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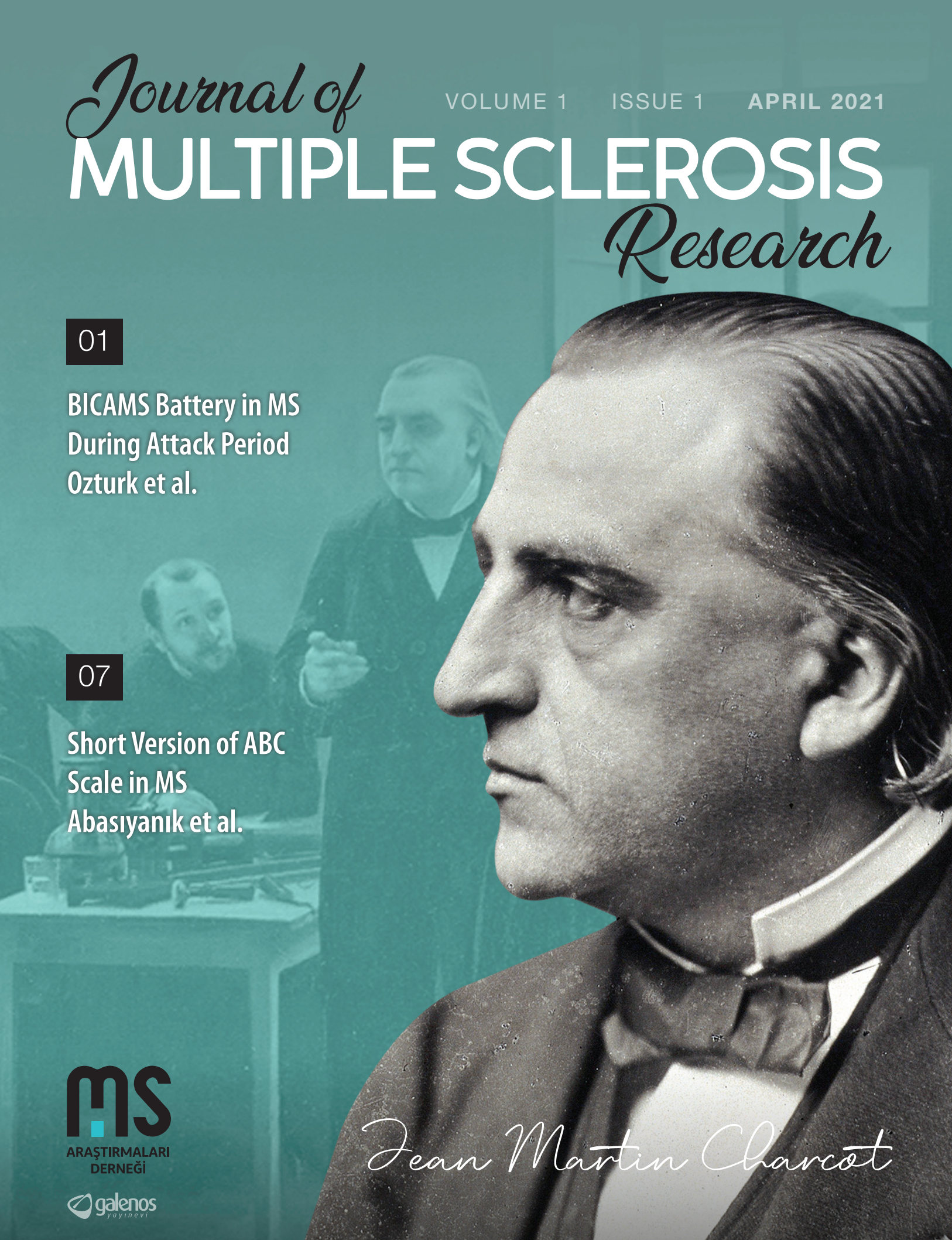
Journal of MULTIPLE SCLEROSIS Research



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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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The *Journal of Multiple Sclerosis Research* publishes original research papers, interesting case reports, invasive procedures, clinical and basic science review articles, editorials, and letters to the editor, about multiple sclerosis and related topics, all of which have the highest scientific and clinical value at an international level.

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Journal of Multiple Sclerosis Research accepts invited review articles, research articles, brief reports, case reports, letters to the editor, and images that are relevant to the scope of multiple sclerosis, neuromyelitis optica, and other related diseases of the central nervous system on the condition that they have not been previously published elsewhere. All manuscripts are subject to editorial revision to ensure they conform to the style adopted by the journal. There is a double-blind reviewing system.

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The Review Process

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Preparation of Manuscript

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

Original manuscripts require a structured abstract. Each section of the structured abstract must be labelled with the appropriate subheading (Objective, Materials and Methods, Results, and Conclusion). Case reports require short unstructured abstracts, whereas letters to the editor do not require an abstract. Research or project support should be acknowledged as a footnote on the title page.

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

Preparation of research articles, systematic reviews, and meta-analyses must comply with study design guidelines:

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:

a. Title

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.

d. Copyright Transfer Form and Authorship Contribution Form

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.

Conflict of Interest Statement: To prevent potential conflicts of interest from being overlooked, this statement must be included in each manuscript. In case of conflicts of interest, every author should complete the ICMJE general declaration form, which can be obtained from http://www.icmje.org/coi_disclosure.pdf.

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.

Objective: The abstract should state the objective (the purpose of the study and hypothesis) and summarize the rationale for the study.

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 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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Original articles should have the following sections:

Introduction: The introduction should include an overview of the relevant literature presented in summary form (one page), and whatever remains interesting, unique, problematic, relevant, or unknown about the topic must be specified. The introduction should conclude with the rationale for the study and its design and objective(s).

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.

Review articles should include a conclusion in which a new hypothesis or study about the subject may be posited. Methods for literature search or level of evidence should not be published. Authors who will prepare review articles should already have published research articles on the relevant subject. There should be a maximum of two authors for review articles.

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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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Tables: Each table should be supplied on a separate file. Tables should be numbered according to the order in which they appear in the text, and a brief caption for each should be supplied. Each column must have a short or abbreviated heading. Explanatory statistical measures of variation, such as standard deviation or standard error of the mean, must be written. Each table must be cited in the text.

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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

*Excludes abstract, acknowledgments, conflict of interest statement, references and tables; maximum word counts.

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Each author should have participated sufficiently in the work to assume public responsibility for the content. Any portion of a manuscript that is critical to its main conclusions must be the responsibility of at least one author. Please check the definition of the role of authors and contributors in the following link:

http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

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When reporting experiments conducted with humans, it must be indicated that the procedures were in accordance with ethical

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standards set forth by the committee that oversees human experimentation. Approval of research protocols by the relevant ethics committee, in accordance with international agreements (Helsinki Declaration of 1975, revised 2013 available at http://www.wma.net/e/policy/b3.html "Guide for the Care and use of Laboratory Animals" www.nap.edu/catalog/5140.html), is required for all experimental, clinical, and drug studies. Studies performed on humans require an ethics committee certificate, including an approval number. It also should be indicated in the "Materials and Methods" section. Patient names, initials, and hospital identification numbers should not be used. Manuscripts reporting the results of experimental investigations conducted with humans must state that the study protocol received institutional review board approval and that the participants provided informed consent.

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All authors are responsible for the manuscript's content.

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.

In addition, all authors are required to disclose any professional affiliation, financial agreement, or other involvement with any company whose product figures are prominent in the submitted manuscript.

Authors of accepted manuscripts will receive electronic page proofs and are responsible for proofreading and checking the entire article within 2 days. Failure to return the proof in 2 days will delay publication. If the authors cannot be reached by e-mail or telephone within 2 weeks, the manuscript will be rejected and will not be published in the journal.

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Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for an abbreviation should precede its first use in the text unless it is a standard abbreviation. All acronyms used in the text should be expanded at first mention, followed by the abbreviation in parentheses; thereafter, the acronym only should appear in the text. Acronyms may be used in the abstract if they occur three or more times therein but must be reintroduced in the body of the text. Generally, abbreviations should be limited to those defined in the AMA Manual of Style, current edition. A list of each abbreviation (and the corresponding full term) used in the manuscript must be provided on the title page.

The ORCID (Open Researcher and Contributor ID) number of the corresponding author should be provided while sending the manuscript. A free registration can be created at http://orcid.org.

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PEER REVIEW

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Submitted manuscripts are subjected to double-blind peer review. The scientific board, which guides the selection of papers for potential publication in the journal, consists of elected experts of the Journal and, if necessary, may be selected from national and international experts in the relevant field of research. All manuscripts are reviewed by the editor, section editors, and at least three internal and external expert reviewers.

The authors of the accepted manuscripts should consent that the editor and section editors can make corrections without changing the main text of the paper. The manuscript format should follow uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication (http://www.icmje.org/).

Ethics

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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CONTENTS

RESEARCH ARTICLE

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Journal of Multiple Sclerosis Research 2021;1(1):1-6

RESEARCH ARTICLE

Use of the BICAMS in Patients with Multiple Sclerosis During Attack Period: A Prospective Controlled Study

Ozan Ozturk[1], Bilge Piri Cinar[2], Serkan Ozakbas[1],

[1]Dokuz Eylul University Faculty of Medicine, Department of Neurology, Izmir, Turkey
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Abstract

Objective: Assessment of cognitive impairment, which cannot be evaluated with ordinary scales, in multiple sclerosis (MS) has been thought to be beneficial. MS significantly impairs the quality of life. During an MS attack, using a tool such as the brief international cognitive assessment for MS (BICAMS) battery, which can be administered quickly and applied and interpreted by individuals without neuropsychology training, provides a rapid and broad assessment of the patient's status.

Materials and Methods: The symbol digit modalities test (SDMT), california verbal learning test II (CVLT II), brief visuospatial memory test-revised (BVMT-R), and expanded disability status score were applied before treatment, at the end of treatment, and at the first month after treatment to evaluate mental and cognitive status in the acute period in patients with MS, who met the inclusion criteria.

Results: This study enrolled 49 patients with MS (F/M, 30/19) and 25 healthy controls (F/M, 16/9). The CVLT II scores were significantly higher after treatment than at baseline evaluation ($p<0.0001$). However, no significant difference was observed in data obtained at the end of treatment and at the first month after treatment ($p=0.517$). The CVLT II scores before treatment and at the first month increased in both groups, which was significantly higher in the MS group than in the control group ($p=0.002$). In the MS group, a marked increase was found in the number of correctly drawn figures on the BVMT-R at the end of treatment compared with that drawn before treatment ($p<0.0001$). Values obtained at the first month after treatment were significantly higher than those measured before treatment ($p<0.0001$). In the MS group, the mean numbers of symbols drawn correctly in 90 s on the SDMT were 42.04±11.73 on the first visit and 45.40±16.32 at the end of treatment, indicating a significant improvement ($p=0.003$), and the mean number of symbols drawn correctly at the first month was 48.14±15.03.

Conclusion: This study found that the BICAMS battery was effectively used in the acute period, the short total application period was 15 min, and a neuropsychologist was not required for application and interpretation. These results suggest the potential application of BICAMS battery in daily practice.

Keywords: Multiple sclerosis, attack, cognitive impairment, cognitive tests

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system. The disease course may be marked by successive periods of worsening and improvement or by the gradual progression of neurological findings. Manifestations that last at least 24 h, with at least 1 month between these and another episode, and producing one or more clinical findings are defined as attacks. Intravenous methylprednisolone (IVMP) is widely used in the treatment of MS attacks. Cognitive impairment is a manifestation seen in all stages from MS onset and in all subtypes, independent of physical disability, and compromises the therapeutic process and quality of life.

Cognitive impairment, which is frequently seen in patients with MS, that adversely affected the therapeutic process and quality of life of the patient has recently attracted considerable interest and has become the main focus of several studies. Rates of cognitive impairment in MS are as high as 43%-70% (1), and cognitive impairment is seen in all MS subtypes regardless of physical disability. Cognitive impairment associated with

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the duration and course of MS and the patient's education level can be observed at all stages from disease onset (2,3). Cognitive functions that are particularly affected in patients with MS include the effectiveness and speed of information processing, executive functions, and long-term memory. Simple attention and verbal skills tend to be generally preserved in the subsequent stages of the disease.

The expanded disability status scale (EDSS) is frequently employed to determine disability levels in MS, but it is not sufficient for the assessment of cognitive status. Comprehensive neuropsychological evaluations, such as the brief repeatable battery neuropsychological tests and minimal assessment of cognitive function in multiple sclerosis, are useful in the assessment of cognitive impairment (4). However, these have limitations, such as being time-consuming and requiring experienced neuropsychologists for interpretation. Thus, in recent years, there has been a particular focus on practical alternatives for determining cognitive impairment in patients with MS, resulting in the development of the brief international cognitive assessment for MS (BICAMS) battery. The BICAMS battery consists of the symbol digit modalities test (SDMT), california verbal learning test II (CVLT II), and brief visuospatial memory test-revised. The battery possesses significant advantages, such as short application time (mean 15-20 min) and administration and interpretation by individuals without neuropsychological training (5-9).

The primary aim of this study was to investigate the presence of cognitive impairment during MS attack using the BICAMS battery. The secondary aim was to evaluate the feasibility of the BICAMS battery in evaluating response to treatment in the attack period of MS based on early and late period cognitive functions.

Materials and Methods

Patient Enrolment

This study included patients diagnosed with MS according to McDonald 2017 criteria(9), diagnosed with relapse, and planned for IVMP treatment. Patients were informed that evaluations would be conducted before attack treatment, at the end of treatment, and 1 month after treatment. Written consent was obtained from patients agreeing to participate in the study. Healthy volunteers who met the inclusion criteria were enrolled as the control group. In the MS group, patients aged 18-55 years who had a definite clinical diagnosis of MS [relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS)], who was in the attack period, who had no more than 2 weeks of relapse since the onset of the current attack, who had sufficient cognitive ability to provide information about histories, and who had signed informed consent forms were included. Individuals with sufficient cognitive levels for providing information about their histories and who had signed informed consent forms were enrolled as the control group. Patients who used drugs that can affect clinical evaluation (antipsychotic use or continuous corticosteroid use including the previous 1-month period), who had neurological diseases that can affect clinical assessment, who had any other neurological and/or psychiatric disease that can affect the results of the cognitive tests were excluded. Ethics approval was obtained from the local ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Procedure

In the MS group, neurological examinations with the EDSS were performed before treatment, end of treatment, and after 1 month of treatment, including the SDMT, CVLT II, and BVMT-R tests. In the control group, the SDMT, CVLT II, and BVMT-R tests were applied at baseline and after 2 weeks. Patients in the study group were followed up for 1 month. The tests were administered to the patients before IP therapy, at the end of treatment (on day 5, 7, or 10, depending on the response to treatment), and after 1 month. Tests were performed before IVMP therapy and at 14:00 hours at the latest so that fatigue developing over the day will not affect the cognitive tests.

Statistical Analysis

Statistical analyses were performed on SPSS 16.0 software for Windows. In addition to descriptive statistical methods (mean, standard deviation, and frequency), the chi-square test was used to compare rates in categorical variables, and the p value calculated for the Fisher test was adopted where necessary. The non-parametric Mann-Whitney U test was applied in the comparison of two non-normally distributed independent variables and Wilcoxon's test was performed for the means of two dependent groups. Spearman's correlation analysis was applied to determine the direction and level of correlation between variables, and p values <0.05 were regarded as significant for all results.

Results

This study included 49 patients with MS (F/M, 30/19) and 25 healthy controls (F/M, 16/9). No significant difference was observed between the two groups in terms of gender or education levels (p=0.51 and p=0.07, respectively). The median age of the MS group was 37 [mean age, 36.41±8.37 (21-51)] years. The median age of the control group was 38 [mean age, 37.40±9.58 (20-55)] years, and no significant differences were observed between the groups (p=0.50). In the MS group, the mean EDSS scores were 3.77±1.35 (2-6.5) before treatment, 2.57±1.21 (1-5) at the end of treatment, and 2.12±1.20 (0-4.5) at the first month after treatment. The EDSS scores at the first month were significantly lower than the pre- and post-

treatment values (p<0.0001 and p<0.0001, respectively). Significant improvement was also noted in the EDSS scores after treatment compared with those before treatment (p<0.0001).

Regarding cognitive functions, verbal memory in the MS group was assessed using the CVLT. Accordingly, the mean numbers of words recalled correctly were 49.90±11.46 before treatment, 56.84±11.91 after treatment, and 57.69±10.79 at the first month after treatment. No significant difference was determined between pre- and post-treatment values, but the difference between post-treatment and first-month values was significant (p<0.0001 and p=0.517, respectively). In the control group, the mean numbers of words recalled correctly were 53.96±9.4 at the first visit and 55.96±9.67 at the first month, showing a significant difference (p<0.0001). No significant difference was observed when the MS group was compared with the control group at either the first visit or the first month (p=0.17 and p=0.337, respectively) (Table 1). Comparison of the change in first-month CVLT scores compared with pretreatment values revealed an increase in both groups, but this increase was significantly higher in the MS group than in the control group (p=0.002).

The number of correctly drawn figures on the BVMT-R was calculated at all three time points. In the MS group, the mean numbers of correctly drawn figures were 20.59±8.41 before treatment, 25.59±8.97 after treatment, and 26.46±9.09 at the first month after treatment. A significant increase in numbers of correctly drawn figures was observed after treatment compared with that before treatment (p<0.0001). First-month values were significantly higher than pretreatment values (p<0.0001), but no significant difference was found when compared with post-treatment numbers (p=0.10). In the control group, the mean numbers of correctly drawn figures in the first visit were 26.80±3.55, and the difference between the MS and control groups was significant (p=0.001). Moreover, in the control group, the mean numbers of correctly drawn figures at the first month was 27.96±2.92, and no significant difference was determined between the MS and control groups in terms of the numbers of correctly drawn figures on the BVMT-R at all three time points (p=0.50) (Table 2). Comparison of the mean numbers of correctly drawn figures revealed a significant difference between the first visit and end of the first month on all three BVMT-R trials (p=0.001). Comparison of changes in pretreatment and first-month BVMT-R scores revealed an increase in scores in both groups, but the change was significantly greater in the MS group than in the control group (p=0.005) (Figure 1).

Table 1. Total number of correctly recalled words in CVLT before and after treatment and at the first month

	MS group (mean ± SD)	Control group (mean ± SD)	p
Pretreatment	49.90±11.46	53.96±9.4	0.17
Post-treatment	56.84±11.91	-	-
First month	57.69±10.79	55.96±9.67	0.337

CVLT: California verbal learning test, MS: Multiple sclerosis, SD: Standard deviation

In the MS group, the mean numbers of figures drawn correctly within 90 s on the SDMT were 42.04±11.73 at the first pretreatment visit and 45.40±16.32 after treatment, indicating significant improvement compared with the pretreatment period (p=0.003). Moreover, the mean number of correctly drawn figures on the first month was 48.14±15.03, which was significantly higher than both the pretreatment (p<0.0001) and post-treatment (p=0.005) values. In the control group, the mean number of correctly drawn figures on the SDMT within 90 s at the first visit was 47.56±8.76, which was not significantly different from the value in the MS group (p=0.055). In the control group, the number of correctly drawn figures at the first month was 49.24±9.06, which was also not significantly different from the first visit value (p=0.08) (Table 3). Moreover, the mean numbers of correctly drawn figures at the first visit and the first month were not significantly different (p=0.001) (Figure 2). Comparison of changes in pretreatment and first-month SDMT scores revealed an increase in both groups, but the increase was significantly greater in the MS group than in the control group (p=0.001).

Degrees of correlation between EDSS scores and results of cognitive tests applied were then examined. A weak correlation was found between CVLT II and EDSS before treatment, at the end

Table 2. Total numbers of correctly drawn figures on the BVMT-R before and after treatment and at the first month

	MS group (mean ± SD)	Control group (mean ± SD)	p
Pretreatment	20.59±8.41	26.80±3.55	0.001
Post-treatment	25.59±8.97	-	-
First month	26.46±9.09	27.96±2.92	0.50

BVMT-R: Brief visuospatial memory test-revised, MS: Multiple sclerosis, SD: Standard deviation

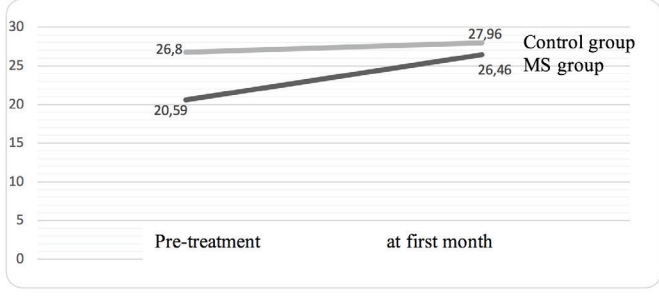

Figure 1. Changes in first-month BVMT-R scores compared to pre-treatment in the MS group

BVMT-R: Brief visuospatial memory test-revised, MS: Multiple sclerosis

Table 3. Numbers of correctly drawn figures within 90 s on the SDMT before treatment, after treatment, and at the first month after treatment

	MS group (mean ± SD)	Control group (mean ± SD)	p
Pretreatment	42.04±11.73	47.56±8.76	0.055
Post-treatment	45.40±16.32	-	-
First month	48.14±15.03	49.24±9.06	0.08

SDMT: Symbol digit modalities test, MS: Multiple sclerosis, SD: Standard deviation

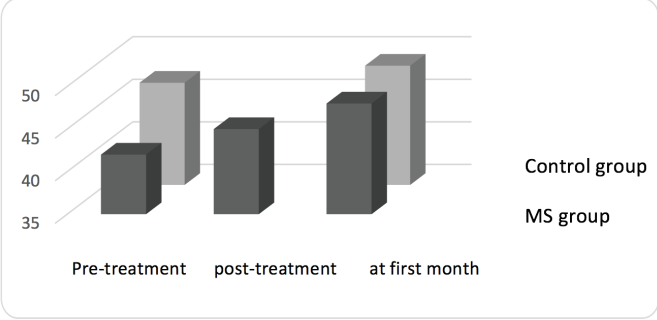

Figure 2. A comparison of the mean numbers of correctly drawn figures in 90 sec on the SDMT before and after treatment and at the first month in the MS and control groups

SDMT: Symbol digit modalities test, MS: Multiple sclerosis

of treatment, and at the first month after treatment (rho=-0.165, rho=-0.264, and rho=-0.245, respectively). BVMT-R and SDMT were found to be moderately correlated with EDSS at all three evaluations (Table 4). In the MS group, analysis of correlations among the cognitive tests revealed a good correlation between CVLT and SDMT before treatment and a moderate correlation between CVLT and BVMT-R and between BVMT-R and SDMT (rho=0.519, rho=0.407, and rho=0.421, respectively). At the end of treatment, a good correlation was noted between CVLT and BVMT-R, between CVLT and SDMT, and between BVMT-R and SDMT (rho=0.624, rho=0.551, and rho=0.494, respectively). These good degrees of correlation also persisted at the first month (rho=0.625, rho=0.476, and rho=0.618, respectively).

Table 4. Correlation between cognitive tests and the EDSS before treatment, after treatment, and at the first month after treatment in the MS group

	Pretreatment (rho value)	Post-treatment (rho value)	First month (rho value)
EDSS and CVLT-II	-0.165	-0.264	-0.245
EDSS and BVMT-R	-0.319	-0.307	-0.285
EDSS and SDMT	-0.366	-0.443	-0.474

SDMT: Symbol digit modalities test, BVMT-R: Brief visuospatial memory test-revised, CVLT: California verbal learning test II, MS: Multiple sclerosis

Discussion

Although individuals with MS present with highly diverse clinical manifestations, initial presentations are generally physical manifestations. Conditions that affect patients from the cognitive perspective are very rarely the reasons for the first presentation. Cognitive impairment is one of the factors, in addition to physical disability, that adversely and significantly affects the treatment process and quality of life of patients with MS. The identification and correction of these cognitive problems are also important in improving the quality of life by contributing to the therapeutic process.

The BICAMS battery consists of three tests evaluating different cognitive areas, namely, CVLT II, BVMT-R, and SDMT. CVLT II assesses verbal learning, verbal memory, and immediate recall. BVMT-R evaluates visual-spatial learning and memory, and the SDMT assesses working memory, visual scanning, and rapid data processing (6). Baetge et al. (10) reported that the both of SDMT and BVMT-R were the most sensitive to cognitive impairment and the two test combinations showed the strongest agreement with the total battery. Studies recommending the use of the BICAMS battery are ongoing, although few studies have used the cognitive batteries in patients with MS in the attack period (11). In the present study, the cognitive functions of patients with MS were evaluated using the BICAMS battery before treatment, during treatment, and at the first month after treatment and were compared with those of healthy controls.

In the MS group, the number of words correctly recalled during the CVLT test increased significantly at the end of treatment and in the first month after treatment compared with that at baseline, although no significant difference was observed between the end-of-treatment and first-month values. This finding suggested that, in addition to improving physical symptoms, pulse therapy for an MS attack leads to improvement in cognitive state and that this improvement persists for an extended time after the attack period. A significant difference was also determined between the first-visit and first-month visit values in the control group. This can be attributed to the learning effect observed in the majority of cognitive tests. Comparison of the MS and control groups at the first visit and first-month visit revealed no significant difference between the two groups in either period. However, the significantly greater change at the first month compared with pretreatment in the MS group compared with that in the control group shows that the attack treatment in MS, rather than the learning effect, had affected the cognitive state.

In the MS group, the mean number of figures drawn correctly within 90 s on the SDMT test revealed significant improvement at the end of treatment and the first month compared with pretreatment values. While a significant difference was observed between pretreatment and first-month values in the MS group, a significant difference was also determined in the

post-treatment and first-month values, suggesting that the improvement in the cognitive status commences in the early period and persists at the first month. Comparison of the MS group with the control group in terms of the mean numbers of correctly drawn figures within 90 s on the SDMT test at the first visit and at the first month revealed no significant difference. Similar to CVLT scores, the difference between pretreatment and first-month values was significantly greater in the MS group than in the control group. Moreover, similar to the CVLT, the SDMT can be used to evaluate the effectiveness of treatment. In agreement with other studies, this shows that the SDMT is a sensitive test of cognitive dysfunction (12,13).

As regards the numbers of figures correctly drawn by the study group at each of the three trials on the BVMT-R, significant improvement was observed in the MS group after treatment and at the first-month compared with pretreatment levels. The significant difference with the control group before treatment suggests that the presence of cognitive impairment during an MS attack can be shown using this easily applied and understood test and that it may be more sensitive than the other two tests. As with SDMT and CVLT, the difference between pretreatment and fist-month values on the BVMT-R in the MS group was significantly higher than in the control group. This difference revealed by the three tests shows that cognitive areas such as information processing, verbal learning, and visuospatial perception are affected during MS attack and that some degrees of improvement occur with corticosteroid therapy. These findings are compatible with the results of a previous study that evaluates the use of the MSFC in the attack period of MS (14). Although the paced auditory serial addition test (PASAT) successfully shows the effectiveness of a treatment, these two similar studies show that the tests used in the present study can be employed instead of PASAT, which is relatively more difficult to apply and requires equipment. In addition, the use of SDMT has previously been recommended instead of PASAT on the MSFC, and our findings confirm the idea that SDMT can be effectively employed instead of PASAT in the attack period (15).

The present study also investigated whether EDSS, which is the most commonly used test for evaluating physical disability, but is not insufficient in the cognitive sphere, is associated with other cognitive tests. A moderate correlation was found between the EDSS and the BVMT-R and SDMT in the attack period, at the end of treatment, and at the first month after treatment, but the weak correlation observed with the CVLT II suggested that BVMT-R and SDMT are more sensitive in evaluating treatment response during attack and follow-up. A moderate or good correlation between the three cognitive tests in the attack period, after treatment, and at the first month after treatment is important in emphasizing the use of these scales in the attack period of MS in evaluating three different areas and providing detailed information about cognitive functions.

In 2018, Giedraitiene et al. (16) applied the BICAMS battery to patients with RRMS and stable MS and in healthy controls. Similar to the present study, the results of the SDMT, BVMT-R, and CVLT II test were worse in the MS group than in the control group. Patients with RRMS registered lower scores than those with stable MS on the SDMT, while no significant difference was observed between the RRMS and stable MS groups on the other tests.

Study Limitations

In this study, the small number of patients was considered the most important limitation. Moreover, the addition of MRI parameters could help explain the paradox often mentioned in MS. The relatively low patient number in this study suggested that the difference in all cognitive tests might be low in the healthy control group. Further longitudinal studies evaluating cognitive functions in MS in both attack and remission periods will provide greater detail about such functions. When cognitive impairment is recognized as one of the most important parameters, showing the feasibility of the BICAMS battery in following response to attack treatment in patients with MS will encourage its wider application. All tests in the battery were easily understood by the patients, and no difficulties were encountered during application. Significant advantages also emerged, such as a total length of application as short as 15 min, and no neuropsychologist is required during application or interpretation. Comparison with the control group results shows the presence of cognitive impairment during the attack period. This study represents concrete evidence of an assumption that has long been held, but of which there has been little proof until now.

Conclusion

Cognitive involvement occurs in patients in the attack period of MS, and this is associated with widespread cerebral impairment in the attack period.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent from all participiants was obtained for the study.

Authorship Contributions

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

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RESEARCH ARTICLE

Further Validity of the Short Version of the Activities-Specific Balance Confidence Scale in Patients with Multiple Sclerosis

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Abstract

Objective: There is scarce data on the utility of the short version of the Activities-specific Balance Confidence Scale in persons with multiple sclerosis (pwMS). Thus, this study aimed to expand the validity of the ABC-6 scale and compare it with the original version of the 16-item ABC scale (ABC-16) in pwMS.

Materials and Methods: In total, 156 patients were included (median age: 35 years, 73.1% female and 26.9% male) in this study. The ABC-16 and ABC-6, timed up-and-go test (TUG), TUG-cognitive, six-minute walk test, timed 25-foot walk, MS walking scale, single-leg stance test, modified fatigue impact scale (MFIS), brief international cognitive assessment for multiple sclerosis, Beck depression inventory-II (BDI-II), and epworth sleepiness scale (ESS) were assessed. Validity was assessed in terms of criterion, convergent, discriminant, and known-group validity.

Results: The correlation coefficient between the ABC-6 and ABC-16 was 0.974 ($p<0.001$). The ABC-16 and ABC-6 were strongly correlated with measures of the expanded disability status scale, all walking and balance tests, and physical and psychosocial subscores of MFIS (rs =-0.520 to -0.811, $p<0.05$). Moderate correlations were found with a cognitive subscore of fatigue, cognitive processing speed, visuospatial memory, and BDI-II (rs =-0.321 to -0.446, $p<0.05$). Low correlations were found in verbal memory and ESS scores (rs =-0.160 to -0.246, $p<0.05$). PwMS with a moderate-severe disability had significantly lower ABC-6 scores than that of patients with mild disability ($p<0.001$).

Conclusion: The ABC-6 demonstrated high validity for measuring balance confidence in pwMS. Our findings strengthen the clinical utility of the ABC-6 in pwMS.

Keywords: Multiple sclerosis, balance confidence, balance impairment, validity

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease characterized by reduced motor and cognitive functions and fall risk (1,2). A total of 56% of patients with MS (pwMS) fall in the previous three months, and 37% of those are recurrent (3). Balance confidence is deemed as a psychological aspect of balance-demanding activities and falls (4). Furthermore, a lower level of balance confidence is demonstrated as related to lower physical activity and participation (5,6).

The 16-item Activities-specific Balance Confidence (ABC-16) scale has been a widely used patient-reported outcome measure for pwMS and other populations to assess balance confidence (7). In addition, the ABC-16 was shown to be the best determinant of falls in pwMS and older adults (8-10). Hence, its use to evaluate or predict falls is recommended. However, proper fulfillment of the original scale requires approximately 5-20 min. Therefore, a six-item version of the ABC-16 scale, named the ABC-6, was created to save time and allow a rapid quantitative assessment in busy clinical settings (11). However, limited data is available about the validity of the ABC-6 in pwMS. Therefore, further research is warranted to confirm its utilization in this population.

Wood et al. (12) reported moderate convergent validity and good internal consistency of the ABC-6 in pwMS. They also

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revealed that both the ABC-6 and ABC-16 had good sensitivity and specificity in distinguishing between pwMS with high fall risk and controls, whereas were less accurate at differentiating low and high fall risk of pwMS. Nevertheless, only physiologic profile assessment and fall history were investigated in their study. Results are promising for the use of ABC-6, but these findings should be confirmed considering the multifactorial nature of balance confidence. Therefore, the present study aimed to expand the validity of the ABC-6 in pwMS, investigating its correlations with walking, balance, fatigue, cognition, and psychosocial measures. A better understanding of related factors of balance confidence can guide rehabilitation strategies and ultimately help reduce activity limitation and encourage task performance.

Materials and Methods

Participants and Procedure

Data collected from the initial assessments of the longitudinal study registered to ClinicalTrials.gov (NCT03878836) were analyzed for this study. The study protocol was approved by the Ethics Board of Dokuz Eylul University (approval number: 2016/27-08). Data were extracted from a patient registry electronic system (iMed, Version 6.1; Merck Serono SA, Geneva, Switzerland).

The study included data from 156 pwMS. Eligible participants were selected according to the following inclusion criteria: a definite diagnosis of MS, Expanded Disability Status Scale (EDSS) below 7, and aged18-65 years. Exclusion criteria included relapse within 30 days, neurological disease diagnosis other than MS, and severe cognitive impairment hindering assessment understanding. Written informed consent was taken from all participants.

Outcome Measures

Basic demographics, including age and sex, were recorded. The clinical information of participants was obtained from the current records. Neurological disability level was measured using the EDSS (13).

Balance Confidence

The primary outcomes were the ABC-16 and ABC-6. The ABC-16 scale includes 16 items related to daily life activities. All items are ranked from 0 (no confidence) to 100 (complete confidence), and the score of the questionnaire is calculated by dividing the total score obtained from 16 activities by 16 (6,7,14). The ABC-6 constitutes the six most challenging tasks (questions 5, 6, 13, 14, 15, and 16) of the ABC-16 and approximately takes 5 min. Therefore, the score of ABC-6 is calculated by dividing the sum of the six items by six (11).

Walking

The Six-Minute Walk Test (6MWT) was implemented to assess the walking capacity. Participants were instructed to walk safely at their fastest speed in 6 min, according to a study by Motl et al. (15) The total distance covered during the 6 min was recorded in meters.

Timed-25 Foot Walking (T25FW) was carried out in a 7.62-meter long corridor; participants were asked to walk as fast and safely as possible to measure the walking speed. The average of two trials was recorded as the test score (16).

Timed Up-and-Go (TUG) test is a widely used instrument that assesses dynamic stability, mobility, turning, and rising out of a chair (17). The dual-task assessment was performed using the TUG test as a motor task and by adding a cognitive task, which is a serial 3 subtraction task. Serial subtraction tasks have been previously used to quantify dual-task cost in pwMS (18,19).

The severity of perceived walking difficulties was assessed using the 12-item MS Walking Scale (MSWS-12). Higher scores indicate an increased impact of MS on walking (20).

Balance

The static standing balance was assessed using the Single-Leg Stance Test. Participants were asked to stand on their dominant feet with eyes open for 60 s. The test ended when participants achieved 60 s or their feet touched the ground or their opposite extremity (21).

Fatigue

The Modified Fatigue Impact Scale (MFIS) is a patient-rated instrument that obtains information about the effects of fatigue and consists of 21 items. It involves physical, psychosocial, and cognitive subscales. Higher scores show more perceived fatigue (22,23).

Cognition

Brief International Cognitive Assessment for MS (BICAMS) composing the oral version of symbol digit modalities test (SDMT), brief visuospatial memory test-revised, and california verbal learning test (CVLT-II) were used in our study. The Turkish version of BICAMS was found valid and suitable for pwMS (24).

Depression

The severity of depressive symptoms was evaluated using the Beck Depression Inventory-II (BDI-II). Higher scores of BDI-II show enhanced depression symptom severity (25).

Sleep

The Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness. Higher scores of ESS indicate increased daytime sleepiness. The reliability of the Turkish form of ESS was found high (26).

Statistics Analysis

Data analysis was conducted using the IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp.). Data distribution was checked using the Kolmogorov-Smirnov test

and investigation of the histogram and plots. Nonparametric tests were used as the ABC-6 and ABC-16 did not show normal distribution. Spearman rank-order correlation was calculated to identify associations between the ABC-6 scale, ABC-16 scale, and other measures. Correlation coefficients of 0.1-0.29 were interpreted as small, 0.3-0.49 as moderate, and 0.5-1.0 as strong correlations. The validity was assessed in terms of criterion, convergent, discriminant, and known-groups validity by testing predefined hypotheses. The correlation coefficient between the ABC-16 and ABC-6 was explored to assess the criterion validity, and a strong correlation was expected. For examining the convergent validity, the following predefined hypotheses were constructed:

1. A strong correlation was expected between the ABC-6 and ABC-16 as they assess the same construct.

2. A moderate to strong correlation was expected between the ABC-6 and walking and balance tests, fatigue, cognitive processing speed, and visuospatial memory as they measure the nonsimilar construct, but these factors may influence balance confidence based on previous research.

A low correlation was foreseen between the ABC-6 and sleepiness and verbal memory for examining the discriminant validity as they do not measure balance-related constructs. Known-groups validity assesses whether an instrument can distinguish between known groups of patients. In this study, the ABC-6 and ABC-16 scores were compared using the Mann-Whitney U test between the disability groups. Groups were described according to the EDSS score as mild disability group (EDSS ≤3.5) and moderate-severe (EDSS >3.5) (27). Significance was set at $p<0.05$.

Results

Demographic and clinical characteristics of 156 participants with pwMS are summarized in Table 1. The clinical course of most patients was relapsing-remitting MS (92.3%).

The median score of the ABC-16 and ABC-6 were 83.12 and 73.33, respectively. Table 2 displays the correlation coefficient between ABC-6, ABC-16, and other outcome measures. All the predetermined hypotheses for the validity assessment were confirmed. The correlation coefficient between ABC-6 and ABC-16 was 0.974 ($p<0.001$). The ABC-6 and ABC-16 were strongly correlated with measures of the EDSS, walking and balance tests, and physical and psychosocial subscores of fatigue. The strongest correlation between ABC-16, ABC-6, and other outcome measures was found among perceived walking difficulties assessed using the MSWS-12 ($rs = -0.811$, $rs = -0.768$, $p<0.001$; respectively). Moderate correlations were found with the cognitive subscore of fatigue, SDMT, BVMT-R, and depression. Low correlations were found in CVLT-II and ESS scores. Correlations coefficients between the ABC-6 and ABC-16 and other measures were similar.

Table 1. Demographic and clinical characteristics of 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%)

EDSS: Expanded disability status scale, MS: Multiple sclerosis

Table 3 shows that patients with higher EDSS reported lower scores in the ABC-6 and ABC-16 scales, and differences were significant for both scales.

Discussion

The primary finding of our study revealed that the ABC-6 test is strongly correlated with measures of neurological disability level, walking and balance tests, and fatigue in PwMS. Furthermore, an almost perfect correlation was found between them. These findings provide insights into the clinical utility of the ABC-6 in pwMS by showing good validity, including criterion, convergent, discriminant, and known-groups validity.

The median ABC-16 score (83.12) was lower than that of the ABC-6 score. This result indicates that ABC-6 contains more challenging activities compared with ABC-16 for pwMS. The median EDSS score was 1.5 in our sample; however, the balance confidence level assessed using ABC-6 (73.33) was not high. This finding supports that selected activities (item 5: reach on tiptoes, item 6: standing on a chair to reach, item 13: being bumped into by people while walking through a mall, item 14: stepping off an escalator with rail, item 15: stepping off an escalator without holding onto the railing, and item 16: walking on an icy sidewalk) are challenging for pwMS.

Balance confidence refers to balance-related self-efficacy, which increases the possibility of the activity being accomplished regardless of physical (7,28). The increasing amount of evidence indicates that balance confidence as measured using the ABC-16 is a predictor of falls in pwMS (8-10). The ABC-16 has the highest explanatory value, whereas performance-based tests could not adequately explain falls in those without clinical disability (10). Few studies were reported; however, ABC-6 also has good sensitivity in distinguishing fallers or participants with high risk fall in Parkinson's disease (71.4%) and pwMS (95%), and values are similar to the ABC-16 (12,29).

Table 2. Correlation coefficients between ABC-6, ABC-16, and other outcome measures

	Median (interquartile range)	Correlation coefficient with ABC-16	Correlation coefficient with ABC-6
Criterion validity			
ABC-16 (0-100)	83.12 (58.43-95.56)	-	0.974
ABC-6 (0-100)	73.33 (45.83-95.0)	0.974	-
Convergent validity			
EDSS (0-10)	1.5 (0-2.0)	-0.668	-0.635
6MWT (m)	465 (380-520)	0.606	0.607
T25FW (s)	4.75 (4.34-5.65)	-0.614	-0.632
TUG (s)	6.78 (6.15-8.41)	-0.630	-0.635
TUG-cognitive (s)	7.69 (6.64-10.55)	-0.520	-0.533
MSWS-12 (0-54)	17.0 (12.0-29.0)	-0.811	-0.768
SLST (0-60 s)	21.87 (5.3-60)	0.572	0.573
MFIS-total (0-84)	27.0 (10.0-48.0)	-0.604	-0.582
MFIS-physical (0-36)	13.0 (4.0-21.0)	-0.679	-0.663
MFIS-cognitive (0-40)	13.0 (4.0-22.0)	-0.446	-0.421
MFIS-psychosocial (0-8)	3.0 (0-5.0)	-0.543	-0.524
SDMT	49.0 (41.0-56.0)	0.321	0.335
BVMT-R	28.0 (22.0-31.0)	0.334	0.329
BDI-II (0-63)	9.0 (5.0-15.0)	-0.423	0.384
Discriminant validity			
CVLT-II	53.0 (42.0-61.0)	0.224	0.246
ESS (0-24)	4.0 (2.0-7.0)	-0.178	-0.160

$p<0.05$ for all correlation coefficients

ABC-16: 16-item activities-specific balance confidence, ABC-6: 6-item activities-specific balance confidence, EDSS: Expanded disability status scale, 6MWT: Six-minute walk test, T25FW: Timed 25-foot walk, TUG: Timed up-and-go, MSWS-12: Multiple sclerosis walking scale, SLST: Single-leg stance test, MFIS: Modified fatigue impact scale, SDMT: Symbol digit modalities Test: BVMT-R: Brief Visuospatial memory test-revised, BDI-II: Beck depression Inventory, CVLT-II: California verbal learning test, ESS: Epworth sleepiness scale

Table 3. Comparison of ABC-6 and ABC-16 scores between pwMS with different disability levels (known-groups validity)

	Mild disability group (n=133)	Moderate-severe disability group (n=23)	p
ABC-6	83.33 (53.33-95.0)	30.0 (10.0-45.83)	<0.001
ABC-16	88.13 (70.0-97.5)	49.38 (24.06-58.44)	<0.001

ABC-16: 16-item activities-specific balance confidence, ABC-6: 6-item activities-specific balance confidence

Wood et al. (12) revealed good reliability and moderate convergent validity of the ABC-6 in pwMS. The ABC-6 was negatively correlated with physiologic profile assessment and fall history. However, this study overlooked other factors thought to be associated with balance confidence. Our previous research showed that psychosocial factors are also related to balance confidence in a large sample of pwMS (30). Depression, fatigue, and cognitive processing speed assessed using SDMT were determinants of the ABC-16. The ABC-6 was also correlated with these measurements in this present study. Our results suggest that the ABC-6 can reflect the relationship with these factors.

In accordance with previous studies on the ABC-16, the ABC-6 was also correlated with physical measurements, including T25FW, 6MWT, TUG, TUG-cognitive, MSWS-12, and balance assessment (6,31). The fact that the correlation values with physical tests are so close to the ABC-16 suggests that items included in the ABC-6 successfully reflect balance confidence. Therefore, the ABC-6 can also be used to save time in clinics or research.

Study Limitations

Most of the pwMS had mild disabilities, which could restrict the generalizability of findings. Notwithstanding this limitation, this study involves some strength, such as relatively large sample size and considerations of other dimensions that are yet to

be investigated in validity studies involving the ABC-6 scale in pwMS.

Conclusion

The ABC-6 showed good criterion, convergent, discriminant, and known-groups validity in pwMS. Our study expands the evidence promoting the utility of the ABC-6 scale to assess balance confidence in pwMS. The ABC-16 and ABC-6 were associated with disability level, physical functions, cognition, fatigue, depression, and sleepiness in pwMS and showed similar correlations with these measures. Thus, the ABC-6 can be used in research and clinical settings as it allows rapid and accurate assessment of balance confidence.

Ethics

Ethics Committee Approval: The Non-invasive Research Ethics Board of Dokuz Eylul University approved the study protocol (protocol number: 2959-GOA and approval number: 2016/27-08).

Informed Consent: Written informed consent was taken from all participants.

Authorship Contributions

Surgical and Medical Practices: C.B., S.O., Concept: Z.A., T.K., C.B., O.E., S.O., Design: Z.A., PY., C.B., O.E., S.O., Data Collection or Processing: : Z.A., PY., Analysis or Interpretation: Z.A., T.K., Literature Search: Z.A., PY., C.B., O.E., S.O., Writing: Z.A., T.K., C.B., O.E., S.O.

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RESEARCH ARTICLE

Challenges of Patients with Neuromyelitis Optica Spectrum Disorder During COVID-19 Pandemic

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Abstract

Objective: At present, millions of people have been infected and hundreds of thousands are falling dead because of Coronavirus disease-2019. People with neuromyelitis optica spectrum disorder (NMOSD) are among patients who use immunosuppressive drugs.

Materials and Methods: Registered patients with NMOSD were contacted via phone during the three-months of pandemic.

Results: Information from 45 patients was gathered, and three (8.57%) of them stopped their treatment due to fear for immunosuppression. All three were on rituximab treatment.

Conclusion: Infusion therapy was assumed to pose more fear in terms of immunosuppression on patients compared with noninfusion route of treatment.

Keywords: Multiple sclerosis, balance confidence, balance impairment, validity

Introduction

March 11, 2020 is a tragic date on which the Coronavirus disease-2019 (COVID-19) pandemic was recognized by the World Health Organization, stunning people globally (1). At present, millions of people have been infected, and hundreds of thousands are falling dead because of the virus (1). It is more stressful as it strikes the most vulnerable elders, people with chronic diseases, and those on immunosuppressants in addition to risk factors such as smoking and obesity (2-4). Demyelinating diseases get more attention for being chronic, with the usage of immunosuppressant treatments. Making definite conclusions is hard about drug usage and how doctors and people with risk factors should manage this issue due to a shortage of time because of the spread of disease (5). Diverse thoughts were presented regarding medicines used for treatment of multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) as well as for the increased risk and protective effect during the pandemic (5,6). All this information puts stress on patients diagnosed with NMOSD (7,8). NMOSD is a condition that affects the elderly population, with more severe attacks and without an immunomodulator choice of treatment as in MS (9). In addition, patients face the risk of being infected during their visits to hospitals, which is an issue during attacks or routine visits (10). Considering all these factors against patients with NMOSD, which could pose difficulties to physicians actively involved in managing these patients (11), their condition was evaluated from their point of view; what are the patients' choices, how they managed the stress when the entire world swirled in the pandemic crisis, and how they deal with sedentary lifestyles during a lockdown.

Materials and Methods

This is a cross-sectional descriptive study of patients with NMOSD registered at a tertiary care center in Izmir, Turkey. Approval was obtained from The Ministry of Health of the Turkish Republic and the ethics committee of Dokuz Eylul University. The requirement for written consent was waived. A total of 71 patients with NMOSD registered at our clinic were included.

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Participants were interviewed by phone during work hours. Phone calls were made by the Multiple Sclerosis Study Group team of Dokuz Eylul University, including a physiotherapist, psychologist, nurse, and neurologist. The inclusion criterion includes their willingness to participate. The exclusion criterion was a severe cognitive decline, which will prevent verbal communication and comprehension.

Verbal consent was obtained from all participants before the interview. All participants were asked the same questions in the same order. From March 2020 to June 1, 2020, the Turkish Government applied lockdown on weekends, travel restrictions in some areas, temporary closure of most workplaces, recommendations to stay at home, social distancing, mask-wearing, and other measures to decrease the risk of spreading COVID-19. This study aimed to evaluate patients in this timeframe. Out of 71 patients, a total of 45 were successfully reached out to. Of the 26 patients not included in this study, 5 did not want to participate and 21 were out of reach or did not answer the phone call; several attempts were made each time. Data regarding gender, age, disease duration, marital status, treatment, and information about the number of people they live together were collected. Next, questions related to COVID-19 pandemic were asked: their level of compliance with a stay at home recommendations; have they been tested positive for COVID-19; how the epidemic influenced their worries about NMOSD; the effect of lockdown in their routine controls, medical supply, and hospital visits for infusion treatment; were they able to practice their normal controls as scheduled; and what were their considerations about choices of treatment. All participants are registered in the Dokuz Eylul University database; thus, the latest expanded disability status scale (EDSS) for each patient were acquired from our registry. During the phone call, patients were asked about any changes in their condition related to NMOSD.

Statistical Analyses

Descriptive analyses were performed using the International Business Machines Statistical Package for the Social Sciences 26.0 software. Chi-square tests were used to compare categorical data. The significance level was set at $p<0.05$.

Results

Of the 71 registered patients with NMOSD, a total of 45 patients (37 female, 8 male) were successfully reached out to. The mean EDSS score of study participants was 2.31±2.32 (range: 0-7.5) (Table 1).

Six patients had got tested for COVID-19, and none were positive. Four patients had stopped their treatment during the restriction period (Table 2).

Five patients (11.1%) had decreased the time spent on physical exercises, six (13.3%) spent more time on sportive activities compared with before the pandemic, and 10 (22.2%) continued as usual. Before the lockdown, 10 patients did not use medication for NMOSD (patient's choice), 16 were on rituximab, 15 on azathioprine, and four on monthly methylprednisolone infusion. During the lockdown, three patients missed their routine control visits, two of them were on azathioprine, and one was receiving monthly methylprednisolone infusions (Table 3).

Out of 45 patients, only six (13.3%) were afraid of contracting COVID-19 (Table 4).

Those on therapy were divided into two groups with infusion (rituximab and monthly methylprednisolone) and non-infusion therapies (azathioprine). Chi-square tests was performed to compare delayed therapy between patients receiving infusion versus noninfusion therapy, Fisher's Exact test p=0.233 (2-sided) (Table 5).

Table 1. Patient characteristics

	N (45)	Mean	SD
Sex	F: 37 M: 8	-	-
Age	-	43.82	12.42
EDSS	-	2.31	2.32
Duration of disease	-	7.87	8.04

N: Number, SD: Standard deviation, EDSS: Expanded disability status scale

Table 2. Delay in treatment

	N (%)
Issues with drug supply	1 (25)
Fear of going out	2 (50)
Pregnancy	1 (25)
Total	4 (100)

Table 3. Delay in scheduled controls

	N (%)
Fear of going out	3 (6.7)
Canceled but had a phone-visit	7 (15.6)
Travel restrictions	2 (4.4)
No delay	33 (73.3)
Total	45 (100)

Table 4. How pandemic influenced your considerations about NMOSD

	N (%)
More worried about contracting COVID-19	6 (13.3)
NMO could get worse	15 (33.4)
No change/NMO is under control	24 (53.3)
Total	45 (100)

COVID-19: Coronavirus disease-2019, NMO: Neuromyelitis optica, NMOSD: Neuromyelitis optica spectrum disorder

Patients who were worried about contracting COVID-19 and those who were stressed about worsening the disease were categorized as a group with "worries," whereas others were grouped as "nonworried," and chi-square test was used to compare those who were on treatment versus those who were not. Continuity correction for chi-square came out as p=0.100, 2-sided (Table 6).

Table 5. Chi-square tests 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.36

Treatment option				
		Non-infusion	Infusion	Total
Treatment delay	No delay	Count 15	15	30
		Expected count 13.6	16.4	30.0
	delay	Count 0	3	3
		Expected count 1.4	1.6	3.0
Total		Count 15	18	33
		Expected count 18.0	18.0	33.0

Table 6. Chi-square tests 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.13

		Disease expectation		
		No worries	Worried	Total
Treatment	No treatment	Count 3	8	11
		Expected count 5.9	5.1	11.0
	Treatment	Count 21	13	34
		Expected count 18.1	15.9	34.0
Total		Count 24	21	45
		Expected count 24.0	21.0	45.0

Discussion

In this cross-sectional descriptive study, we tried to check if patients had stopped their treatment, how their drug supply was, how their scheduled hospital visits were managed, and how had the pandemic influenced their life regarding their disease. All registered patients diagnosed with NMOSD were contacted via phone. Out of the 71 registered patients, 45 were successfully reached out to. NMOSD has more severe attacks compared with MS, and incomplete recovery is another devastating feature that leads to accumulating disability with each exacerbation (12). Thus, preventive treatment is strongly recommended for all patients (13). Therefore, we expected that patients with NMOSD will be stricter with their treatment plan. Of those on treatment, only four (11.4%) had stopped their medicine, of which three (8.57%) were due to fear of immunosuppression. Comparing these results to patients with MS who stopped their treatment during the pandemic is necessary to see the actual influence of disease characteristics on adherence to therapy. During the three-month recommendation for not going out and weekend lockdown, visits were organized remotely via phone for patients who have scheduled controls on these days. A total of 12 participants had scheduled control during the lockdown. We managed to reach only seven of them. Two patients missed their control visit because of travel restrictions in their district, and the other three missed their scheduled control because of fear of going out. Unfortunately, they were not phone-visited, and two of them continued using azathioprine tablets. The other patient was on monthly methylprednisolone and missed it because of the fear of going out. Whether two patients on azathioprine have continued their treatment if they were on infusion therapy is unknown. Regardless, three patients demonstrated to be more worried about contracting COVID-19, and with a chance to stay out of contamination, they probably continued the treatment of NMOSD. This brings to light an issue of a safe environment for treatment and scheduled visits, and may include safe traveling to the hospital; it is an idea derived out of a small number of cases. Trials with more extensive sample data are warranted. Much speculation was observed about COVID-19 and immunosuppressant usage. Published literature mainly consists of cases showing various patient responses with use of immunosuppressant that contracted COVID-19 (5,6). This situation may agitate patients with NMOSD on treatment and force them to halt their ongoing treatment. The future regarding COVID-19 is unknown, but we know for sure that NMOSD would cause severe disability if left untreated. In addition, the biological activity of treatment choices available for NMOSD is delayed by 4-6 months after initiation (13). Making any conclusions about continuation of the treatment based on individual cases is unwise. Randomized clinical trials are necessary to validate these assumptions.

Among the therapy choices of our patients, 15 were on azathioprine, 16 on rituximab, 4 on methylprednisolone, and 10 without any maintenance treatment (patient's choice). All four patients who stopped their treatment were on rituximab treatment, and one stopped the treatment due to pregnancy. Patients could acknowledge infusion therapy as a more definitive treatment option that decreases immunity as opposed to tablets. The crosstabulation test showed no statistically significant result (p=0.233) regarding the relationship between those who stopped their treatment and therapy options. This could be attributed to the small number of cases in the treatment delayed groups (3) and the total number of participants. The difference between those undergoing treatment and those who did not undergo treatment due to worries about COVID-19 and NMOSD were also evaluated, wherein any statistically significant result was not observed (p=0.100), which could be attributed to the small number of participants. Limitations of

our study include the small number of participants and the fact that 26 (36.6%) patients were excluded. Thus, their influence on our results is unknown.

Conclusion

Results revealed that only those who were on infusion therapy stopped the treatment because they had no scheduled control during the lockdown and phone-visit could not be completed, which make us believe that people need more explanation from their doctors and be protected from the influence of social media or any information coming from sources other than their health institution. We consider this as our future reference in dealing with patients on infusion therapies, should any situation like lockdown or second wave of spread occur.

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Ethics

Ethics Committee Approval: The research protocol was approved by Dokuz Eylul University Ethics Committee (date: 06.07.2020, code: 2020/17-26).

Informed Consent: Verbal informed consent was obtained prior to the interview.

Authorship Contributions

Concept: S.O., C.B., P.H., O.S., A.T.O., Z.A., S.D., Design: S.O., C.B., P.H., O.S., A.T.O., Z.A., S.D., Data Collection or Processing: S.O., C.B., P.H., O.S., A.T.O., Z.A., S.D., Analysis or Interpretation: S.O., C.B., P.H., O.S., A.T.O., Z.A., S.D., Literature Search: S.O., C.B., P.H., O.S., A.T.O., Z.A., S.D., Writing: S.O., C.B., P.H., O.S., A.T.O., Z.A., S.D.

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RESEARCH ARTICLE

Relationship between Physical Disability and Black Holes in Multiple Sclerosis: Upper Extremity Functions - an Important Parameter

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Abstract

Objective: Typical lesion locations in multiple sclerosis (MS) and hypointense lesions that persist >6 months on T1-weighted magnetic resonance imaging (MRI) are known as black holes. This study aimed to investigate the potential relationship between brain MRI lesion localization and the presence of black holes and upper extremity function in patients with MS in remission.

Materials and Methods: The nine-hole peg test (NHPT), timed 25-foot walk test (T25FWT), and expanded disability status scale (EDSS) scores were calculated with neurological examinations in the period when MRI was performed (±1 week).

Results: This study included 47 patients diagnosed with MS. The mean patient age was 34.24±8.38 (19-54) years. The mean EDSS score of the study group was 1.7±0.85 (0-3). The mean NHPT time was 17.27±2.70 s (13.74-27.23 s). The mean T25FWT time of the study group was 4.35±0.62 s (3.30-6.05 s). Juxtacortical lesions were present in 46 (97.0%) patients, cortical lesions in 2 (4.3%), brain stem lesions in 38 (80.9%), and cerebellar lesions in 16 (34%). Permanent black holes were found in 37 (78.7%) patients, with more than one black holes being detected in 33 of these patients. The mean NHPT time was significantly longer in patients with permanent black holes detected by MRI of the brain than in those without black holes (p=0.034). A weak correlation was found between the EDSS score and NHPT time (r=0.192, p=0.046).

Conclusion: The presence and number of permanent black holes can be used as a marker of disability. Upper extremity functions may well represent disability, especially in patients with low EDSS scores.

Keywords: Multiple sclerosis, physical disability, upper extremity functions, black holes

Introduction

Various clinical symptoms may be seen in multiple sclerosis (MS), depending on the affected region of the central nervous system, such as weakness in one or more extremities, optic neuritis, paresthesia, diplopia, and bladder problems (1). The first clinical manifestation that produces findings such as medulla spinalis involvement, isolated optic neuropathy, or hemisphere involvement in which MS-specific lesions are observed by magnetic resonance imaging (MRI), but the spread criteria are not met at that time, is known as a clinically isolated syndrome (CIS) (1,2). MRI is crucial in the timing of diagnosis of conversion from CIS to MS and in monitoring the disease course and effectiveness of treatment (3). While lesions can be seen in different locations, periventricular, corpus callosum, juxtacortical, brainstem, spinal cord, temporal lobe, optic nerve, cerebellum, and cerebellar peduncle involvement is typical for MS (4). Although the morphological characteristics of the lesions have been described in greater detail in recent years (5), typical features are an ovoid shape, perpendicularity to the ventricle, and size >3 mm (4).

In addition to the typical lesion locations in MS, hypointense lesions persisting for >6 months on T1-weighted MRI are known as "black holes," and these show permanent axon loss (6). The Barkhof-Tintore criteria employed to evaluate MRI lesions in the diagnosis of MS were subsequently revised, and the Swanton criteria began its implementation through a modification of the 2010 McDonald criteria. However, black holes were not included in either the McDonald or MAGNIMS MRI diagnostic

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criteria. However, the presence, numbers, and volume of black holes are thought to be important in patient follow-up because of their relatively simple evaluation and close association with a physical disability. Although upper and lower extremity functions are closely related to physical disability in MS, lower extremity functions are more markedly affected at higher expanded disability status scale (EDSS) scores, while upper extremity functions are often overlooked. In a previous study, EDSS and upper extremity functions were found to be more significantly associated with lower extremity functions (7). The present study investigated the potential relationship between brain MRI lesion localization and the presence of black holes and both upper and lower extremity functions in patients with MS in remission.

Materials and Methods

Patient Enrolment

Patients under follow-up in our MS clinic and diagnosed with relapsing-remitting MS (RRMS) according to the McDonald 2017 criteria but in the remission period were included in the study. The remission period is defined as MS that is not in the attack or progression period, at least 3 months after the attack. In this cross-sectional study, patients who underwent brain MRI performed with a 1.5 Tesla scanner were routinely evaluated in the remission period using T2-weighted axial, sagittal, fluid-attenuated inversion recovery (FLAIR) axial, and T1 axial sections. Lesion localizations at MRI were classified as periventricular, juxtacortical, cortical, brainstem, and cerebellar lesions, and the presence of black holes was also assessed. Spinal lesions were not included in the study, since not all patients had cervical MRI data, and the relationship between black hole presence and disability was investigated.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The data was obtained from our hospital records prospectively for the study. Ethics approval was obtained from the ethics committee of Dokuz Eylül University and written informed consent was obtained from the patients.

Various scales were employed to evaluate disability during patient follow-up, and the most widely used was the EDSS (8). EDSS scores were calculated as a value between 0 and 10 based on functional scoring, including visual, brainstem, cerebellar, pyramidal, bowel, and bladder functions, sensory functions, and ambulation (9). One of the principal disadvantages of the EDSS, used in MS for many years, is that upper and lower extremity functions cannot be separately evaluated.

The nine-hole peg test (NHPT) is regarded as the gold standard in the assessment of upper extremity skills and is frequently applied to patients with MS (10). The timed 25-foot walk test (T25FWT) is employed to evaluate the lower extremity skills of patients with MS (11). In this study, the EDSS scores of the patients were calculated with neurological examinations in the period when MRI was performed (±1 week). Moreover, NHPT was assessed for upper extremities, and the mean times were noted. The T25FWT was repeated twice, and the mean times were recorded. All patients were examined and physically evaluated by a single physician, and MR images were evaluated blindly by another physician (both physicians are MS specialists).

Statistics Analyses

Obtained data were statistically analyzed using the SPSS 19.0 package program. Descriptive statistics of the study variables are shown as mean, standard deviation, and minimum-maximum values, and descriptive statistics of categorical variables are shown as frequency and percentage. The conformity of the variables to the normal distribution was examined by both visual and normal distribution tests. Independent sample t-test analysis was used for two-group comparisons of normally distributed variables, and the chi-square test was used for categorical variables. The relationship between continuous variables was analyzed by Pearson or Spearman correlation analysis when necessary, according to its suitability for normal distribution; p-value <0.05 indicated significance.

Results

The study included 47 patients diagnosed with MS based on the McDonald 2017 criteria and currently in remission (F/M, 38/9). The mean patient age was 34.24±8.38 (19-54) years. The first clinical event was polysymptomatic in 59.6% of the patients. Disease onset with brainstem, motor, cerebellar, and sphincter involvement, a poor prognostic factor marker, was noted in 31 (66%) cases. The mean disease duration of the study group was 19.08±12.22 months, and the mean EDSS score was 1.7±0.85 (0-3) points. Upper and lower extremity functions were evaluated using the NHPT and T25FWT, respectively. The mean NHPT time of the patients was 17.27±2.70 (13.74-27.23). The mean T25FWT time of the study group was 4.35±0.62 s (3.30-6.05 s).

Brain MRI examinations were performed using T2-weighted axial, sagittal, FLAIR axial, and T1 axial sections. Periventricular lesions were present in all patients. Juxtacortical lesions were found in 46 (97.0%) patients, cortical lesions in 2 (4.3%), brain stem lesions in 38 (80.9%), and cerebellar lesions in 16 (34%). Permanent black holes were found in 37 (78.7%) patients, with more than one black holes being detected in 33 of these (89.1%) (Figure 1). When the group with black holes and the group without black holes were compared in terms of disease duration, no significant difference was observed between the two groups (p=0.08).

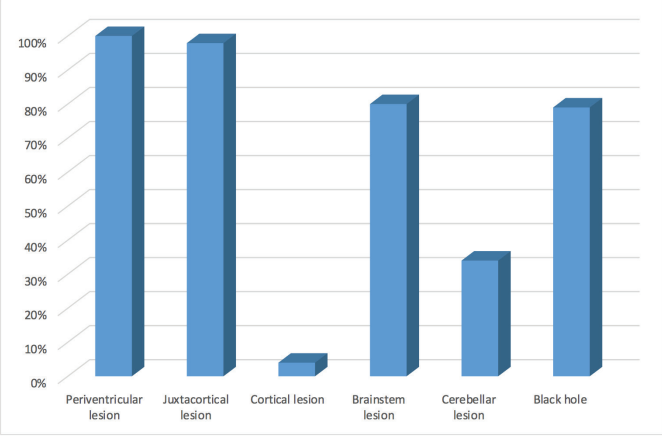

Figure 1. Brain MRI lesion characteristics of the study group

MRI: Magnetic resonance imaging

The mean NHPT time was significantly longer in patients with permanent black holes detected by brain MRI than in those without black holes (p=0.034). A weak correlation was determined between the EDSS score and NHPT (r=0.192, p=0.046). No significant difference was found in the T25FWT times between patients with and without permanent black holes (p=0.062). No significant correlation was observed between EDSS and T25FWT time (p=0.058). In addition, no significant difference was found in lesion localization and physical parameters in MRI.

Discussion

MRI is crucial in the diagnosis and follow-up of MS and is one of the main guides in both prognosis and evaluation of treatment response. Although T2 hyperintense lesions detected at MRI are critical in the diagnosis of MS, their correlation with both physical and cognitive disability is low (12-14). Moreover, although the number of T2 hyperintense lesions at disease onset gives some indications about the prognosis, the association of lesion burden with clinical manifestations decreases as the disease progresses (12). T1 hypointense lesions, a powerful indicator of axonal damage and demyelination, that exist >6 months are known as black holes, and studies have revealed a closer relationship between physical disability and T2 hyperintense lesions (15). A relationship has been shown between the intensity of the hypointensity and axonal damage, and a study concluded that axonal damage increases in line with hypointensity (16). In addition, a potential association was found between the intensity of T1 hypointense lesions and EDSS (16). Previous studies have shown that an increase in the number or volume of black holes is associated with a poor clinical course, the T1 lesion burden is associated with EDSS scores, and increasing T1 lesions are associated with a worsening clinical course (17).

Although physical disability in MS is most frequently evaluated using the EDSS, this system has several limitations, such as the fact that it does not assess the cognitive field or upper and lower extremity functions. However, the evaluation and regular monitoring of both upper and lower extremity functions are significant in clinical follow-up. In addition, lower upper extremity functions can be used in combination with the EDSS when evaluating physical disability in MS. In a previous study, patients with MS (pwMS) with two fundamental motor tasks were evaluated and compared with healthy controls; pwMS performed worse than HC on both tasks. Moreover, upper and lower extremity motor skills in pwMS worsen as disability increases (18). In another study, progressive decline in lower extremity motor performance and hand functions with each increase in EDSS score suggests that 9-HPT is a good marker of decreased hand function and should be included in the clinical monitoring of patients (19).

In the present study, upper and lower extremity functions were evaluated with 9-HPT and T25FWT. These parameters and the relationship between EDSS and presence of black holes were examined. In this study, while no connection was detected between black holes, regarded as evidence of neurodegeneration, and EDSS, a significant correlation was found between the presence of permanent black holes and NHPT used to assess upper extremity functions. The absence of any association between EDSS and permanent black holes may be due to the inadequacy of EDSS in evaluating upper extremity functions. Alternatively, this may be due to our patient's low physical disability scores assessed using the EDSS. In the present study, no relationship was determined between black holes and lower extremity functions, an important physical status parameter. While this can be explained by the low physical disability scores of the study group, it can also be regarded as a finding: although T25FWT is used for lower extremity functions, it is insufficient for showing lower limb capacity despite indicating lower extremity performance. A study evaluating the association of several imaging modalities with worsening clinical disability scores over 10 years in RRMS showed that the number and volume of permanent black holes exhibited the best performance (20).

In addition, imaging and neuropathology comparisons of more than 100 MS lesions revealed a powerful association of the degree of hypointensity with axonal density (15).

Contrast-enhancing lesions detected by MRI are also significant in the diagnosis and follow-up of MS since they are employed as evidence of spread over time in MS diagnostic criteria and as an indicator of disease activation. However, when performing contrast-enhanced MRI, it is difficult to evaluate betweenwhiles because of challenges in the application, such as the dose and timing of administration of contrast agent. No biomarker of neurodegeneration, which plays an important role in the progression and for which treatments are often inadequate, has emerged other than contrast-enhancing lesions, regarded

as evidence of disease activation and inflammation in MS. The presence of permanent black holes has the potential for use as a marker of neurodegeneration and as an outcome measure in trials of potential protective agents. In a previous study, black hole development was evaluated over the course of 3-year interferon beta-1b therapy in an RRMS group, and the number of contrast-enhancing lesions after 1 year of treatment was found to predict the change in black hole volume over the following 2 years. In that study, the black hole volume remained stable in patients without contrast-enhancing lesions but increased in the patient group with contrast-enhancing lesions (21). In the present study, contrast-enhancing lesion analysis could not be performed because not all patients had contrast-enhanced imaging, and this was considered as a limitation of this study.

Greater use of the detection of permanent black holes and even their degree of intensity are expected, which can be performed using standard T1-weighted images and commercial imaging software when performing MRI in the follow-up of the disease course or treatment of MS. An assembly of MS specialists in 2008 concluded that black holes, optical coherence tomography, brain volume, and magnetization transfer rate are criteria that can show neurodegeneration (22). These criteria may be employed more frequently for follow-up purposes and as a progression indicator in the future clinical follow-up of patients with MS. However, a standardized approach can be established by demonstrating the correlation of black holes, indicators of permanent axonal loss, with both physical and cognitive parameters by studies involving large sample sizes.

Study Limitation

Beside of the small number of patients in this study is that spinal lesions cannot be included when assessing upper extremity functions because not all patients have undergone a spinal MRI.

Conclusion

Upper extremity functions are often overlooked during routine evaluation. This may be related to the need for equipment for its assessment and the insufficient attention to upper extremity functions. However, the contribution of upper extremity functions, which significantly affect the daily life of an individual, to the disability of the disease should not be ignored. In addition, showing the relationship between upper extremity functions and the presence of black holes, which is a poor prognostic marker, is important, especially in pwMS with low EDSS, and our findings can draw attention to upper extremity functions.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the ethics committee of Dokuz Eylül University.

Informed Consent: Informed consent from all participiants was obtained for the study.

Authorship Contributions

Surgical and Medical Practices: B.P.C., G.K., Concept: B.P.C., M.A., S.O., Design: B.P.C., M.A., S.O., Data Collection or Processing: B.P.C., G.K., S.O., Analysis or Interpretation: B.P.C., S.O., Literature Search: B.P.C., G.K., M.A., S.O., Writing: B.P.C., G.K., M.A., S.O.

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RESEARCH ARTICLE

The Relationship Between Fatigue and Lower Extremity Function in People with Multiple Sclerosis with the Absence of Clinical Disability

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Abstract

Objective: Impairment in the lower extremity function and mobility is a symptom often among people with multiple sclerosis (pwMS), even in the absence of clinical disability. Fatigue is one of the most common symptoms reported by at least 80% of pwMS during any disease. This study investigated the relationship between fatigue and lower extremity function, which is assessed by the Six Spot Step test (SSST) in pwMS with the absence of clinical disability.

Materials and Methods: A total of 477 pwMS with an Expanded Disability Status scale (EDSS) score of ≤1.5 were included in the study. The SSST was used to evaluate the complex sensorimotor function of lower extremity function, such as lower extremity muscle strength, coordination, and balance. Participants with SSST performance above 8 seconds were classified as impaired. In addition, a Modified Fatigue Impact scale-5-item version was used to evaluate perceived fatigue. Demographic (gender, age) and clinical data (disability level and disease duration) of the participants were obtained from interviews and medical records.

Results: Impairment in SSST performance was detected in 171 (35.85%) pwMS. Univariate regression analysis revealed that fatigue was significantly associated with the SSST ($p<0.001$). Furthermore, fatigue was still an associated factor in the multivariate regression analysis after adjusting for age, gender, and disability level ($p<0.001$).

Conclusion: This study showed that even in the absence of disability, fatigue could be related to impairment in SSST performance. Considering the reflection of SSST performance on functional mobility, ambulation, and daily life in pwMS, it is essential to include the fatigue in the evaluation and treatment of pwMS with the absence of clinical disability.

Keywords: Lower extremity function, mobility, Six Spot Step test, fatigue, gender

Introduction

Multiple sclerosis (MS) is a chronic, progressive, demyelinating, and multifactorial disease of the central nervous system, causing various symptoms and signs (1). Impairment in the lower extremity function and mobility is a symptom quite often among pwMS. According to community-based studies, having walking difficulty is a most compelling symptom for both pwMS and their care partners (2). Martin et al. (3) investigated the balance and walking patterns of pwMS with no pyramidal impairment, according to the Expanded Disability Status scale (EDSS) pyramidal functional system. As a result, even absence of clinical disability, pwMS have a slower, lower stride length, and more extended double limb support walking patterns than healthy controls. This finding was further confirmed by Liparoti et al. (4) by comparing the walking patterns of pwMS and healthy controls using a temporal-spatial gait analysis system. They showed that pwMS had changes in gait patterns in walking speed, step features such as length and width, and double support time. Besides, gait abnormalities and balance problems are occurring in advanced stages of MS and affect the pwMS with the absence of clinical disability (5).

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Fatigue is one of the most common symptoms reported by at least 80% of people with MS (pwMS) during any period of the disease regardless of disability level and duration (6). Even though the pathophysiological mechanism of fatigue is complicated and is still not completely understood, it is well-known that fatigue is related to anxiety, depression, and sleep quality in pwMS (7). In addition, fatigue has adverse effects on physical performance and psychological state, and socio-economic statuses such as early retirement, reduction in working hours, and use of health services (8). However, there is limited evidence and controversial results regarding the relationship between fatigue and lower extremity function in the MS population (9-13). Moreover, no study investigated this relationship in the pwMS with the absence of clinical disability.

Walking difficulties in pwMS could be related to many factors such as muscle weakness, cerebellar ataxia, dynamic balance impairment, and loss of coordination (14). The tests used in the clinical measurement, such as Timed 25 Foot Walk test, Timed and Up Go, and Six Minute Walk test, focus on walking speed, balance, and walking endurance (15). However, the Six Spot Step test (SSST), which was developed as the lower extremity equivalent of the 9-hole peg test, is a more complex test than unidirectional walking on a flat surface, which evaluates complex sensorimotor functions of walking such as lower extremity muscle strength, spasticity, coordination, and balance (16). For this reason, SSST could be better to detect the disability that may occur for any reason in lower extremity function than another clinical measurement. Therefore, the main aim of the current study was to investigate the relationship between fatigue and lower extremity function, assessed by SSST in pwMS with the absence of clinical disability. The second aim was to determine the other possible risk factors that could be associated with lower extremity function, such as the demographic and clinical characteristics of participants.

Materials and Methods

Study Design

This cross-sectional study was performed at the MS Clinic of Dokuz Eylul University. This study was performed in line with the principles of the Declaration of Helsinki (as revised in Brazil 2013). The data included in the analyses were collected from another open-ended study labeled, "Follow-up of physical, psychosocial and cognitive influences in persons with multiple sclerosis: a prospective cohort study" (ClinicalTrials.gov Identifier: NCT03878836). The study protocol was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University Ethics Committee (protocol number: 2959-GOA and approval number: 2016/27-08). Furthermore, this study was accomplished in line with the principles of the Declaration of Helsinki (as revised in Brazil 2013), and written consent was received from all participants.

Participants

The inclusion criteria had MS based on the 2017 version of McDonald's criteria, ≤1.5 scores on the EDSS (equal to no disability), and a relapse-free period of 30 days. The exclusion criteria were as follows; having another neurological disorder and having any orthopedic surgery history comprising the ankle-foot, knee, hip, or spine, affecting gait and balance.

Outcome Measures

Demographic and clinical characteristics of the pwMS, such as age, gender, and disease duration, were recorded from the medical report.

EDSS scoring, as the most common measure for the disability level in pwMS, was performed according to the neurological examination of functional systems, which consisted of pyramidal, cerebellar, brainstem, sensory, bladder, and bowel, visual and cerebral (17). The ambulatory state of the patients was also recorded. The same senior MS neurologist examined all participants and also calculated their global EDSS scores.

The Modified Fatigue Impact scale-5 items version presents an evaluation of the perceived fatigue level. It consists of 5 items, and participants rate questions from 0 (never) to 4 (almost always) according to experiences during the past four weeks. The total score ranged from 0 to 20. The increase in the total scores indicates higher impacts of fatigue on daily life (18). The original version of the Fatigue Impact scale was found as reliable and valid for Turkish pwMS (19).

The SSST evaluates the complex sensorimotor function of gaits, such as lower extremity muscle strength, coordination, and balance. The test includes six items of 20-cm width circles and a 1x5 m test path. Five wooden cylinder circles consisting of 134 grams are located in the center of each circle, without one at the starting point. The participants were asked to pushes the cylinder blocks out of the area as fast as possible using the lateral and medial surfaces of the foot alternately. Before the test, the dominant foot of the participant was questioned by the physical therapist (16). Therefore, the test started with the dominant foot and was performed as four trials (medial and lateral of the dominant leg, medial and lateral of the non-dominant leg, respectively)-the average time of four trials as recorded as the SSST score. Participants with SSST performance above eight seconds were classified as impaired (20).

Statistical Analysis

The Kolmogorov–Smirnov test and histograms were used to check the normal distribution of data. The multivariate analysis of covariance test was performed to test the differences between the groups for impaired in SSST and those non-impaired. Covariates included age, gender, the EDSS score, and disease duration. Univariate and multivariate logistic regression

were used to determine whether impairment in SSST and age, gender, the EDSS score, disease duration, and fatigue are related. Statistical significance was set at p<0.05. Data were analyzed using the IBM® SPSS® Statistics software (Version 25.0. Armonk, NY: IBM Corp.) (Table 1).

Result

Four hundred and seventy-seven pwMS were included in the data analysis. Disability in SSST performance was detected in 171 (35.85%) pwMS. There was a significant difference in age, gender, the EDSS score, disease duration, and fatigue between people with impairment in SSST and non-impaired participants (p<0.05) (Table 1).

Univariate regression analysis revealed that fatigue was one of the related factors with SSST (OR= 1.090; 95% CI:1.048-1.135, p<0.001). In addition, there was a relationship between the impairment in SSST performance and fatigue after adjustment for age, gender, the EDSS score, and disease duration (OR= 1.095; 95% CI: 1.047-1.146, p<0.001). Table 2 presents the detailed information related factors with the impairment in SSST performance.

Discussion

The current study has indicated that fatigue, gender, and age are related to SSST performance in pwMS with an absence of clinical disability. Additionally, according to the cut-off score of eight-second recommended by Callesen et al. (20) impairment in SSST performance was detected in 35.85% of our participants. The recent systematic review, which describes the gait patterns of pwMS, showed that gait abnormalities detected via threedimensional capture systems occur even minimally disability group of MS (21). Ayan et al. (22) also reported gait impairment in pwMS with the absence of clinical disability using clinical measurement. Remarkably, this study emphasized that even pwMS with an absence of clinical disability have impairment in the lower extremity function. Because the SSST includes complex sensorimotor functions of walking such as lower extremity muscle strength, spasticity, coordination, and balance, it is worth evaluating the related factors that can affect the performance of SSST.

The present study includes the first assessment that evaluated the relationship between fatigue and lower extremity function in pwMS with the absence of clinical disability. Larocca (2) investigated the MS symptom that most affected daily life, which they experienced at least two times during one week. They showed that fatigue was the symptom that pwMS reported and challenging most, with a rate of %76. Besides, Koch et al. (23) reported that being fatigue in MS is not related to age, disease duration, gender, disability level, and disease course. In addition, Kalron (10) classified the pwMS as fatigued and non-fatigued to examine the association between fatigue

Table 1. Demographic and clinical characteristics of the participants

	All (n=477)	Impaired (n=171)	Non-impaired (n=306)	F	p	Observed power
Age (years)	33.96 (9.74)	37.74 (10.14)	31.75 (8.45)	44.456	**<0.001**	1.000
Gender, n (%)						
Female	355	150 (87.7)	205 (67.0)	25.609	**<0.001**	0.999
Male	122	21 (12.3)	101 (33.0)			
EDSS score, possible range: 0-10	0.59 (0.65)	0.68 (0.67)	0.53 (0.63)	4.273	**0.039**	0.541
Disease duration (years)	5.86 (5.90)	7.21 (6.46)	5.14 (5.47)	13.647	**<0.001**	0.958
MFIS-5, possible range: 0-20	5.70 (4.79)	6.95 (5.33)	4.96 (4.31)	18.086	**<0.001**	0.989

Significant p values are presented in bold, values are presented as mean (SD) unless specified, EDSS: Expanded disability status scale, MFIS: Modified fatigue impact scale- 5-item version

Table 2. Possible factors related to the impairment in SSST

	Impairment in Six Spot Step test					
	Univariate			Multivariate		
	OR	95.0% CI	p	OR	95.0% CI	p
Age	1.072	1.049-1.096	**<0.001**	1.070	1.044-1.096	**<0.001**
EDSS	1.410	1.056-1.884	**0.020**	1.014	0.729-1.411	0.935
Disease Duration	1.060	1.026-1.094	**<0.001**	1.025	0.987-1.065	0.195
Gender (ref = female)	3.519	2.103-5.890	**<0.001**	3.525	2.024-6.138	**<0.001**
Fatigue	1.090	1.048-1.135	**<0.001**	1.095	1.047-1.146	**<0.001**

OR: Odds ratio, CI: Confidence interval, SSST: Six spot step test

and spatio-temporal parameters of walking by the treadmill. He showed that pwMS with fatigue had a smaller step, shorter stride length, prolonged stance, double support phase, and a shorter single support phase than pwMS without fatigue. As a result, they showed increased fatigue levels in the lower walking speed group than the normal walking speed group. Also, they reported a significant moderate negative correlation between perceived fatigue and walking speed during the short walking test, which is assessed with the 10-meter walking test. Similarly, we found that perceived fatigue is one of the related factors with the lower extremity function.

There is a difference between females and males regarding walking speed, cadence, and step length in the general population. Also, men have more hip and knee flexion range than women (24). Existing evidence shows that the female/male ratio suffering MS is 2.3-3.5:1, and the progression is worse for men than women regardless of disease course (12). However, there are limited studies that investigate the effects of gender on the walking pattern in MS. Pau et al. (25) investigated the differences between men and women regarding spatio-temporal and kinematic gait parameters. They found that men have reduced ankle plantar-flexion, increased knee flexion, and hip flexion than women.

On the other hand, Klineova et al. (26) demonstrated no association between the Timed 25 Foot Walk test and gender. Interestingly, in our study, women have a longer SSST average time than men. This can be explained by men's hip and knee range of motion demonstrated by Pau et al. (25). While performing the SSST, during pushes the cylinder blocks out of the area, it could take advantage for the benefit of the men. It is desirable for future work, effects of the gender on lower extremity function in MS.

Study Limitations

There are some limitations to the current study. First, we did not use the kinetic and kinematic methods, giving more detailed information about impairment in the lower extremity function. Second, we did not assess the psychosocial aspect of the participants, such as depression, anxiety, or quality of life, affecting the perceived fatigue level. However, the strength of this study is that we used large sample sizes, which can give more solid results to the relationship between fatigue and lower extremity function.

Conclusion

This study includes the evidence that the walking performance of MS patients without a significant disability may decrease due to fatigue and showed that the SSST could be used to measure fatigue-related lower extremity performance reduction. Considering the reflection of SSST performance on functional mobility, ambulation, and daily life in pwMS, it is important to include the fatigue in the evaluation and treatment of pwMS with the absence of clinical disability.

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Ethics

Ethics Committee Approval: The research protocol was approved by Dokuz Eylul University Ethics Committee (protocol number: 2959-GOA and approval number: 2016/27-08). This study was performed in line with the principles of the Declaration of Helsinki (as revised in Brazil 2013).

Informed Consent: Written consent was received from all participants.

Authorship Contributions

Surgical and Medical Practices: C.B., S.O., Concept: A.T.O., S.D., O.E., C.B., S.O., Design: A.T.O., S.D., O.E., C.B., S.O., Data Collection or Processing: A.T.O., S.D., Analysis or Interpretation: A.T.O., Literature Search: A.T.O., S.D., O.E., C.B., S.O., Writing: A.T.O., O.E., S.O.

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