties caused by cognitive deficiency (10). Intervention studies developed to reduce CI in pwMS have

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Received: 01.12.2022 **Accepted:** 25.12.2022

increased. However, underlying factors need to be well-defined to design future intervention studies. Several studies have reported a high prevalence of psychiatric symptoms in pwMS, especially depression and anxiety (11), which are closely associated with other MS symptoms, such as fatigue, sleepiness, and pain. Meanwhile, other studies suggest that depression and fatigue are the most critical factors in the quality of life of pwMS (12). Moreover, these symptoms correlated with the cognitive but not the physical components of fatigue (13). Previous studies examined the relationship between information processing speed and fatigue, depression, and anxiety. However, these did not evaluate all these variables together and did not reach a large sample size that included all disability levels. Therefore, this study aimed to investigate the relationship between fatigue, anxiety, depression, and CI assessed by SDMT in pwMS.

Materials and Methods

Participants

The Non-Invasive Research Ethics Committee of Dokuz Eylul University approved the study on December 2022 (protocol number: 7368-GOA). The criteria for pwMS inclusion were: aged 18-55 years, a defined diagnosis of MS according to the McDonald criteria (14), a relapse-free period of 6 months before the study, and a signed written informed consent. The exclusion criteria were a history of severe head trauma, comorbid neurological and/or psychological disorders, substance abuse, mental retardation, or learning disability.

Outcome Measures

We recorded participant demographics and disease-related outcomes. We measured cognitive processing speed using the oral version of the SDMT (15), fatigue and its four components (physical, social, cognitive, and psychological) with a shortened version of the Modified Fatigue Impact Scale in MS (MFIS-5) (16), and depression and anxiety with the Hospital Anxiety and Depression Scale (HADS) (17). The SDMT was applied by psychologist and physiotherapist. Level of disability was assessed with Expanded Disability Status Scale (EDSS) by the neurologist at the MS Clinic of the Faculty of Medicine of Dokuz Eylul University.

Statistical Analysis

The normality of data was assessed with Shapiro-Wilk and Levene's tests. Numeric variables were shown as means, standard deviations (SD), percentages for discrete variables, and medians (interquartile range) according to data distribution. Group comparisons were conducted by the independent samples t-test and the Mann-Whitney U test according to data distribution for continuous variables, and the chi-squared test for categorical variables. Spearman's correlation coefficient was used to determine relationships between numerical variables. Participants with or without CI were compared based on a SDMT z-score cut-off of less than -1 SD. Hierarchical linear regression analyses were used to test the relationship between CI, fatigue, depression, and anxiety symptoms. In the regression analyses, EDSS, disease duration, age, gender, and education years were entered in the first step as initial control variables. In the second step, total MFIS-5, HADS-anxiety, and depression scores were entered. The statistical significance level was accepted to be $p<0.05$. Statistical analysis was carried out using SPSS statistical software 25.0 (IBM Corp., Armonk, NY, USA).

Results

Demographics, medications used, and clinical characteristics are summarized in Tables 1-3. This study included a sample of 269 participants of which 206 (76.6%) were female, 155 (57.6%) were married, 132 (49.1%) were employed, and 134 (49.8%)

Table 1. Demographic characteristics of the participants

	Mean (SD)
Age (years)	33.66±9.57
Gender, n (%)	
Female	206 (76.6%)
Male	63 (23.4%)
Marital status, n (%)	
Married	155 (57.6)
Single	114 (42.4)
Educational years	11.97±3.5
Educational status, n (%)	
Primary school	38 (14.1)
Secondary school	14 (5.2)
High school	83 (30.9)
University	134 (49.8)
Employment status, n (%)	
Employee	132 (49.1)
Unemployed/retired	102 (37.9)
Student	35 (13.0)

SD: Standard deviation

Table 2. Medications used for MS

	n (%)
Fingolimod	110 (41.3)
Interferon-beta	73 (26.6)
Glatiramer acetate	43 (16.0)
Natalizumab	13 (4.7)
Dimethyl fumarate	14 (5.1)
Ocrelizumab	2 (0.7)
Cladribine	1 (0.4)
Rituximab	1 (0.4)

MS: Multiple sclerosis

educated more than 11 years. The median value of EDSS was 1.0 (1.5), and the disease duration was 4.0 (8.0) years. The SDMT mean raw score was 50.49 (±12.74).

The clinical and cognitive features of the pwMS with CI or without CI are shown in Table 4. Fourty-two pwMS with CI have older age, lower education level, higher EDSS, HAD depression, MFIS-5 total score, cognitive, physical and psychosocial (p<0.05), but not in higher disease duration and HAD anxiety scores. Eighty-three pwMS with depression (30.8%) had lower SDMT scores, higher EDSS, HADS anxiety, and MFIS-5 total and subscores (p<0.001). Meanwhile, 109 pwMS with anxiety (40.5%) had higher HADS depression and MFIS-5 total and subscores (p<0.001) but not SDMT, age, disease duration, and EDSS. HADS scores did not correlate with age and disease duration.

A weak negative correlation was found between the SDMT and HAD-depression scores (r=-0.181, p=0.03), but not for the HAD-anxiety scores; and in SDMT and MFIS-5 total score, and physical and psychosocial subscores (respectively, r=-0.125, r=-0.126, r=-0.162, p<0.05), but not for cognitive subscores. HADS-depression and -anxiety scores were moderately correlated with MFIS-5 total score and subscores (correlation coefficients ranged from 0.411 to 0.567). EDSS was correlated with MFIS-5 total score and subscores (p<0.001), but not HAD scores.

Table 3. Clinical characteristics of the participants

	Median (IQR)
EDSS*	1.0 (1.5)
Disease duration (years)	4.0 (8.0)
HADS depression	4.0 (6.0)
HADS anxiety	6.0 (7.0)
PwMS with anxiety, n (%)**	109 (40.5)
PwMS with depression, n (%)**	83 (30.9)
MFIS-5 total	6.0 (9.0)
MFIS-5-physical	2.0 (5.0)
MFIS-5-cognitive	3.0 (4.0)
MFIS-5-psychosocial	1.0 (2.0)

*EDSS: Expanded Disability Status Scale, HADS: Hospital Anxiety and Depression scale, MFIS-5: The five item Modified Fatigue Impact Scale in MS, **HAD ≥8, IQR: Interquartile range, PwMS: People with multiple sclerosis

Association of SDMT with the MFIS-5 and the HAD Scores

Hierarchical regression analyses were performed to assess the relationship between SDMT and MFIS-5 total scores, HADS-depression and -anxiety scores after controlling for EDSS, disease duration, age, gender, and education years (Table 5). The model was significant [F (8,265) = 25.274, p<0.001) and explained 44% of the variance (R^2=0.44). Age [β=-0.437, (-0.581; -0.293), p<0.001] was associated with lower scores of SDMT, and education [β=1.639, (1.287; 1.991), p<0.001] was associated with higher scores of SDMT. HADS-depression and -anxiety scores, MFIS-5 total scores, male gender, duration of disease, and EDSS were not associated with SDMT scores.

Discussion

This study examined the relative effect between CI as measured by SDMT and the level of depression, anxiety, and fatigue in pwMS, controlling for confounding demographic and clinical variables. Our findings showed no association between information processing speed, fatigue, anxiety, or depression symptoms. Lower education level, longer duration of illness, and older age were associated with lower information processing speed in pwMS.

The relationship between CI and depression in pwMS is not yet clearly defined. This may be due to the inability to evaluate depressive symptoms in detail and the notion that depressive mood has little effect on memory. The absence of severe

Table 4. Results of cognitive and clinical features in the pwMS with and without CI

	MS patients with CI*	MS patients without CI	p
SDMT (mean, SD)	28.88±6.40	54.49±9.06	**<0.001**
HAD-anxiety	8.0 (7.0)	6.0 (8.0)	**0.354**
HAD-depression	7.0 (7.25)	4.0 (6.0)	**0.020**
MFIS-5			
Total	10.0 (10.25)	6.0 (8.0)	**0.354**
Cognitive	4.0 (4.0)	3.0 (3.0)	**0.024**
Physical	4.0 (6.0)	2.0 (4.0)	**0.008**
Psychosocial	2.0 (3.0)	1.0 (2.0)	**<0.001**
EDSS	1.75 (1.5)	1.0 (1.5)	**<0.001**
Disease Duration	5.0 (13.0)	3.0 (7.0)	**0.059**

Data are presented as median (IQR, Interquartile range)

SDMT: Symbol Digit Modalities Test, HAD: Hospital Anxiety and Depression scale, MFIS-5: The five item Modified Fatigue Impact Scale in MS, EDSS: Expanded Disability Status Scale, PwMS: People with multiple sclerosis

*Scored below 5th percentile in terms of cognitive performance

Table 5. Association of SDMT with the MFIS-5 and HAD scores

Variable	B	SE B	β	R^2	ΔR^2	p-value
Step 1						
Age	-0.434	0.73	-0.326*	0.43	0.42	<0.001
Gender	-2.860	1.410	-0.095*			
Education (years)	1.687	0.177	0.470*			
EDSS	0.210	0.513	0.021			
Disease duration (years)	-0.144	0.107	-0.071			
Step 2						
Age	-0.437	0.073*	-0.328	0.44	0.42	<0.001
Gender	-2.694	1.442	-0.90			
Education (years)	1.639	0.179*	0.457			
EDSS	0.274	0.542	0.027			
Disease duration (years)	-0.155	0.107	-0.077			
HAD depression	-0.309	0.217	-0.101			
HAD anxiety	-0.023	0.182	-0.009			
MFIS-5 total	0.038	0.152	0.016			

*p<0.05

[a]Regression model with HAD anxiety and depression and MFIS total as independent variable and EDSS, disease duration, age, gender, education years. EDSS: Expanded Disability Status Scale, HAD: Hospital Anxiety and Depression scale, MFIS-5: The five item Modified Fatigue Impact Scale in MS

depressive mood and a higher positive mood were associated with better cognitive performance. However, a decreased positive mood and high depressive mood did not show a close association, contrary to expectations. Although these indicate that anhedonia is associated with poorer memory function among pwMS, clinicians should evaluate other mood dimensions in MS (18).

Previous studies confirmed that depression and fatigue are independent predictors of quality of life in pwMS. Studies have also shown that fatigue, depression, and anxiety negatively affect cognitive function in pwMS (19-21). But as seen in this study, the relationships of these neuropsychological symptoms and other clinical factors are frequently intertwined and difficult to disentangle. For example, we found that pwMS with depression performed worse in information processing speed and had higher levels of disability, anxiety, and fatigue. However, anxiety and depression were not associated with age and disease duration. PwMS with anxiety had higher depression and fatigue but did not differ in CI, age, duration of illness, or disability. There was a weak negative correlation between information processing and depression but not with anxiety. Finally, cognitive performance was associated with the total score, and physical and psychosocial subscores of MFIS-5, but not with the cognitive dimension of fatigue. Consistent with our results, a study by Gill et al. (22) showed that HAD depression was positively associated with fatigue and HAD-anxiety scores were negatively associated with SDMT and EDSS. Additionally, disability level was only negatively and weakly associated with fatigue subscores and overall scores but not with anxiety and depression.

Studies have reported that demographic characteristics such as education and age were important predictors of cognitive function in pwMS (23-25). We investigated the relationship between information processing speed and fatigue, depression and anxiety while controlling for disability level, disease duration, age, gender, and years of education. Longer disease duration, fewer years of education, and younger subjects were also independently associated with lower SDMT scores. This could be because the disease progresses with age and, therefore, longer disease duration is characterized by more neuropathological changes. Furthermore, education has been used to represent cognitive reserve, making it significantly associated with cognition (26).

In the literature, the relationship between disability and CI in pwMS is contradictory and unclear (24,27). In this study, disability levels were not significant predictors of information processing speed. In addition, we showed that cognitive performance was not associated with fatigue, depression, and anxiety symptoms, even if the model explained 44% of the variance significantly after controlling for the confounding factors. Consistent with our findings, in a study conducted in Belgium that evaluated 66 pwMS, lower SDMT scores were associated with higher EDSS scores and psychological fatigue, but not with anxiety or depression. Thus, while disability and fatigue levels negatively affected cognitive function in pwMS, depression and anxiety do not seem to have a significant effect (28). A longitudinal

study by Beal et al. (29) reported that younger age, longer disease duration, more extent of functional limitation, and progressive forms of MS were predictive of more significant depressive symptoms. However, these variables did not predict the changes in depressive symptoms over time, albeit present at all periods (29).

The relationship between physical and cognitive disability in pwMS and the presence of depression and anxiety is unclear. Nevertheless, our findings show that SDMT is not closely related to depression and anxiety and that depression has no significant effect on SDMT performance. This implies the substantial value of the SDMT in the evaluation of CI in pwMS.

Study Limitations

Some limitations should be paid attention to when interpreting our data. First, given the retrospective cross-sectional design, the self-report scores of neuropsychological symptoms and fatigue might be prone to recall bias. Next, higher patient samples using extensive neuropsychological test batteries, fatigue scales, and a psychiatric interview could be done in future studies. Finally, our sample only included relapsing-remitting MS and thus, lacks representation of people with primary and secondary progressive MS types.

Conclusion

Age, education, and disease duration were substantial predictors of SDMT. Future research should investigate whether depression, anxiety, and fatigue symptoms occur with adverse effects of CI in pwMS. The results support the routine use of the SDMT in clinical practice for assessing CI in pwMS.

Ethics

Ethics Committee Approval: The Non-Invasive Research Ethics Committee of Dokuz Eylul University approved the study on December 2022 (protocol number: 7368-GOA).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: P.Y., Z.A., Design: P.Y., Z.A., Data Collection or Processing: P.Y., Z.A., E.K., Analysis or Interpretation: P.Y., Z.A., E.K., Literature Search: P.Y., Z.A., Writing: P.Y., Z.A., E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/jmsr.galenos.2022.2022-11-2
Journal of Multiple Sclerosis Research 2022;2(3):80-84

RESEARCH ARTICLE

Cognitive Assessment Has Never Been Faster! The Clock Drawing Test as a Screening Test for Cognitive Impairment in MS Clinical Practice

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Abstract

Objective: Cognitive changes are commonly seen in patients with multiple sclerosis (MS), which is a chronic autoimmune, demyelinating disease. The Clock Drawing Test (CDT) is an easy to use and highly reliable cognitive assessment tool that evaluates planning, visuospatial abilities, and abstract thinking. In this study, the CDT was scored with the Shulman, Manos-Wu, and Watson methods, which are the most frequently used scoring methods, and the correlation was examined between clinical evaluation tests.

Materials and Methods: A total of 109 participants with a diagnosis of MS were included in the study. Participants were followed longitudinally, three times in total, at intervals of 3-6 months. Clinical tests and the CDT (scored with the Shulman, Manos-Wu, and Watson methods) were applied to the participants. The relationships between the CDT, the clinical evaluations, and the demographic data were analyzed by Pearson's correlation analysis. Differences between the participants' first and follow-up clinical tests and the CDT scores were assessed by repeated-measures analysis of variance.

Results: Significant moderate to strong correlations were detected between the CDT score and the Expanded Disability Status Scale, the Nine Hole Peg Test, the 25-Foot Walk Test, education, age, and disease duration. No significant differences were observed between the baseline and follow-up CDT or the clinical evaluation test scores.

Conclusion: The CDT scored by three different methods was moderate to strongly correlated with clinical tests frequently used to assess motor symptoms. This finding suggests that the CDT is a useful cognitive evaluation tool that is closely related to general clinical evaluation tests.

Keywords: Clock drawing test, multiple sclerosis, cognition

Introduction

Cognitive changes are common in patients with multiple sclerosis (MS), starting with the development of the radiological and clinically isolated syndrome. The prevalence of cognitive impairment in the adult MS population ranges from 34% to 65% and varies according to the method applied. Difficulties in attention, memory, information processing speed, verbal fluency, visuospatial perception, social cognition, and executive functions have been reported in patients with MS (1,2).

Cognitive disorders impair work life, social relationships, and activities of daily living independently of a physical disability. It is thought that evaluating cognitive functions from the early period in patients with MS not only enables diagnosis of the cognitive disorder but also provides information about disease progression and better treatment management (3).

An evaluation of cognitive functions cannot be made objectively using the Expanded Disability Status Scale (EDSS) score during the follow-up of MS patients and is ignored particularly when physical disability progresses. The Mini-Mental State Examination

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Received: 09.12.2022 **Accepted:** 26.12.2022

(MMSE) is the most widely used cognitive assessment tool to determine cognitive impairment in patients with a neurological disorder. The MMSE cannot be used to evaluate executive or memory functions in patients with MS. Many tests used to evaluate cognitive functioning in patients with MS are superior to the MMSE, such as the Symbol Digit Modalities Test (SDMT), the Brief Repeatable Battery of Neuropsychological Tests (BRN-B), the Brief International Cognitive Assessment for MS, the Minimal Assessment of Cognitive Function in MS, and the MS neuropsychological screening questionnaire (4).

The problems encountered when applying these tests in an intensive outpatient clinic include the need for a quiet environment, practitioner training, and time. Practical, rapid, and non-specific tests and regular cognitive control of patients are a necessity for physicians and patients during follow-up. The Clock Drawing Test (CDT) is a paper-pencil test, which has long been recommended for evaluating general cognitive functions, as it is easy, quick, and has high validity and reliability.

In our study, we measured the usability of the CDT for distinguishing cognitive impairment and longitudinal tracking in MS clinical practice. The CDT can be used to evaluate high-level cognitive functions, such as planning, sequencing, visuospatial perception, and abstract thinking (5). The CDT offers the opportunity to obtain detailed information about the cognitive level of MS patients. Different methods have been developed to evaluate the CDT. The three most widely used CDT scoring methods are Shulman, Manos-Wu, and Watson. In this study, all three methods were used to score the CDT. The EDSS, SDMT, Nine Hole Peg Test (NHPT), and 25-Foot Walk Test (25 FWT) are routine tests used during follow-up to evaluate MS patients. However, no study has compared which of these three tests is the best. In this study, our first aim was to investigate the utility of the CDT for detecting cognitive impairment. The second aim was to show the compatibility of the results with the MS clinical evaluation parameters and the ease of scoring in clinical practice using the three different methods.

Materials and Methods

Participants

In total, 109 participants who were followed up with the diagnosis of MS were enrolled in our study. All patients were aged 18-61 years and were diagnosed with relapsing-remitting MS according to the McDonald (2017) criteria. The exclusion criteria were a history of dementia, concomitant comorbid disease, or an attack in the last 3 months.

This study included the results of an evaluation performed at 3-6 month intervals from prospectively collected patient follow-up charts. The participants were followed longitudinally, three times in total, at intervals of 3-6 months. The EDSS, SDMT, 25 FWT, NHPT, and CDT were administered to the participants.

All participants provided informed consent following the Declaration of Helsinki. This study was approved by the Bursa Yuksek Ihtisas Training and Research Hospital Ethical Committee (protocol number: 2011-KAEK-25 2022/06-13 date: 29.06.2022).

The demographic and clinical data of the participants are presented in Table 1.

Clinical and Cognitive Tests

a. EDSS: The EDSS is a clinical evaluation test that assesses the degree of disability in individuals with MS. The EDSS score ranges from 0 to 10 with a higher score indicating a higher degree of disability.

b. SDMT: The SDMT evaluates cognitive speed and information processing speed. It is widely used in patients with MS.

c. 25 FWT: The 25 FWT is used to assess leg functioning and mobility. The individuals taking the 25 FWT were asked to walk as quickly as possible. The times for two trials were averaged to obtain the score. However, in this explanatory study, we used the forward and backward scores separately.

d. NHPT: The NHPT is widely used to assess finger dexterity in patients with MS. Time is recorded in seconds and the individual is asked to perform the test as quickly as possible.

e. CDT: The CDT is administered using plain white paper and the patient was asked to draw an analog clock. After drawing the clock, the individual was asked to show the time as 11.10. The clocks were evaluated with the three different scoring methods. (Figure 1: CDT evaluation).

The scoring methods of the tests are given below:

Shulman

Five points indicated a faultless clock and were considered "perfect". A clock with minor errors scored 4 points. Three points were given if the individual could not accurately show 10 past 11 but the number organization of the clock and the dial plate were correct. Two points were given if the numbers were present yet the accurate representation of 10 past 11 was impossible due to the organization of the numbers. One point

Table 1. Demographic and clinical characteristics of the participants

RRMS (n=109)	Mean (SD)
Age (years)	39.50 (10.05)
Education (years)	8.31 (4.18)
Age at first symptom (years)	29.89 (9.03)
Disease duration	9.73 (5.86)
Treatment duration (years)	8.27 (5.67)
EDSS	2.89 (2.09)
Gender (F/M)	82/27

Data presented as mean, SD: Standard deviation, RRMS: Relapsing-remitting multiple sclerosis EDSS: Expanded Disability Status Scale, F: Female, M: Male

for severe impairment in organization and 0 points was given if there was no representation of a clock (6).

Watson

A pre-drawn circle was given to the individuals following the Watson method. Drawing of the hands was not included in the score for this method. The circle/dial plate was divided into four quadrants. The fourth quadrant consisted of the numbers 9-12 and was the most important one for scoring. One point was given for errors made in quadrants 1, 2, or 3. Errors made in quadrant 4 received a score of 4. The scores ranged from 0 to 7, and a higher score indicated more abnormalities (7).

Manos-Wu

The Manos-Wu method (8) of CDT scoring included a transparent dial that perfectly fit the clock drawing of the participant. If the hands were correct and the organization of the numbers was accurate, the individual was given 10 points. Some significant errors cannot be scored if there was an error that made the transparent circle inapplicable. However, this method successfully discriminates dementia at a rate of 78% (9).

Statistical Analysis

The possible differences between the baseline, first follow-up, and second follow-up clinical tests and between the different CDT scoring approaches (Schulman, Watson, and Manos-Wu) were assessed with separate repeated-measures analyses of variance (ANOVAs) with time as a factor defined by the three levels as baseline, first follow-up, and second follow-up. Bonferroni post-hoc analyses were applied. The correlations between the CDT scoring technique, the clinical test score (EDSS, SDMT, 25 FW, and NHPT), and the demographic variables (age and education) were assessed by Pearson's correlation analysis. All hypotheses in the correlation analyses were a priori. Thus, no corrective methods were used for the correlation analysis. A p-value <0.05 was considered significant.

Results

Clinical Evaluations and the CDT Scores over Time

A significant difference was detected between the EDSS score [F (2,96)=3.471, p=0.043]. However, post-hoc analysis indicated no significant differences between the baseline, first follow-up and second follow-up EDSS scores. Repeated-measures ANOVA showed a significant difference between the baseline, first follow-up, and second follow-up of the 25 FW-Backward score, but the post-hoc analysis revealed no difference.

No significant differences were detected between the baseline, first follow-up, and second follow-up scores on the SDMT [F (2,104)=0.896, p=0.391], NHPT-right [F (2,100)=0.47, p=0.952], NHPT-left [F (2,98)=0.19, p=0.968], or 25 FW-Forwards [F (2,98)=3.480, p=0.066] tests.

No differences were observed between the baseline, first follow-up, and second follow-up scores on the CDT-Schulman

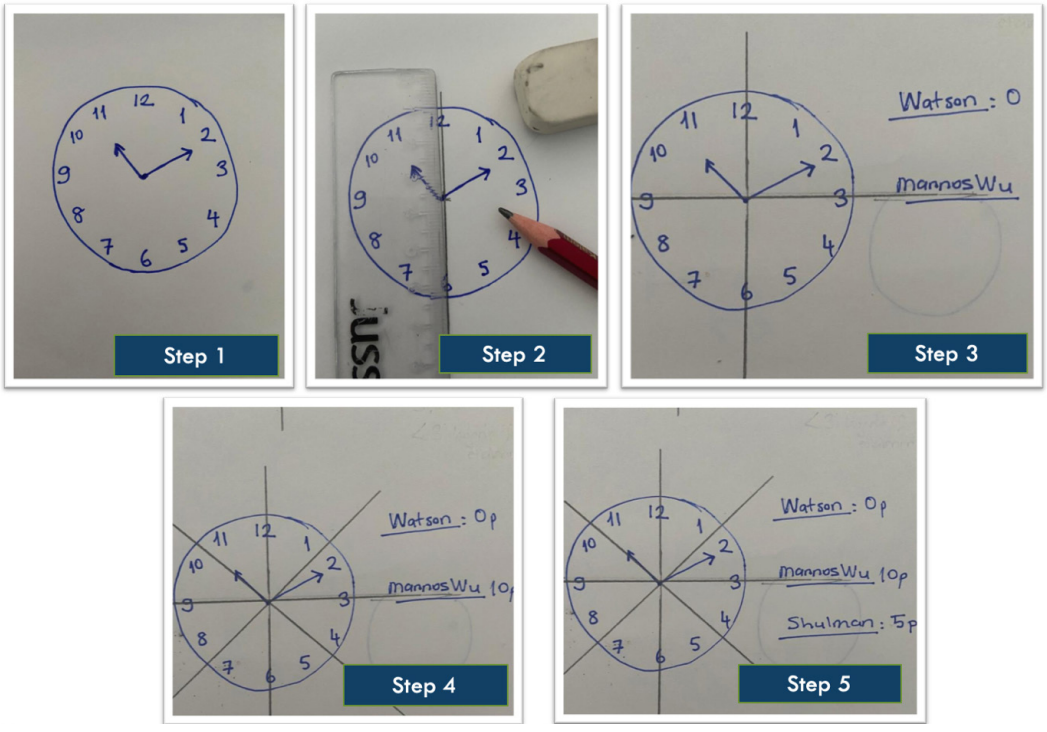

Figure 1. The midpoint of the clock was found with a compass, and it was divided into four dials with a ruler. The test was scored first according to Watson, then Mannos-Wu, and finally by the Shulman evaluation methods. Tests and clock drawings were repeated at regular follow-ups with controls

[F (2,98)=2.983, p=0.067], CDT-Watson [F (2,98)=2.029, p=0.138], or CDT-Manos-Wu [F (2,100)=2.546, p=0.088].

Correlation Analysis

Moderate to strong correlations were detected between the CDT-Manos-Wu and the EDSS (r=-0.449, p<0.001), NHPT-right (r=-0.233, p=0.016), NHPT-left (r=-0.262, p=0.007), 25 FW-backward (r=-0.289, p=0.003), SMDT (r=0.575, p<0.001), age (r=-0.264, p=0.006), education (r=0.295, p=0.002), and disease duration (r=-0.253, p=0.009). In addition, moderate to strong correlations were observed between the CDT-Schulman and the EDSS (r=-0.434, p<0.001), NHPT-right (r=-0.272, p=0.005), NHPT-left (r=-0.252, p=0.009), 25 FW-Forwards (r=-0.252, p=0.040), 25 FW-Backward (r=-0.277, p=0.005), SDMT (r=0.575, p<0.001), age (r=-0.386, p<0.001), education (r=0.295, p=0.002), and disease duration (r=-0.202, p=0.037). Low to moderate correlations were detected between the CDT-Watson and the EDSS (r=0.291, p=0.002), NHPT-right (r=0.280, p<0.001), SMDT (r=-0.352, p<0.001), and age (r=0.349, p<0.001) (Table 2).

Discussion

We found that the CDT, which evaluates visuomotor skills and executive functions, such as planning, sequencing, and abstract thinking, was moderate to strongly correlated with the tests frequently used to assess motor and cognitive skills in patients with MS, particularly when scored with the Manos, Wu, or Schulman methods. Following our hypotheses, the results revealed no longitudinal differences in the CDT scores in our sample, but a moderate-strong correlation with the clinical tests was observed, which also had no longitudinal differences This finding supports our view that the CDT is an effective neuropsychological test for patients with MS.

Cognitive functions should be evaluated during the diagnosis and follow-up of neurological and neuropsychiatric diseases. Ideal assessment methods are expected to be quickly applicable, repeatable, well tolerated, unaffected by education, culture, and language, easily scored, sensitive, specific, with no inter-rater differences, and correlated with other cognitive screening tests. Many studies have been conducted on whether the CDT is an ideal test to evaluate cognitive functions. As a result, the CDT can be used to evaluate high-level cognitive functions, such as planning, sequencing, visuospatial relationships, and abstract thinking, in diseases, such as vascular dementia, Alzheimer's type dementia, Huntington's disease, Parkinson's disease, stroke, traumatic brain injury, and delirium. This result suggests that the CDT is a good screening test to evaluate cognitive functions and provide an early diagnosis of cognitive disorder (5,6).

Cognitive disorders in patients with MS have gained popularity in the last 20 years, which has facilitated research on the topic. Cognitive functions are affected at varying levels from the early stages of the disease. A comparative study with the BRN-B to evaluate cognitive impairment in MS was performed by Barak et al. (5). In that study, evaluations were made using the Shulman method. As results, the CDT-Shulman scores were not correlated with age, gender, disease duration, or the EDSS score, but they were significantly correlated with the EDSS mental functional system score. A moderate-strong correlation was demonstrated between the CDT-Shulman score and age, disease duration, and education level. In the same study, significant correlations were detected between the BRN-B test and the CDT, as well as a positive correlation was observed between the Paced Auditory Serial Addition Test and the CDT (5). In addition, the CDT has sensitivity of 93.4% and specificity of 85.8% in discriminating cognitively intact from impaired MS patients, as defined by the EDSS.

In a study from our country, Baysal Kırac et al. (10) reported no significant difference between the CDT scores of early MS patients and healthy controls. Although 19.6% of the patients were impaired according to the Rey Auditory and Verbal Learning Test (RAVLT-1), which interprets learning, and 17.4% were impaired on the RAVLT-2, which interprets long-term memory, the results were not significant when compared with the control group (10).

Many different scoring methods are available, fueling a debate about which is the best. Researchers have shown that the scoring method described by Shulman is superior to the Watson method for diagnosing cognitive impairment (11).

Table 2. Comparisons between the Clock Drawing Test scores and the clinical assessment scales

	Manos-Wu	Shulman	Watson
EDSS	r=-0.449	r=-0.434	r=0.291
NHPT-R	r=-0.233	r=-0.272	r=0.280
NHPT-L	r=-0.262	r=-0.252	-
25 FWT		r=-0.252	-
SDMT	r=0.575	r=0.575	r=-0.352
Age	r=-0.264	r=-0.386	r=0.349
Education	r=0.295	r=0.295	-
Disease duration	r=-0.253	r=-0.202	-

EDSS: Expanded Disability Status Scale, NHPT: Nine Hole Peg Tests, 25 FWT: 25-Foot Walk Test, SDMT: Symbol Digit Modalities Test, R: Right, L: Left

Although it is easy to use and to score and draws objectively from the Watson method, our study showed that it may not be as comprehensive as the others (6).

Emek Savas et al. (12) investigated the validity and reliability of the most frequently used CDT methods, including the Manos-Wu and Shulman methods. They found that the CDT scores of healthy individuals were significantly affected by age and education using the Manos-Wu method, whereas only education affected the scores according to the Shulman method. In both cases, test-retest reliability and inter-rater reliability were high, and the two tests were strongly correlated with each other (12).

Study Limitations

Several limitations of this study should be discussed. The CDT was not compared with the EDSS cognitive sub-functional score. Patients were not screened for fatigue, depression, or anxiety disorder. An upper extremity disability may have impacted the CDT results. Cognitive test results may not be reliable in MS patients with cerebellar or upper extremity dysfunction, and patients in this group should be evaluated separately. The absence of a healthy control group was a limitation of this study. However, the evaluation of prospectively obtained follow-up tests and a comparison with the frequently used SDMT, which has become routine to evaluate cognitive function in MS outpatient clinics, are the strengths of our work.

The CDT is a useful, brief, and sensitive cognitive assessment tool for screening cognitive functions quickly in MS patients at follow-up clinics. As cognitive functioning changes with motor functioning in patients with MS, longitudinal use of the CDT may suggest disease progression. Further studies should focus on the longitudinal changes in the CDT and correlate clinical test results to determine how the CDT is affected.

Conclusion

This study showed the relationships between the CDT score and the clinical tests used to evaluate MS. The findings support our view that the CDT is a good assessment tool for patients with MS. We think that comparing individuals with MS and individuals without neurological disease in future studies is very important to determine the discrimination validity of the CDT.

Ethics

Ethics Committee Approval: This study was approved by the Bursa Yuksek Ihtisas Training and Research Hospital Ethical Committee (protocol number: 2011-KAEK-25 2022/06-13 date: 29.06.2022).

Informed Consent: All participants provided informed consent following the Declaration of Helsinki.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., A.O.S., D.O., Y.O.I., Concept M.S., A.O.S., D.O., Y.O.I., Design: M.S., A.O.S., D.O., Y.O.I., Data Collection or Processing: M.S., A.O.S., D.O., Y.O.I., Analysis or Interpretation: M.S., A.O.S., D.O., Y.O.I., Literature Search: M.S., A.O.S., D.O., Y.O.I., Writing: M.S., A.O.S., D.O., Y.O.I.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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