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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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Each manuscript submitted to the *Journal of Multiple Sclerosis Research* is subject to an initial review by the editorial office to determine if it is aligned with the journal's aims and scope and complies with essential requirements. Manuscripts (all double-blind and peer-reviewed) sent for peer review will be assigned to one of the journal's associate editors, who is an expert on the manuscript's content. During the review, the statistics department editor will evaluate articles that need detailed statistical evaluation. All accepted manuscripts are subject to English language editing. Once papers have been reviewed, the reviewers' comments are sent to the editor, who will make a preliminary decision on the paper. At this stage, based on the feedback from reviewers, manuscripts can be either accepted or rejected, or revisions can be recommended. Following initial peer review, articles judged worthy of further consideration often require revision. Revised manuscripts generally must be received within 3 months from the date of the initial decision and must include "point-to-point response to the comments of reviewers" and a copy of the revised text by highlighting the changes made in the revised manuscripts. Extensions must be requested from the associate editor at least 2 weeks before the 3-month revision deadline expires; *Journal of Multiple Sclerosis Research* will reject manuscripts received beyond the 3-month revision deadline. Manuscripts with extensive revision recommendations will be sent for further review (usually by the same reviewers) upon their re-submission. When a manuscript is finally accepted for publication, the technical editor will make a final edit, and a marked-up copy will be e-mailed to the corresponding author for review and for any final adjustments.

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.

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

Title Page

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;

- It is the report of a study written by the researchers who actually did the study.
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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.

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

References: References should be cited in the text, tables, and figures with numbers in parentheses. References should be numbered consecutively according to the order in which they first appear in the text. All authors should be in the references. Journal of Multiple Sclerosis Research research adheres to the NLM style.

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.

INSTRUCTIONS TO AUTHORS

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.

Figures: Figures should be professionally drawn and/or photographed. Figures should be numbered according to the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure should be accompanied by a legend that does not exceed 50 words. Abbreviations must be used only if they have been introduced in the text. Authors are also required to provide the level of magnification for histological slides. The internal scale must be explained, and the staining method used must be identified. Figures should be submitted as separate files, not in the text file. High-resolution image files are not preferred for initial submission as the file sizes may be too large. The total file size of the PDF for peer review should not exceed 5 MB.

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:

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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.

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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.

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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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Submitted manuscripts are also subjected to the evaluation of plagiarism and duplicate publication by an automated software. Authors are obliged to acknowledge if they published study results in full or in part in the form of abstracts.

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Journal of Multiple Sclerosis Research 2021;1(2):27-31

RESEARCH ARTICLE

Effects of the Coronavirus Disease-2019 Pandemic on Physical Activity Level, Depression, and Anxiety in Persons with Multiple Sclerosis

Asiye Tuba Ozdogar[1]*, Pınar Yigit[1], Zuhal Abasıyanık[1,2], Seda Dastan[1], Pelin Hancer[1], Ozge Sagıcı[1], Cavid Baba[3], Serkan Ozakbas[3], *on behalf of Multiple Sclerosis Research Group*

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[2]Izmir Katip Celebi University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey
[3]Dokuz Eylul University Faculty of Medicine, Department of Neurology, Izmir, Turkey

Abstract

Objective: The mandatory restrictions during the Coronavirus disease-2019 (COVID-19) pandemic in regular physical activity and exercise affected the daily life of millions of people. Changes due to the COVID-19 outbreak in persons with multiple sclerosis (pwMS) are unknown. Therefore, this study aimed to examine the effects of the COVID-19 outbreak on physical activity level, depression, and anxiety in pwMS.

Materials and Methods: A total of 263 pwMS were assessed in the prospective follow-up study. Study participants in the last year were contacted by phone (from May 5 to June 5, 2020) depending on previous assessment dates, wherein 201 (154 female, 47 male) were reached during the pandemic. MS demographic and clinical characteristics were handled from the last routine examination in March 2019 to March 2020. Physical activity, anxiety, and depression information before the COVID-19 pandemic were also obtained from the assessment within the same day.

Results: The physical activity assessed using the godin leisure-time exercise questionnaire (GLTEQ) improved during the pandemic ($p=0.018$). Anxiety and depression levels significantly decreased during the pandemic ($p<0.001$). Significant correlations were found between the GLTEQ and anxiety and depression subscores in the hospital anxiety and depression scale ($r=-0.149$, $r=-0.161$, $p<0.05$, respectively) during the pandemic. However, a correlation was not found between these variables before the pandemic ($p>0.05$).

Conclusion: This study provides some evidence about the pandemic effects on physical activity level, depression, and anxiety in pwMS. The precaution taken to control the pandemic was already covered for three months; however, anxiety, depression, and inactivity behavior, which were also prevalent before COVID-19, was reduced.

Keywords: Multiple sclerosis, COVID-19, pandemic, physical activity, anxiety, depression

Introduction

The Coronavirus disease-2019 (COVID-19) outbreak is the most severe pneumonia outbreak to date. At the end of 2019, a new coronavirus, known as severe acute respiratory syndrome coronavirus 2, suddenly appeared in Wuhan, China. The World Health Organization declared an internationally concerned public health emergency on January 31, 2020. As of April 16, 2020, COVID-19 spread worldwide and caused >2 million cases and >137,000 deaths (1). In Turkey, the first case was confirmed on March 9, 2020, and the first death on March 17, 2020 (2).

Wang et al. (3) evaluated 1,210 participants for the effect of the COVID-19 pandemic on their psychological situation, which revealed that 53.8% of participants had moderate to severe psychological effects during the pandemic. Another study revealed that anxiety and stress disorder rates of healthcare professionals of a hospital in China were 23% and

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27%, respectively (4). The neuropsychiatric effects of the viral pandemic were previously shown on the general population; however, its effects on persons with multiple sclerosis (pwMS) are unclear.

Neuropsychiatric involvement is one of the most common symptoms in pwMS. Anxiety and depression were reported in 57% and 40% of patients, respectively. These are above the rates according to the general population (5,6). Therefore, they are more vulnerable to the neuropsychiatric effects of the COVID-19 pandemic. Patel et al. (7) showed that depression and anxiety levels affect the quality of life, fatigue level and disability scores, and disease progression. Just like other society members, pwMS are affected by the emotional distress and health anxiety caused by the COVID-19 outbreak. However, pwMS follow incompatible coping strategies that made them more sensitive to the harmful neuropsychiatric effects of the outbreak (8). Most pwMS receive immunosuppressive or immunomodulatory therapy. Patients taking immunosuppressive agents theoretically have an increased risk of being affected by viral pandemics, with a higher health anxiety level. Moreover, pwMS have difficulty accessing group and cognitive and physical rehabilitation therapies that hypothetically contribute to stress and anxiety (9).

Physical activity is defined as any physical movement resulting from skeletal muscle contraction, including exercise, sports, professional work, transportation, and housework, which results in increased energy consumption above the resting levels (>1.6 MET) (10). Physical activity is highly recommended in pwMS. Evidence shows that physical activity improves walking performance, balance, cognitive state, fatigue, depression, and quality of life in pwMS (11). However, low physical activity and exercise levels and high levels of sedentary behavior were reportedly common in pwMS (12).

Public health officials recommended reducing travel and stay at home as a primary means of limiting human exposure to the virus due to the ongoing COVID-19 outbreak. Mandatory restrictions in regular physical activity and exercise participation affected the daily life of millions of people. Changes due to COVID-19 outbreak in pwMS, whose anxiety and depression level is higher than the general population, but with low physical activity and exercise levels, are unknown. Therefore, this study aimed to examine the effects of the COVID-19 outbreak on physical activity level, depression, and anxiety in pwMS.

Materials and Methods

Participants and Procedures

This study was implemented in the MS Center of Dokuz Eylul University Hospital, Izmir, Turkey. The research protocol was approved by the Turkish Ministry of Health and Dokuz Eylul University Ethics Committee (code: 2020/15-32). Written consent was obtained from all participants for data before the pandemic and verbal consent before the evaluation during the pandemic.

This study used the physical activity, anxiety, and depression data of the ongoing project entitled, "Follow-up of physical, psychosocial, and cognitive influences in persons with multiple sclerosis: A prospective cohort study," as baseline data. This project conducted physical, cognitive, and psychosocial assessments by physiotherapists, psychologists, MS nurses at 6-month intervals, in addition to routine clinical examination by a senior MS neurologist. Moreover, the questionnaires were filled by the patients. Study participants in the last year were contacted by phone (from May 5 to June 5, 2020) depending on previous assessment dates. The starting day was approximately 8 weeks after the date the Government of Turkey decided to administratively allow those with chronic illnesses and close the schools (March 16, 2020). While many government agency employees did not go to work, private-sector workers or health personnel continued to work at limited hours, except for curfew days. In Turkey, curfew was implemented for 8 days in April and 15 days in May.

The eligibility criteria were as follows: definite MS diagnosis according to the recent diagnostic criteria (13) and age between 18 and 70 years. Exclusion criteria included the following: Having a relapse within 30 days, an additional diagnosis of neurological disease other than MS, having any severe cognitive disorder hindering the test instructions, and communication problems.

Outcome Easures

The MS demographic and clinical characteristics, including gender, age, marital and employment status, disease duration, disease course, and expanded disability status scale (EDSS), were handled from the last routine examination from March 2019 to March 2020. Physical activity, anxiety, and depression information before the COVID-19 pandemic were also obtained from the assessment within the same day.

Physical Activity Assessment

Godin leisure-time exercise questionnaire (GLTEQ) was applied for physical activity evaluation. GLTEQ is a very common and validated questionnaire in MS researches (13,14), which includes three items regarding the number of bouts of strenuous, moderate, and mild physical activity lasting for >15 min in a typical week. The total score is calculated using the following formula: (frequency of mild×3)+(frequency of moderate×5)+(frequency of strenuous×9). Scores of 24 and above mean sufficiently active, 23-14 is moderately active, and 13 and below are insufficiently active (15).

Anxiety and Depression

Anxiety and depression were evaluated using the Turkish version of the hospital anxiety and depression scale (HADS) (16), which is a reliable and validated self-reported scale in MS

(17) that includes 14 items, 7 of which evaluate anxiety and 7 assess depression. Both subscales are separately calculated by summating the 7 items, and higher scores indicate more significant anxiety and depression level. Eight points or above for subscales indicate clinically significant anxiety and depression in MS (17).

Statistical Analysis

International Business Machines Corporation® Statistical Package for the Social Science® Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp.) was used for statistical analysis. The normality distribution of the data was checked with the Shapiro-Wilk test, investigating the histograms and plots. Descriptive analysis (mean, median, standard deviation, range, percentages, and numbers) was performed for each baseline characteristic, including sex, age, disease course, disease duration, and EDSS score. The Wilcoxon signed-rank test was used to compare the scores before and during the COVID-19 pandemic, and effect sizes were calculated using Cohen's d. Effect sizes of 0.2, 0.5, and 0.8 describe small, medium, and large effects, respectively (18). Bivariate correlation analysis was performed to investigate the relationship between physical activity and depression and anxiety using the Spearman rank-order correlation. The level of significance was set as $p \leq 0.05$.

Results

By March 2020, 263 pwMS were assessed in the prospective follow-up study, wherein 201 (154 female, 47 male) were reached by phone during the pandemic. Sixty-two patients were excluded from the study, either because they were unreachable by phone (n=55) or they did not want to answer the questions on the phone (n=7). The mean EDSS of the study participants was 1.09±1.34 (range between 0 and 7) (Table 1). None of them was positive for COVID-19.

Before and during the pandemic values were analyzed, which revealed that the physical activity assessed by GLTEQ improved during the pandemic (p=0.018). Anxiety and depression levels statistically significantly decreased during the pandemic (p<0.001) (Table 2).

Table 1. Demographic and clinical characteristics of participants

	Mean (SD)
Age (years)	35.54±10.12
Gender, n (%)	
Female	154 (76.6%)
Male	47 (23.4%)
Disease course, n (%)	
Relapsing-remitting MS	198 (98.5%)
Secondary progressive MS	2 (1%)
Primary progressive MS	1 (0.5%)
EDSS	1.09±1.34
Disease duration (years)	7.08±7.13

EDSS: Expanded disability status scale, MS: Multiple sclerosis, SD: Standard deviation

Assessments before the pandemic revealed 158 insufficiently active pwMS, whereas 142 pwMS were inactive during the pandemic. Forty-two pwMS, without regular exercise habits before the pandemic, started to exercise regularly during the pandemic. Twenty participants who regularly exercise before the pandemic, stopped exercising during the pandemic (Figure 1). Clinically significant depression before the pandemic according to the 8-point threshold of HADS was observed in 58 pwMS; however, this number dropped to 36 during the pandemic. The number of patients with anxiety decreased from 84 to 48 (Figure 2).

As shown in Table 3, significant correlations were found between the GLTEQ and anxiety and depression subscores of HADS (r=-0.149, -0.161, p<0.05; respectively) during the pandemic. However, the correlation between these variables before the pandemic was statistically non-significant (p>0.05).

Discussion

This study compared physical activity, anxiety, and depression levels of pwMS before and during the pandemic. Results revealed anxiety in 23.88% of participants, whereas 17.91% had depression during the pandemic. In addition, 29.35% of participants were active during the pandemic.

Recent systematic reviews and meta-analyses reported that the rates of anxiety and depression in pwMS were 31% and 22%, respectively (19). Furthermore, Chiaravalloti et al. (20) assessed 131 pwMS regarding anxiety and depression levels and compared the data collected before the pandemic. They reported no changes in terms of anxiety level and a slightly increased depression level during the pandemic according to the pre-pandemic period. Our study revealed an anxiety rate of 42% and depression of 29% in the pre-pandemic period. These rates significantly decreased after the COVID-19 pandemic, which depended on two factors. First, immediately after the beginning of the outbreak, a comprehensive information letter was published about the potential effects of the COVID-19 pandemic on pwMS. The letter contained detailed information made by the MS clinic of Dokuz Eylul University, where patients were followed up, which was spread to a broad audience by the MS Research Association, with close cooperation via its web page and social media pages. The information letter published by the center, where the people are followed, effectively reduced the increased anxiety and depression due to incorrect information circulating in the society. Second, the increased physical activity levels positively affected the psychological state. Costabile et al. (21) showed that exercise plays a crucial role during the pandemic to overcome mental distress, improve active lifestyle,

Table 2. Results of physical activity and depression-anxiety before and after COVID-19 pandemic

	Pre-pandemic	During pandemic	p	Cohen's d
GLTEQ	0 (0-9)	0 (0-15)	0.018*	1.26
HADS-anxiety	7 (4-10)	3 (1-7)	<0.001*	0.83
HADS-depression	4 (2-8)	2 (1-5)	<0.001*	0.32

Wilcoxon signed-rank test, Values are presented as median (Q1-Q3), *Statistically significant (p≤0.05), GLTEQ: Godin leisure-time exercise questionnaire, HADS: Hospital anxiety and depression scale, COVID-19: Coronavirus disease-2019

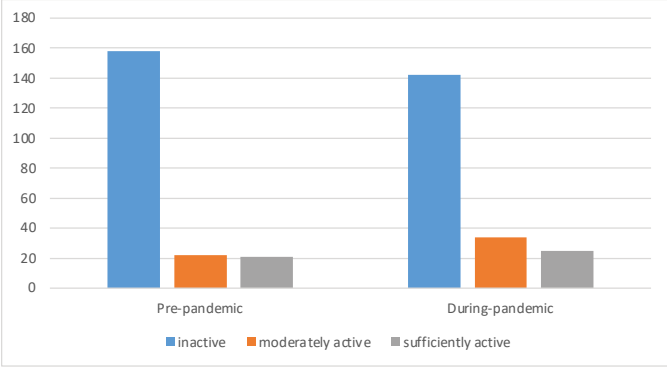

Figure 1. Physical activity rates of participants before and during the pandemic

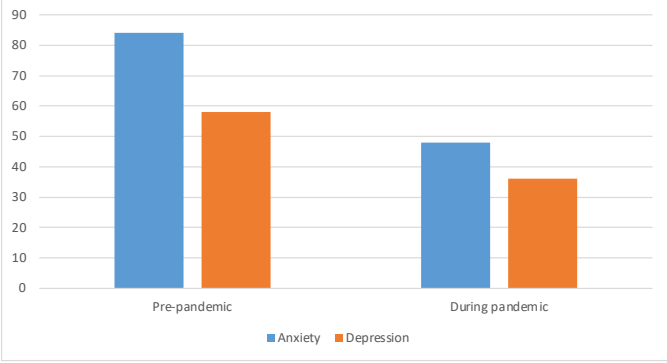

Figure 2. Depression and anxiety rates before and during the pandemic

increase positive emotions, and decrease negative feelings, such as depression and anxiety. More recently, a systematic review investigating the effects of exercise on depression and anxiety showed a significantly negative correlation of changes from moderate to large (22). Furthermore, Kandola et al. (23) provided extensive information about the relation between physical activity and psychological state. In addition, they point out information gaps concerning intensity and pathophysiological mechanisms of physical activity. Similarly, a weak negative relationship was found between depression and anxiety and physical activity levels during the pandemic in our study. However, a relationship was not found between physical activity and anxiety and depression before the pandemic since the psychological state of people is affected by more factors related to daily life before the pandemic. Contrarily, health-related factors affected the psychological state more during the pandemic. In addition, the intensity of physical activity is not enough to reduce anxiety and depression levels before the pandemic.

The effects of physical activity on fatigue, strength, balance, quality of life, and mobility were shown in pwMS; however, they have less physical activity level versus the general population (24). The present study revealed that 71.14% of participants were inactive in the pre-pandemic period, whereas 70.65% were inactive during the pandemic. However, the physical activity level in pwMS increased according to GLTEQ during the pandemic. While 42 patients started to exercise, 20 patients gave up exercise habits during the pandemic. Despite the precaution and physical restrictions, some of the pwMS continued their physical activities by changing the form of activity due to the permanent acquisition of physical activity behavior.

Study Limitations

Our study has several limitations. First, the type of exercise was not reported. Patients reported that indoor activities replaced outdoor activities due to quarantine restrictions. The physical activity levels were not objectively measured due to pandemic conditions. In addition to the physical activity level, sitting time could also be questioned. However, it was not included because a comparison could not be made since our previous evaluations did not include a sitting time assessment. Lastly, life situation-related questions, such as working status, were not included. The strength of this study is the awareness of the anxiety, depression, and physical activity levels of our patients just before the pandemic, which enables us to see the effects of the pandemic on the same patients.

Table 3. Spearman's correlation coefficients between the GLTEQ and HADS-anxiety and depression

	Pre-pandemic		During pandemic	
	HADS-anxiety	HADS-depression	HADS-anxiety	HADS-depression
GLTEQ	r=-0.037 p=0.6	r=-0.064 p=0.365	r=-0.149* p=0.035	r=-0.161* p=0.023

Spearman rank-order correlation, *Statistically significant (p≤0.05), GLTEQ: Godin leisure-time exercise questionnaire, HADS: Hospital anxiety and depression scale

This study provides some evidence about the effect of the pandemic on anxiety, depression, and physical activity levels in pwMS. The precaution taken to control the pandemic was already covered for three months; however, anxiety, depression, and inactivity behavior, which were also prevalent before COVID-19, was reduced. This study also includes hints that early and explicit information during extraordinary periods has a preventive effect on reactive anxiety and depression in pwMS.

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Ethics

Ethics Committee Approval: The research protocol was approved by Dokuz Eylul University Ethics Committee (code: 2020/15-32). This study was performed in line with the principles of the Declaration of Helsinki (as revised in Brazil 2013).

Informed Consent: Written consent was obtained from all participants for data before the pandemic and verbal consent before the evaluation during the pandemic.

Authorship Contributions

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

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

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RESEARCH ARTICLE

The Effect of Cognitive Rehabilitation on Peripheral Blood B Cell Distribution and Specific Gene Expression Levels in MS patients

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Abstract

Objective: Multiple Sclerosis (MS) is an autoimmune, demyelinating, and neurological disorder of the central nervous system (CNS). For years, cellular immunity is thought to be the possible potential mechanism in the immunopathogenesis of the disease; however, nowadays, studies show that humoral immunity has a major part and also plays an important role. Neuropsychological tests in known to detect mild, moderate, or severe cognitive impairments that occur in patients, particularly memory and executive functions are affected. Studies showed that computer-assisted cognitive rehabilitation (CCR) studies that are performed with special software improve memory functions and change the levels of memory proteins, neurotrophic factors, and neurotransmitters in the peripheral blood.

Materials and Methods: Patients with MS (n=18) who are included in the study participated in the CCR for 6 months, and blood samples were gathered at the beginning and after the neuro-rehabilitation stage of the study. Flow cytometry is used to immunophenotype the PBMCs. The expression level of B cell-associated genes that were detected by another microarray study was determined by a real-time polymerase chain reaction. The immunophenotype and gene expression levels of the patients and 20 healthy volunteers, from whom only peripheral blood samples were taken, were compared.

Results: After the CCR, non-significant increased natural killer cells were observed. Regulatory B cell percentages were increased following the rehabilitation period, which differed only from healthy donors. The significantly increased *transforming growth factor-beta* and ATPase Na+/K+ Transporting Subunit Beta 3 gene expressions after rehabilitation was evaluated as a shift of cell activity toward immunosuppression.

Conclusion: The findings suggest that treatment methods, such as cognitive rehabilitation, that are not based on biological foundations may also have molecular and cellular effects. This supports its role in the regression of inflammation and clinical progression.

Keywords: B lymphocytes, cognitive rehabilitation, gene expression, multiple sclerosis

Introduction

Multiple sclerosis (MS) is defined as a chronic inflammatory disease of the central nervous system (CNS) that is characterized by demyelination and axonal damage caused by T cells of the adaptive immunity. Cellular immunity is thought to be the most important possible causal mechanism in the immunopathogenesis of MS; however, studies show that humoral immunity also plays a critical role. Particularly, the findings of the studies show that B cells are important in the pathogenesis of MS and the presence of degradation products of plasma cells, myelin-specific antibodies, and possibly complement factors activated by these antibodies, in both chronic MS plaques and acute MS lesions. In addition, the presence of immunoglobulin G (IgG) and complement deposits, especially in lesion areas with lower myelin destruction, support the assumptions that antibodies are effective in lesion formation.

Other findings showed the active role of B cells in the pathogenesis of the disease, which are intrathecal immunoglobulin production and the presence of oligoclonal bands that are only found in the cerebrospinal fluid (CSF), somatic hypermutation of B cells that are detected in MS lesions and patient CSF samples, plasmapheresis that clears antibodies, and monoclonal antibody treatments, such as rituximab/ocrelizumab targeting B lymphocytes, improve MS

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findings. Moreover, a correlation was found between the B cell, plasmablast, and immunoglobulin M levels in the CSF and clinical progression and the number of contrast-enhancing lesions (1-3).

Jean-Martin Charcot, the first neurologist to describe the clinical and pathological characteristics of MS, pointed to cognitive impairments as "significant loss of memory, slowing of cognition, and in their entirety, atrophy of intellectual and emotional abilities" (4). These days, cognitive impairments are seen in 70% of patients with MS (5). Information processing speed, executive functions, attention, and long-term and working memory deficits are the most common conditions (6). Cognitive rehabilitation is a set of therapeutic activities that have been studied in recent years and are designed to reconsider the individual's memory and other cognitive functions (7). Studies showed that cognitive exercises can lead to a significant increase in attention and thus a reduction in attention-related problems compared to non-specific training (8). Neurobehavioral interventions and methods that applied cognitive rehabilitation had positive effects on the cognitive performance and other connected abilities of patients with MS and have succeeded in increasing the functionality of the individual in daily life (9). The study results, in which Messinis et al. (9) used the RehaCom software, showed and stated that after the treatment in patients with MS have a significantly improved verbal episodic and visuospatial memory, response inhibition, processing speed/working memory, semantic fluency, attention/visual-motor scanning speed, and group switching abilities. Computer-assisted cognitive rehabilitation studies are also known to improve memory functions and change memory proteins, neurotrophic factors, and neurotransmitter levels in the peripheral blood (4-9).

This study aimed to evaluate the possible effect of computerized neurocognitive rehabilitation on the peripheral B cells in patients with MS and investigate the relationship of neurorehabilitation with the clinical presentations of patients.

Materials and Methods

Study Group

Patients with MS (n=18, RRMS) who are followed in Haydarpaşa Numune Training and Research Hospital, Neurology Clinic, MS Outpatient Clinic, and age and gender-matched healthy individuals (n=20) as the control group, were included in the study (project no: HNEAH-KAEK 2016/110). The study group included patients over the age of 18 years who were diagnosed following the revised McDonald criteria of 2017 and did not have an attack in the last 3 months, whereas the healthy control group were those over the age of 18 years who did not have an autoimmune disease, any infectious disease in the last 3 months, and did not use corticosteroids or immunosuppressive drugs. Additionally, none of the patients was in an attack period. All participants provided written informed consent before the study.

Computer-Assisted Cognitive Rehabilitation

"NOROSOFT" is software that included mental exercise programs for the computer-assisted cognitive rehabilitation (CCR) method. The program consists of 5 modules: attention, memory, reasoning, visual, and verbal tasks. Volunteer patients were asked to do the application for 50 min, 5 days a week. Sessions had a 20-min daily exercise segment that allowed patients to perform in each module, and 30 min of specific training based on each patient's "Rao's Brief Repeatable Battery of Neuropsychological Tests" scores. Weekly follow-ups of patients were supervised by the institutional interface of the program and were evaluated by a physician monthly. The peripheral blood samples were collected from the study group at the beginning and after 6 months of the CCR. Healthy donors were not included in this program and only peripheral blood samples were obtained.

Isolation of Peripheral Blood Mononuclear Cells (PBMCs) and Immunophenotyping

Peripheral blood cells of the participants were isolated using the density gradient centrifugation method and frozen at -80 °C in 10% dimethyl sulfoxide and fetal bovine serum. Frozen cells were simultaneously thawed and viability tests with trypan blue were used. Cells were stained with anti-human monoclonal CD19-APC, CD24-PerCP, CD138-PE, IgD-APC/Cy7, CD38-Alexafluor 700, CD27-FITC (Biolegend) and Multitest CD3 FITC/16+56 PE/CD45 PerCP/CD19 APC (Becton Dickinson) antibodies for 30 min at 4 °C. Cells that are evaluated on the flow cytometer (BD FACS Aria II) were then analyzed by FlowJo software.

Target Genes Identification and RNA Isolation

Data from our previous microarray study were used to identify candidate genes (10). In that study, RNA expression profiles of PBMCs of 5 RRMS, 6 benign MS, and 5 healthy donors were determined with the Sureprint G3 Human Gene Expression V3 microarray (MA) system. In this context, a total of 26083 Entrez genes were evaluated, and target genes that differed between RRMS and healthy donors were determined. Selected genes and primer sequences are listed in Table 1.

For the validation of the identified candidate genes, RNA isolation from the frozen PBMCs of all cases was performed following the manufacturer's instructions (QIAGEN RNeasy Mini kit, Hilden, Germany). The purity and concentration of the acquired RNA were measured by spectrophotometer. Those with an optical density of 260/280 nm between 1.9 and 2.1 were included in the study.

Real-time Quantitative Polymerase Chain Reaction (qPCR)

cDNA synthesis was performed with the Transcriptor First Strand cDNA Synthesis Kit (Basel, Switzerland) following the

Table 1. Identified genes and their primer sequences

Gene	Primer sequence	Gene	Primer sequence
BLK_Frw	TAGATCACAGGGTCGGAAGG	-	-
BLK_Rev	GGCAGCGGATCTTATAGTGC	*SWAP70_Frw*	CGGTGCTGAAGGTTCCTCAT
TGFB1_Frw	GTACCTGAACCCGTGTTGCT	*SWAP70_Rev*	GACACAGAGGGTCCAACACA
TGFB1_Rev	CAACTCCGGTGACATCAAAA	*KCNS3_Frw*	AATCGCTACCAGGAACGCAA
ATP1B3_Frw	CAGTCTGTCCTGATGGAGCA	*KCNS3_Rev*	CGATCTCCACTCCTTCCAGC
ATP1B3_Rev	TGGCACTCCTTCAGGCTTTA	*ACTB_Frw*	TGGCACCACACCTTCTACAA
BANK1_Frw	GTTCAGACCCCGCACATATT	*ACTB_Rev*	CCAGAGGCGTACAGGGATAG
BANK1_Rev	CCTTCCCCTTCCATTTCATT	*HPRT1_Frw*	AGTGATGATGAACCAGGTTATGA
BLNK_Frw	GAGCAGTGGTCCGATGACTT	*HPRT1_Rev*	GCTACAATGTGATGGCCTCC
BLNK_Rev	TGGGCTTACTGGGAAGTGTC	*GAPDH_Frw*	CCATCAATGACCCCTTCATT
FCRL2_Frw	CTCTGGGGACTGTTTGGTGT	*GAPDH_Rev*	TTGACGGTGCCATGGAATTT
FCRL2_Rev	GGTTGGGCTTGAATAGGTGA	-	-

instructions of the manufacturer. LightCycler 480 instrument and the Fast Start DNA Master SYBR Green I kit (Roche, Basel, Switzerland) were used for the real-time PCR (RT-PCR) method. The concentrations of the primers were set at 600-800 nM. The glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene was chosen as a housekeeping gene. After processing, the amplification curves and melting peaks were evaluated.

Statistical Analysis

The peripheral blood cell subsets were determined by Cell Quest (BD), and FlowJo was used for data analysis. The analysis of variance and Tukey's posthoc test were used for the comparison of more than two groups. Paired t-test was used to compare pre- and post-rehabilitation data. The formula 2-DDCT (DD CT=target gene CT-GAPDH CT) was used to determine the CT values of target genes and their relative amounts compared to the reference gene, GAPDH, for the relative target gene quantification. Correlation analyzes were performed with the Pearson correlation test. Analyzes were performed on Statistical Package for the Social Sciences 21.0. Graphs were created with the GraphPad Prism 5 and p-values of <0.05 were considered statistically significant.

Results

Clinical and Demographic Data

All clinical and demographic details of patients with MS (n=18) and healthy participants (n=20) who are included in the study are presented in Table 2. All enrolled participants with MS received immunomodulatory treatment (interferon-beta, fingolimod, or glatiramer acetate).

Patients affected by rehabilitation were also evaluated using neuropsychological test batteries in this study. Our previous study evaluated the effects of computerized rehabilitation on improved executive functions and verbal, visual memory, and motor functions, and the same patients were included in this study.

Table 2. Clinical and demographic data of the participants

	Multiple sclerosis (n=18)	Healthy controls (n=20)
Sex (F/M)	12/6	12/8
Age (year, mean ± SD)	39.6±11.4	39.3±8.7
Disease onset age (year, mean ± SD)	28.05±10.82	-
Disease duration (year, mean ± SD)	10.7±5.6	-
Last edss (mean ± SD)	2.72±1.1	-
Total number of attacks (mean ± SD)	7±4.5	-
Annual number of attacks (mean ± SD)	0.73±0.48	-

SD: Standard deviation, F: Famele, M: Male

Comparison of PBMC Phenotypes

According to the immunophenotyping results of patients with MS (Table 3), the percentage of CD19-expressing B cells did not differ between the groups, and the percentage of $CD3^+$ T cells were significantly decreased in the groups before ($p<0.01$) and after the rehabilitation ($p<0.05$). However, this effect was found to be independent of the rehabilitation effects. The $CD3^-CD16^+CD56^+$ natural killer (NK) cells were significantly elevated only in the post-rehabilitation group ($p<0.05$) compared to healthy individuals. The $CD3^-CD16^+CD56^+$ NK cells were found to be significantly higher than the healthy ones only in the post-rehabilitation group ($p<0.05$). The percentages of $CD3^+CD16^+CD56^+$ NKT cells were similar between the study groups (Figure 1).

The peripheral B cell distribution was not different between the study groups; however, unswitched memory B cells ($CD19^+IgD^+CD27^+$) displayed lower values in the pre- and post-rehabilitation groups compared with the healthy donors ($p<0.05$). Switched ($CD19^+IgD^-CD27^+$) ($p=0.0525$) memory B cells were found to be significantly lower only in the post-rehabilitation group compared to healthy individuals

Table 3. Peripheral cell subgroup percentage and gene expression levels

	Before CCR	After CCR	Healthy controls	Before CCR vs. after CCR	Before CCR vs. HC	After CCR vs. HC
Cell Types	Mean ± SD	Mean ± SD	Mean ± SD	p	p	p
$CD19^+$ B cell	6.12±6.63	4.47±4.69	5.93±2.86	0.1343	0.905	0.2541
$CD3^+$ T cell	65.87±20.86	59.49±15.21	79.8±8.05	0.2313	**0.0091**	**<0.0001**
NK cell	19.4±18.24	23.21±14.10	11.45±5.96	0.3385	0.0772	**0.0016**
NKT cell	9.15±6.10	11.83±11.98	11.62±7.04	0.3185	0.2575	0.9472
Naive B cell	63.44±13.02	64.33±17.53	50.56±18.51	0.542	**0.0169**	**0.0269**
Immature B cell	10.23±7.49	7.58±4.53	8.88±8.25	0.08	0.6006	0.5593
Unswitched Memory B cell	10.58±7.70	10.76±6.84	18.98±9.83	0.6297	**0.0084**	**0.0054**
Switched Memory B cell	14.19±8.53	13.61±7.07	21.6±11.65	0.8824	**0.0369**	**0.0217**
Breg cell	4.63±5.89	7.63±5.89	2.86±2.51	0.1285	0.2268	**0.0094**
Plasmablasts	5.28±6.36	7.02±7.12	4.31±3.36	0.1959	0.5531	0.1349
BLK expression	0.19±0.21	0.12±0.12	0.52±0.47	0.3987	**0.0057**	**0.0039**
TGFB expression	0.35±0.30	0.53±0.34	0.55±0.36	**0.0169**	0.1111	0.8814
ATP1B3 expression	0.95±0.65	1.16±0.61	1.14±0.57	**0.0437**	0.4303	0.9488
BANK1 expression	0.22±0.22	0.17±0.18	1.44±1.42	0.9828	**0.0002**	**0.0043**
SWAP70 expression	0.81±0.59	0.68±0.52	1.38±1.053	0.2488	**0.045**	0.0306
KCNS3 expression	1.06±1.26	0.65±1.12	0.16±0.31	0.9735	0.0588	0.2449
FCRL2 expression	0.18±0.19	0.074±0.093	0.34±0.21	0.2473	**0.0413**	**0.0004**
BLNK expression	0.34±0.52	0.13±0.076	0.50±0.41	0.1257	0.4145	**0.0025**

SD: Standard deviation, CCR: Computer-assisted cognitive rehabilitation, HC: Healthy controls

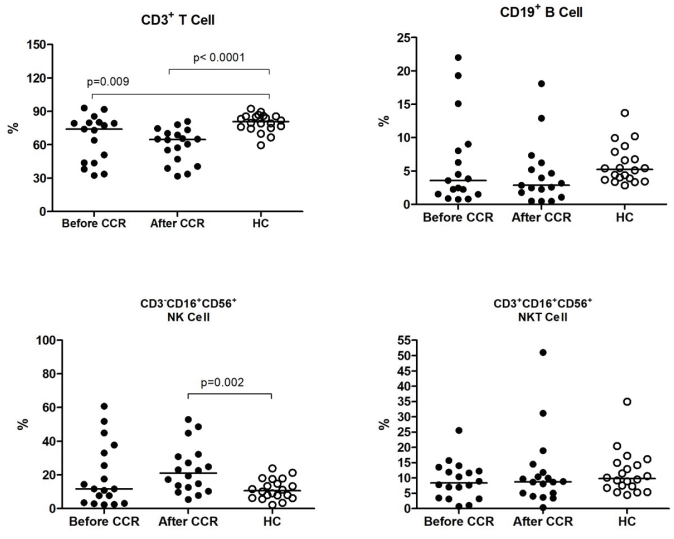

Figure 1. Distribution of peripheral blood B, T, and natural killer cells (NK and NKT) between the study groups

CCR: Computer-assisted cognitive rehabilitation, HC: Healthy controls

(p<0.05). These results suggest that rehabilitation does not differentiate between these subgroups of B cells. The regulatory B cell (Breg, CD19+CD24++CD38++) subgroup, which has immunosuppressive cell characteristics, was found to increase following the rehabilitation and was remarkably different from the healthy group (p<0.05) (Figure 2).

Plasmablasts ($CD19^+CD38^{++}CD138^-$), which are antibody-producing cell precursors and antibody-producing plasma cells ($CD19^+CD38^+CD138^+$), were determined not different between the study groups. Additionally, the subgroup of regulatory B cells (Breg, $CD19^+CD24^{++}CD38^{++}$) that show immunosuppressive cell characteristics were increased after rehabilitation and this situation differed only from the healthy controls (Figure 2).

Expression Validations of Candidate Genes by RT-PCR

The expression levels of the genes that are determined from the microarray data analysis were evaluated in the total PBMCs in the blood samples that are gathered from patients with MS before and after the CCR. The gene expression levels of *BLK*, *BANK1*, *SWAP70,* and *FCRL2* were found to be remarkably lower in patients with MS than in the control groups. However, the CCR did not cause any changes in these gene expressions. No difference was found in transforming growth factor-beta (*TGFB*) and ATPase Na+/K+ Transporting Subunit Beta 3 (*ATP1B3*) gene expression between study groups, and the significant increase in expressions (p=0.0169 and p=0.0437, respectively) after the CCR was observed. No difference was found between the study groups in the expression levels of *KCNS3* and *BLNK* (Figure 3).

Discussion

MS is an autoimmune and progressive disorder that develops due to axonal degeneration, demyelination, and inflammation

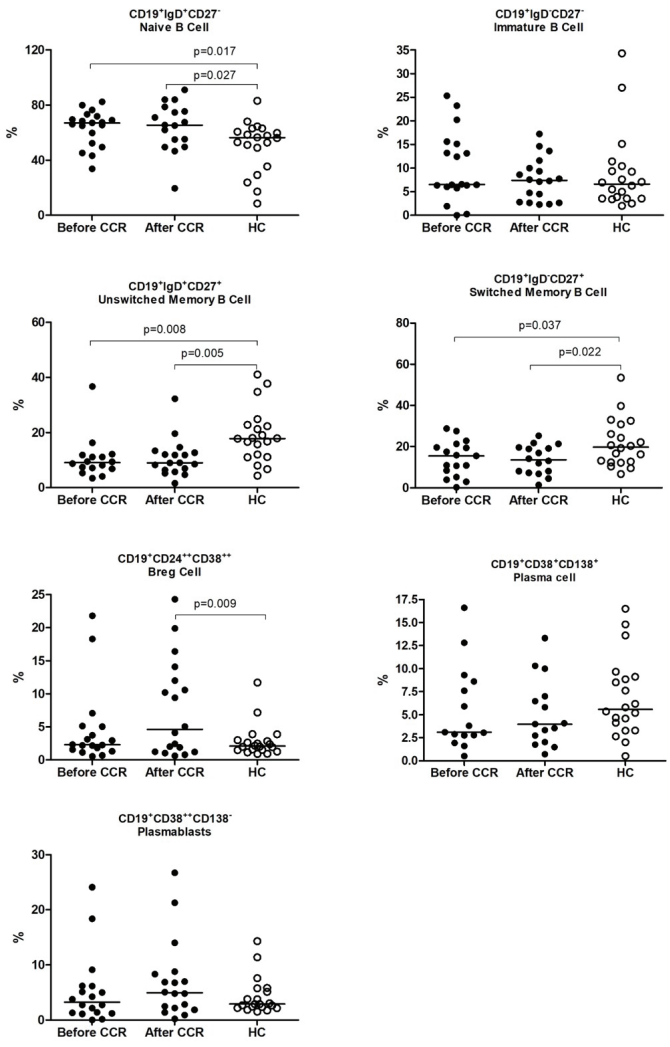

Figure 2. Distribution of peripheral blood B cell subtypes among the study groups

CCR: Computer-assisted cognitive rehabilitation, HC: Healthy controls

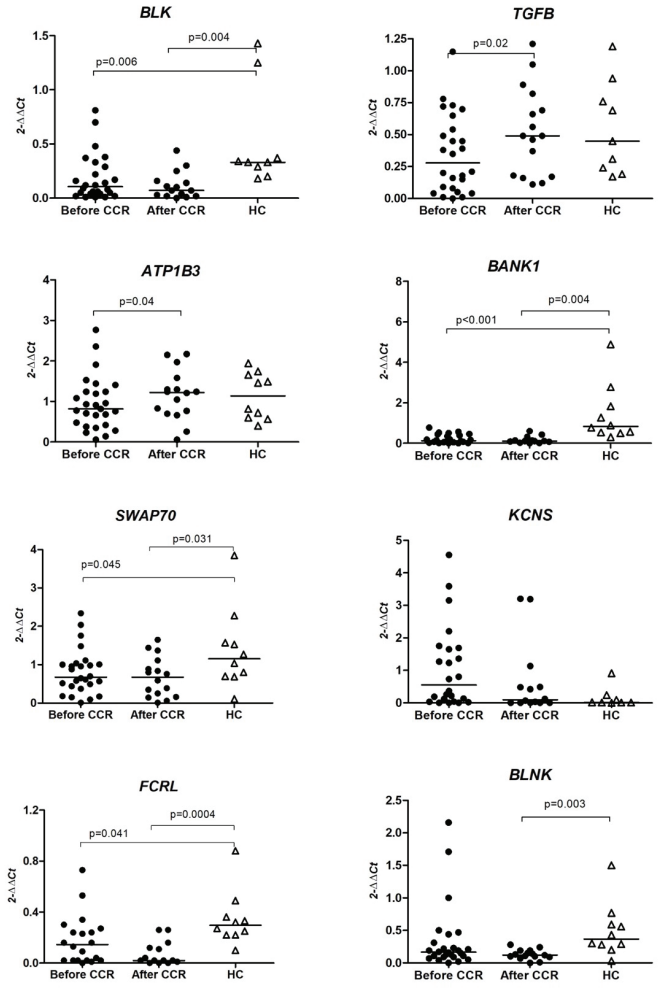

Figure 3. Distribution of relative gene expressions in the study group

CCR: Computer-assisted cognitive rehabilitation, HC: Healthy controls

and affects the CNS. It is one of the most frequent and most studied neurodegenerative diseases in young adults (11).

The pathological feature of MS include the formation of focal areas of myelin loss in the CNS, called lesions or plaques, and although it spreads to the CNS, the optic nerves, subpial spinal cord, brainstem, cerebellum, and juxtacortical and periventricular white matter regions are primarily affected (12). T cells are known for many years to play an active role in disease pathogenesis. However, in recent years, B cells were determined to be important in the pathogenesis, especially with the role of presenting myelin antigen to T cells, apart from the antibody production.

Optic neuritis is the first attack in 25% of patients and is associated with conversion to clinically precise MS in 34%-75% of patients after 10-15 years from clinical onset (13). Sensory symptoms that originate from myelitis or brainstem syndromes are the first clinical findings (14). Motor symptoms are the first symptoms of the disease, which affect the majority of patients. However, in addition to these, studies report that 70% of patients with MS have cognitive impairments (5). The most prevalent cognitive deficits in MS appear to be deficits in information processing speed (6). In addition, the psychological problems of the patients cause more distress than the developing physical symptoms. A positive relationship was stated between the physical disability and the course of depression (15). The effects of rehabilitation in patients were also evaluated using neuropsychological test batteries. Our previous study revealed that improvement in executive functions was determined after computerized rehabilitation while the efficacy of rehabilitation on verbal, visual memory, and motor functions were evaluated, and the same patients were included in this current study (16).

Studies have reported that patients with depression have increased proinflammatory cytokine levels (17). The study

by Moreira et al. (18) on cognitive behavior therapy (CBT) revealed that CBT is effective for the treatment of depressive manifestations and diminishes levels of Interleukin (IL)-6 and tumor necrosis factor α in young adults. In the light of these findings, treatments are suggested to have a positive effect on cognition and excluding anti-inflammatory drug therapy or/and physical rehabilitation may also be beneficial in suppressing the proinflammatory phenotype that predominates in patients with MS. Therefore, anti-inflammatory regulatory B cells (Breg) were determined to increase with neurorehabilitation while proinflammatory effector memory B cells reduce. Moreover, gene expression of *FCRL2*, which works toward B lymphocyte proliferation, decreased, and the expression of *TGFB* and *ATP1B3* genes, which inhibit B cell proliferation, increased after neurorehabilitation.

Rehabilitation did not affect the distribution of any cells or subgroups; however, cognitive rehabilitation increases Breg cells, which have an anti-inflammatory role in our study. B cells potentiate the immune response in consequence of produced antibodies and activated T cells using antigen presentation. Recent studies show that the suppressive Breg cell group can suppress the inflammatory response with anti-inflammatory cytokines, such as TGF-beta, IL-10, and IL-35. Additionally, Breg cells also control the inflammation by suppressing Th1/Th17 cell differentiation and increasing regulatory T lymphocytes (Treg). Furthermore, decreased Breg levels have been associated with the exacerbation of many neuroimmunological diseases (19). Therefore, the increase in Breg cells suppressed effector T cells and decreased memory B cells.

Patients with MS were determined to have increased NK cells after rehabilitation. Additionally, determining the changes in the NK cell functions after rehabilitation is important since the result will strengthen our finding, which is not included in the literature.

The increasing levels of TGF-beta gene expression, which is known to be produced by Bregs and has a suppressor effect on effector cells, are also consistent with these results. TGF-beta is a cytokine that controls B cell functions and shows this effect by apoptosis in B cells, thereby reducing antibody production and decreasing surface antibody expression of stimulated B cells. The suppression of TGF-beta activity only in B cells led to hyperplasia in lymphatic tissues, an increase in serum Ig levels, and the development of autoantibodies. Emerging findings suggest that TGF-beta is exclusively noteworthy in the control of autoreactive B cells (20). Furthermore, the results indicate that the cognitive improvement that is seen in patients with MS who receive neurorehabilitation therapy may be partially associated with the increased TGF-beta.

The B cell structural protein 1 (BANK1) gene with ankrin repeats, which encodes B cell-specific structural protein, has been associated with autoimmune diseases (21) and shown to negatively affect the CD40-mediated protein kinase B (AKT) pathway, which is part of the dopamine signaling pathway (22). AKT also plays a role in many cellular activities, such as apoptosis, transcription, proliferation, glucose metabolism, and cell migration (21). BLK, one of the tyrosine kinase families, is associated with rheumatoid arthritis and other autoimmune diseases, and the risk alleles identified in the GWAS studies were consistent (22) with reduced levels of BLK gene expression in B cells and B cell lines (23).

Computerized rehabilitation did not cause any changes in *BLK*, *BANK1, SWAP70,* and *FCRL2* gene expressions in our study, which suggests that the percentage of peripheral B cells did not differ between the groups and may suppress the B cell functions, which were related to these genes. Additionally, no difference was found in *TGFB1* and *ATP1B3* gene expression between the study groups after computer rehabilitation, which can be interpreted as a shift of cell activity toward immune suppression.

The study by Simpfendorfer et al. (24) reported that a low threshold of B cell antigen receptor (BCR) signal and interactions between B cell and T cell play a role in the relationship mechanism between BLK and autoimmune disease. FCRL molecules are described as a new class of molecules that belong to the Ig superfamily with potential activating and inhibitory roles (25). FCRL enhances toll-like receptor-mediated B cell proliferation, activation, and survival via MAPK and NFkB pathways (26). Thus, any change in FCRL expression and its intensity in B cells is thought to be crucial to stabilize BCR signaling and subsequent response of B cell (25). SWAP-70 is defined as a nuclear protein, and its association with IgG is thought to play a role in faster and stronger signaling of pre-activated memory B cells (27). B cell-binding protein (BLNK) acts as a scaffold to assemble molecular complexes, which are involved in signal transduction from the pre-B receptor and the B cell antigen receptor (28). BLNK phosphorylation was shown to elicit different signaling effectors after BCR activation (29). ATP1B3, which is another factor of expression level that is evaluated in our study, is an isoform of Na-K ATPase beta subunit that has been demonstrated to suppress active B lymphocytes and inflammatory NFkB pathway (30). The effect of rehabilitation on gene expression was undetermined, but TGF-beta and ATP1B3, which have a suppressor effect on B cells, was found to increase without reaching significance after neurorehabilitation, and *FCRL*, which mediates B cell activation, significantly decreases in MS subjects. Suggesting that the B cell changes that are observed in immunophenotyping studies that shift to the anti-inflammatory direction and the accompanying cognitive improvement based on the expression of these B cell-specific genes are also possible.

Study Limitations

The limitation of our study includes the number of participants who participated and their follow-ups. Future studies, especially on immunophenotyping and gene expression, should have a sufficient sample size of participants.

Conclusion

After cognitive rehabilitation in patients MS, anti-inflammatory B cells were increased, the levels of genes that support B cell development decreased, and the genes that suppress B cells increased. These findings support that treatment methods that are not based on biological foundations as cognitive rehabilitation may also have molecular and cellular effects, thus causing regression in inflammation and clinical progression.

Ethics

Ethics Committee Approval: The study protocol was approved by the Istanbul University, Istanbul Medical Faculty Clinical Research Ethics Committe (date: 27.03.2018 number: 2018/450).

Informed Consent: All subjects provided written informed consent prior to study related procedure.

Authorship Contributions

Surgical and Medical Practices: E.Ar., R.T., Concept: R.T., V.Y., E.T., Design: R.T., V.Y., E.T., Data Collection or Processing: E.A., M.S., E.Ar., Analysis or Interpretation: V.Y., Literature Search: E.A., V.Y., Writing: E.A., V.Y., E.T.

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

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RESEARCH ARTICLE

Association Between Lower Limb Spasticity and Falls in Persons with Multiple Sclerosis

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Abstract

Objective: Falls and spasticity are among the most prevalent complaints in persons with multiple sclerosis (pwMS). Limited evidence exists on the direct relationship between lower limb spasticity and falls in pwMS. This study aimed to explore the association between lower limb spasticity, walking, and falls in pwMS.

Materials and Methods: Thirty-nine patients were included (age: 35.4±9.52; 54% female, 46% male). The timed 25-foot walk (T25FW) and multiple sclerosis walking scale-12 (MSWS-12) were applied to evaluate walking. Participants reported their number of falls within the last three months. The severity of spasticity in lower limb muscles, comprising hip adductors, knee flexors and extensors, and plantar flexors, was tested using the modified ashworth scale.

Results: Fifteen participants were fallers. Spasticity levels in the ankle plantar flexors were significantly greater (p=0.009) in fallers. The number of falls correlated with ankle plantar flexors and knee extensors (rho=0.497, rho=0.329; p<0.05, respectively). The severity of spasticity in all muscle groups was negatively correlated with walking (rho=0.335-0.692, p<0.05).

Conclusion: There was a significant correlation between the degree of ankle plantar flexor and knee extensor spasticity and the number of falls in pwMS. This significant association between spasticity and fall history highlights the importance of designing therapeutic interventions optimizing lower limb spasticity.

Keywords: Multiple sclerosis, falls, walking, gait, spasticity

Introduction

Multiple sclerosis (MS) is an inflammatory disease characterized by delay and/or blockage in nerve conduction in neurons via myelin fibers and axonal damage. Various heterogeneous symptoms occur due to the dysfunctional nerve conduction (1,2).

Spasticity is among the most common motor manifestations of MS resulting from central nervous neurodegeneration (3). Despite periodic changes, nowadays, spasticity is defined as "involuntary muscle hyperactivity in the presence of central paresis" by the Interdisciplinary working group movement disorders (4).

The prevalence of spasticity ranges from 52% to 84% in the MS population (5,6). Although spasticity occurs in the upper limbs, lower limb spasticity is predominant in MS. Several studies have revealed that lower limb spasticity related to walking, postural control, and severe disability profoundly affects the quality of life in persons with multiple sclerosis (pwMS) (7,8). Furthermore, spasticity affects daily life activities in those with MS (9).

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Falls are one of the most frequent problems influencing the quality of life in MS. Many motor, sensory, cognitive, psychosocial, and clinical factors related to falls have been described recently (10-12). So far, the association between spasticity and falls has been explained based on the assumption that lower limb spasticity influences mobility in pwMS. There is limited empirical evidence on the direct link between lower limb spasticity and falls in pwMS. This pilot investigation aimed to expand previous findings on the relationship between spasticity and walking exploring the correlations between lower limb spasticity and falls in pwMS.

Materials and Methods

Participants and Procedure

The participants were directly recruited from the MS Clinic of the Dokuz Eylul University. Written informed consent was received from all subjects. A secondary data analysis was approved by the Dokuz Eylul University Ethics Committee (approval number: 2017/14-07). The inclusion criteria comprised a clinically definitive diagnosis of MS, age range between 18-64 years, relapse-free within 30 days. Participants were excluded based on the presence of a neurological disorder beside MS, non-ambulatory, musculoskeletal disorder that may affect balance and gait, and severe cognitive impairment preventing understanding of the assessments.

Assessments

Participants underwent an expanded disability status scale assessment by a senior neurologist (13). Age, sex, and clinical course of MS were recorded.

Spasticity

Spasticity of the lower limb muscles, including hip adductors, knee flexors, extensors, and ankle plantar flexors of both limbs, was bilaterally tested by a physiotherapist using the modified ashworth scale (MAS) including every other assessment. The MAS is a six-point scale (from 0 to 4) assessment. The average MAS scores of both legs were calculated for the data analysis (14).

Falls

A fall was defined as "an event where the participant unintentionally landed on the ground or a lower level." Participants reported their number of falls within the last three months. Since falls were reported retrospectively, this period was chosen to avoid recall bias. Faller participants were those who reported at least one fall over the last three months.

Walking

The fastest walking speed was tested using timed 25-foot walk (T25FW) test in a 7.62-meter walkway (15). The impact of the disease on walking ability from the patient perspective was evaluated using the 12-item multiple sclerosis walking scale-12 (MSWS-12) (16).

Statistics Analyses

All data analyses were conducted using SPSS version 25.0 (Armonk, NY: IBM Corp). Since the MAS comprises a 1+ score, raw scores were converted to a 0-5 point scale (17). Variable distributions were checked for normality using the Shapiro-Wilk W test, the histogram and plot investigation. Chi-square/ Fisher's Exact test and Mann-Whitney U tests were used to test for group disparities. Spearman Rank correlation coefficients were measured to ascertain the association between spasticity, number of falls, and walking. The correlation coefficients between 0.1 and 0.29, 0.3 and 0.49, and 0.5 and 1.0 were considered weak, moderate, and strong correlations, respectively. The significance level was set at $p<0.05$.

Results

The medians and interquartile ranges of the entire group, fallers, non-fallers for the demographics and clinical information are illustrated in Table 1. Of the 39 pwMS, 15 (38.46%) were fallers.

Group differences for the degree of spasticity and walking between fallers and non-fallers are displayed in Table 2. The

Table 1. Demographic and clinical characteristics of the participants

	Total (n=39)	Fallers [n=15 (38.46%)]	Non-fallers [n=24 (61.54%)]
Age (years)	35.4±9.52	37.7±9.28	34.5±8.95
Gender, n (%)			
Female	21 (53.84%)	9 (60%)	13 (54.17%)
Male	18 (46.15%)	6 (40%)	11 (45.83%)
EDSS (0-10)	2.69±1.25	2.8±1.25	2.62±1.27
Clinical course of MS, n (%)			
Relapsing-remitting	35 (89.7%)	13 (86.7%)	22 (91.7%)
Secondary-progressive	4 (10.3%)	2 (13.3%)	2 (8.3%)

p>0.05 for all variables, EDSS: Expanded disability status scale, MS: Multiple sclerosis

Table 2. Comparison of spasticity and walking scores between fallers and non-fallers

	Fallers (n=15)	Non-fallers (n=24)	p
Hip adductors	1 (0-1.5)	0.5 (0-1)	0.484
Knee extensors	0 (0-1)	0 (0-0.5)	0.135
Knee flexors	1 (0.25-1.75)	0 (0-1)	0.071
Ankle plantar flexors	2.5 (2.0-3.0)	1 (0.25-2)	0.009*
T25FW	7.59 (4.44-9.19)	5.91 (5.04-8.34)	0.246
MSWS-12	39 (29-44.5)	37.5 (20.5-46)	0.484

*p<0.05, T25FW: Timed 25-foot walk, MSWS-12: Multiple sclerosis walking scale

Table 3. Correlation coefficients between the degree of spasticity in lower limbs and other outcome measures

	Number of falls		T25FW		MSWS-12	
	rho	p	rho	p	rho	p
Hip adductors	0.144	0.38	0.595	<0.001*	0.440	0.05*
Knee extensors	0.329	0.04*	0.390	0.014*	0.335	0.037*
Knee flexors	0.315	0.055	0.372	0.02*	0.372	0.02*
Ankle plantar flexors	0.497	0.05*	0.692	<0.001*	0.610	<0.001*

*p<0.05, T25FW: Timed 25-foot walk, MSWS-12: Multiple sclerosis walking scale

degree of spasticity in the ankle plantar flexors was significantly greater (p=0.009) in fallers than in non-fallers. Other outcomes disclosed no significant differences between the two groups (p>0.05).

Correlations coefficients between the spasticity scores and the number of falls, and walking scores are represented in Table 3. There were moderate associations between the number of falls and spasticity in the ankle plantar flexors and knee extensors (rho=0.497, rho=0.329; p<0.05, respectively). Spasticity of the entire lower limb was correlated with walking scores. Strong correlations between spasticity severity in the ankle plantar flexors and T25FW (rho=0.692) and MSWS-12 (rho=0.610) were found. The degree of spasticity of the hip adductors was strongly correlated with T25FW (rho=0.595). There were moderate correlations between spasticity severity in the knee flexors and knee extensors and walking performance (rho=0.335-0.390, p<0.05).

Discussion

This study aimed to clarify the direct association between lower limb spasticity and falls in pwMS. The three main findings from this pilot study included (1) A significant association between the number of falls and severity of the spasticity in ankle plantar flexors and knee extensors; (2) Greater spastic severity in ankle plantar flexors than in non-fallers; (3) Performance and perceived walking ability were associated with the severity of spasticity in hip adductors, knee flexors, extensors, and ankle plantar flexors.

These results were similar to some studies reporting an association between lower limb spasticity and walking in pwMS (5,18). Additionally, it has been revealed that individuals with lower limb spasticity have more impaired spatiotemporal parameters and decreased range of motion than those without spasticity (8,19). However, most previous studies have questioned overall spasticity, which was not reported in different muscle groups. Spasticity affects different muscle groups in different locations, including hip adductors, knee extensors and flexors, and triceps surae muscles in pwMS (3). Similar to this study was Norbye et al. (18) who evaluated the same muscle groups with MAS and reported a similar significant correlation between the 2-minute walk test and severity of spasticity in plantar flexors and knee extensors (rho=-0.69 and rho=-0.45, respectively). Plantar flexor spasticity is more associated with gait in both studies confirms the importance of ankle motor control on gait (20). Further exploration is needed to examine the effects of plantar flexor spasticity on gait metrics using instrumental tests at different disability levels.

The significant relationship between spasticity in knee extensors, ankle plantar flexors, and the number of falls complies with the findings of Nilsagård et al. (21). They found a significant association between the mean spasticity level of the lower limbs and falls, and spasticity was a predictor of falls. In contrast, Cattaneo et al. (22) did not delineate an association between the spasticity scores of the most spastic quadriceps, plantar flexors, and falls. In this study, the mean value of both limbs was analyzed, similar to the Nilsagård et al. (21). Moreover, the only measurement that differed between fallers and non-fallers was plantar flexor spasticity. This could be explained by the fact that the activation of plantar flexors suppresses the dorsiflexors during walking and decrease the foot clearance during the swing phase. However, the degree of spasticity in the hip adductors, knee flexors, and walking outcomes was not significantly correlated with the number of falls in this study. We believe this finding may be attributable to having a similar overall disability score in the fallers and non-fallers.

Study Limitations

Although we included a similar number of participants in studies examining spasticity in pwMS, the small sample size is a limitation of our study. Moreover, our findings for associating spasticity and fall cannot be generalized to non-ambulatory pwMS since only ambulatory participants were included. Although there is no gold-standard measurement, we evaluated spasticity using MAS based on subjective clinical assessment rather than instrumented measurements. Furthermore, detailed assessment methods that include rapid passive joint movements, could be more effective in evaluating the existence and severity of spasticity.

Conclusion

Our findings demonstrated a significant association between the degree of ankle plantar flexor and knee extensor spasticity and the number of falls in pwMS. The plantar flexors were the muscle group most associated with falling and walking. Furthermore, our results confirmed the previous studies regarding the significant association between walking and

lower limb spasticity in pwMS. This significant association between spasticity and fall history highlights the importance of designing therapeutic interventions to optimize lower limb spasticity. Moreover, larger sample studies are needed to explore the relationship between spasticity severity in the lower extremities and falls across different disability levels.

Ethics

Ethics Committee Approval: A secondary data analysis was approved by the Dokuz Eylul University Ethics Committee (approval number: 2017/14-07).

Informed Consent: Written informed consent was received from all subjects.

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Authorship Contributions

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

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RESEARCH ARTICLE

The Association of Obesity with Walking and Balance Control in Fully Ambulatory People with Multiple Sclerosis According to Two Different Classifications

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Abstract

Objective: Previous studies have reported that people with obesity have slower walking speed, poor balance control, and more energy expenditure during gait than patients without obesity. However, little is known about the effect of obesity on walking and balance control in people with multiple sclerosis (MS). This study aimed to investigate the associations of obesity with walking and balance control in fully ambulatory people with MS using two different obesity classifications.

Materials and Methods: This study included 210 fully ambulatory people with MS. Obesity classification recommended for MS and obesity classification by the World Health Organization (WHO) were used. Outcome measures included walking speed [timed 25-foot walk (T25FW)], walking endurance [six-minute walk test (6MWT)], perceived walking impairment [12-item ms walking scale (MSWS-12)], and balance control [timed up and go (TUG) test].

Results: According to recommendations for MS and WHO classification, 105 (50%) and 28 (13.3%) participants were classified as obese, respectively. Both groups revealed that patients who are overweight and obese have lower scores in T25FW, 6MWT, and TUG tests, whereas higher scores on the MSWS-12 than patients without obesity, with a significant difference ($p<0.05$).

Conclusion: People who are overweight and obese with MS have poorer performance on walking speed, walking endurance, perceived walking impairment, and balance control than non-obese counterparts. Future longitudinal studies should investigate the effects of losing weight on walking and balance in people with MS.

Keywords: Multiple sclerosis, obesity, walking, balance

Introduction

Multiple sclerosis (MS) is a demyelinating and progressive disease of the central nervous system caused by genetic, lifestyle, and environmental factors (1). Obesity is one of the risk factors for developing MS. Elevated body mass index (BMI) has been associated with a younger age at MS onset and a higher risk for developing MS (2). Additionally, recent research has reported that obesity is associated with greater neuroinflammation, relapse risk, and disability progression (3). Obesity also has adverse effects on depression, functional capacity, and health-related quality of life in people with MS (4,5). Study reports on the prevalence of obesity in MS and the general population are inconsistent (5-7).

Balance problems are common symptoms in MS, even early in the disease course (8). Balance and gait dysfunction is present in 50%-80% of people with MS, and over 50% of patients reported a falling episode at least once a year (8). Of those with mobility impairments, 70% described it as the most

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challenging symptom (9). Obesity is also a risk factor for poor balance and walking difficulties in MS in addition to muscle weakness, cerebellar ataxia, abnormal tone, sensory loss, visual impairments, cognitive impairment, neuropathic pain, and fatigue (9,10).

Kalron (11) reported significant differences in walking speed, step length, step width, and double support period in patients with MS and obesity compared to those with MS and normal weight. Contrarily, Pilutti et al. (10) found no significant difference in various mobility outcomes, such as walking speed and endurance, based on the BMI status. Sebastião et al. (12) showed that patients with MS and obesity have lower cardiorespiratory fitness than overweight and non-obese groups. Studies that investigate the relationship between the lower limb functions and obesity in people with MS have presented mixed results. However, data to understand the effects of obesity on walking and balance control in fully ambulatory people with MS is insufficient.

Two different methods are presented for the classification of obesity in MS. The first one is the standard way that was developed by the World Health Organization (WHO) (13), the second one was recommended by Pilutti and Motl (14). However, no consensus was determined on which to use in MS. Thus, this study aimed to investigate the effect of obesity on walking and balance control in a large sample of fully ambulatory people with MS using two different obesity classifications.

Materials and Methods

Study Design

This cross-sectional study was conducted at the MS Center of Dokuz Eylul University. The baseline data of continuing research entitled, "Follow-up of physical, psychosocial, and cognitive influences in people with MS: a prospective cohort study" (ClinicalTrials.gov Identifier: NCT03878836) was used in the study and approved by the Dokuz Eylul University Ethics Committee (approval number: 2021/12-34 and protocol number: 2959-GOA). The study was conducted following the principles of the Declaration of Helsinki (as revised in Brazil 2013). Written consent was obtained from all participants.

Participants

The inclusion criteria were having MS based on the 2017 McDonald's criteria (15), ability to walk at least 20 m without resting, and a relapse-free period of 30 days. Exclusion criteria were neurological disorder other than MS; relapse throughout the study period; history of orthopedic surgery including ankle-foot, knee, hip, or spine that influences balance and walking. Baseline data of participants were extracted from the registry database [iMed (version 6.8; Merck Serono SA, Geneva, Switzerland)] from October 2016 to October 2020. The data used in these analyses were from our ongoing study that included patients who started or undergoing disease-modifying therapies changes, thus all participants had a relapsing-remitting type of MS.

Obesity classification included two methods, the one recommended by Pilutti and Motl (14). and the WHO classification. Using the recommended method, participants with a BMI of >24.7 kg/m^2 (this cut-off score has been shown as the best threshold that distinguishes body fat-defined obesity in MS) were classified as people with obesity (14). According to the WHO classification, participants were divided into three groups as normal weight (<25.0 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (>30.0 kg/m^2) (13).

Outcome Measures

Demographic and clinical characteristics (gender, age, MS course, and disease duration) were used as baseline data.

The expanded disability status scale (EDSS) scoring, as the universal measure to the disability level in people with MS, is performed according to the neurological examination of seven functional systems (cerebellar, pyramidal, sensory, brainstem, bladder and bowel, visual, and cerebral). The ambulatory state of the patients is also recorded (16). All patients were examined by the same senior MS neurologist, who also calculated the EDSS scores.

The walking speed was assessed by the timed 25-foot walk (T25FW). The T25FW is the best-defined and reliable method to evaluate walking disability in people with MS. Participants were asked to walk in 7.62 m (25 feet) as fast and safely as possible. Time is recorded in seconds. The task was performed twice, and the T25FW score was calculated as the average time of two trials (17).

The six-minute walk test (6MWT) was used to assess walking endurance. The standard guidelines were used while performing the 6MWT. Distance (meters) covered in 6 min was reported. A higher score indicates higher walking endurance (18).

The timed and up go (TUG) test is an objective, reliable, and simple measurement method to evaluate balance and functional mobility. During the test, the participant was asked to stand up from a standard chair, walk 3 m, turn around, walk back to the chair, and sit. The score is the time (seconds) to perform the test (19).

The multiple sclerosis walking scale-12 (MSWS-12) was developed to assess the walking impairment that is perceived by people with MS, which consists of 12 questions with Likert-type answers. A higher score indicates poorer walking performance (20). The valid Turkish version of the MSWS-12 was used (21).

Data Analysis

Normal distribution of data was checked using the Kolmogorov-Smirnov test and histograms. Box plots were used to define the

outlier values for each outcome. The comparison between the groups was performed using an independent-samples t-test for the continuous variables, and the chi-square test for the categorical variables. The multivariate analysis of covariance test was performed to test the differences between the groups. Covariates included age, sex, and the EDSS score. Assumptions for multivariate analysis of covariance were reached according to matrix scatter plots and the Wilk λ test. Partial spearman's correlation coefficients were investigated between the BMI and walking and balance parameters while controlling for EDSS. Statistical significance was set at p-values of <0.05. Data were analyzed using the International Business Machines ® Statistical Package for the Social Sciences ® Statistics software (Version 25.0. Armonk, NY: IBM Corp.).

Results

The data analysis included 210 people with MS. According to the classification that was recommended by Pilutti and Motl (14) (50%) were classified as obese. No significant difference was observed between the groups regarding gender and disease duration (p>0.05). A significant difference was found in age, disability level, and BMI between patients with obesity and without (p<0.05) (Table 1).

Using the WHO criteria, 28 (13.33%) were classified as obese. Significant differences were observed regarding age, gender, disability level, and BMI between the groups (normal weight, overweight, and obese) (p<0.05). Disease duration was not significantly different (p>0.05) (Table 2).

Patients in both classification methods significantly differed in the T25FW, 6MWT, TUG, and MSWS-12 scores with small to medium effect sizes (p<0.05). Table 3 and scatter plots (Figure 1-4) present the detailed comparisons of walking speed, walking endurance, perceived walking impairment, and balance control between the groups. A significant weak correlation was found between the BMI and walking and balance parameters (Table 4).

Discussion

The current study has indicated that obesity is associated with slower walking endurance, walking speed, and balance control, and higher perceived walking impairment in people with MS regardless of the BMI classification methods. The lower limit for obesity based on the classification by Pilutti and Motl (14). is a BMI of >24.7 kg/m^2. With this cut-off, half of our participants fall into the category of obesity. Our data were compared with the general population to evaluate the frequency. In this context,

Table 1. Demographic and clinical characteristics of participants (according to the recommended classification)

	All (n=210)	Non-obese (n=105)	Obese (n=105)	F	p	Observed power
Age (years)	32.7 (9.5)	29.6 (7.3)	35.8 (10.4)	25.032	**<0.001**	0.999
Sex, n (%)						
Female	368 (68.5)	208 (73.0)	160 (63.5)	3.617	0.059	0.473
Male	169 (31.5)	77 (27.0)	92 (36.5)			
EDSS score, possible range: 0-10	1.0 (0.9) (min/max: 0-4)	0.8 (0.7) (min/max: 0-2.5)	1.2 (0.9) (min/max: 0-4)	8.901	**0.003**	0.844
Disease duration (years)	4.8 (4.2)	4.7 (4.1)	5.0 (4.3)	0.247	0.620	0.078
BMI, kg/m^2	24.7 (4.3)	21.2 (2.1)	28.2 (2.8)	422.514	**<0.001**	1.00

Significant p-values are presented in bold. Values are presented as mean (SD) unless specified. EDSS: Expanded disability status scale, BMI: Body mass index

Table 2. Demographic and clinical characteristics of participants (according to the WHO classification)

	Non-obese (n=113)	Overweight (n=69)	Obese (n=28)	F	p	Observed power
Age (years)	30.038 (7.84)	36.16 (11.30)	33.79 (8.20)	8.734	**<0.001**	0.969
Sex, n (%)						
Female	91 (80.5)	44 (63.8)	21 (75.0)	3.207	**0.043**	0.608
Male	22 (19.5)	25 (36.2)	7 (25.0)			
EDSS score, possible range: 0-10	0.85 (0.80) (min/max: 0-4)	1.27 (0.86) (min/max: 0-3)	0.79 (0.85) (min/max: 0-2.5)	6.462	**0.002**	0.902
Disease duration (years)	4.76 (4.13)	4.80 (4.50)	5.15 (3.58)	0.102	0.903	0.065
BMI, kg/m^2	21.46 (2.24)	27.03 (1.31)	32.07 (1.73)	419.132	**<0.001**	1.00

Significant p-values are presented in bold. Values are presented as mean (SD) unless specified. EDSS: Expanded disability status scale, BMI: Body mass index

Table 3. Comparison of walking and balance control between people with obesity and people without obesity adjusted for age, sex, and disability level

	According to recommended classification					According to WHO classification					
	Non-obese (n=105)	Obese (n=105)	F	p	η^2	Observed Power	Non-obese (n=113)	Overweight (n=69)	Obese (n=28)	F	p	η^2	Observed power	Post-hoc
T25FW, sec	4.7 (0.6)	4.9 (0.7)	4.313	**0.039**	0.021	0.543	4.69 (0.58)	4.94 (0.76)	4.83 (0.11)	3.348	**0.037**	0.032	0.628	Non-obese > Overweight
6MWT, m	493.9 (53.5)	464.9 (55.8)	6.033	**0.015**	0.029	0.686	488.77 (53.85)	470.47 (53.94)	463.73 (61.18)	4.134	**0.017**	0.039	0.726	Non-obese > Overweight; Non-obese > Obese
TUG, sec	6.1 (0.8)	6.6 (0.8)	17.901	**<0.001**	0.080	0.988	6.15 (0.75)	6.61 (0.98)	6.67 (0.146)	8.984	**<0.001**	0.081	0.972	Non-obese > Overweight; Non-obese > Obese
MSWS-12, possible range: 12-60	13.4 (1.9)	15.0 (4.0)	8.403	**0.004**	0.039	0.823	13.52 (1.98)	15.13 (4.24)	14.53 (3.41)	5.447	**0.005**	0.051	0.843	Non-obese > Overweight

Significant p-values are presented in bold. Values are presented as mean (SD). Suggested norms for η^2: small=0.01; medium=0.06; large=0.14

T25FW: Timed 25-foot walk, 6MWT: 6 minute walk test, TUG: Timed up and go test, MSWS-12: 12-item Multiple sclerosis walking scale, WHO: World health organization

Figure 1. Comparison of balance control between the groups
WHO: World health organization

Figure 2. Comparison of walking endurance between the groups
WHO: World health organization

Figure 3. Comparison of walking speed between the groups
WHO: World health organization

the limit used to determine obesity in the MS population is approximately the limit of "overweight" compared to the WHO cut-off scores for the general population. The prevalence of overweight and obesity has been found in 65.05% of women and 58% of men in the general Turkish population using the WHO classification. Our study revealed that 41.7% of women

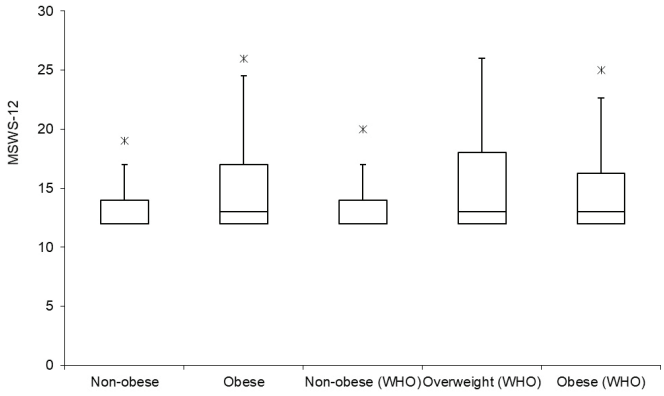

Figure 4. Comparison of perceived walking impairment between the groups

WHO: World health organization

Table 4. Correlation between body mass index and walking and balance parameters

	Body mass index			
	Spearman's correlation		Partial correlation[a]	
	r	p	r	p
T25FW	0.164	**0.017**	0.181	**0.009**
TUG	0.293	**<0.001**	0.280	**<0.001**
6MWT	-0.239	**<0.001**	-0.235	**0.001**
MSWS-12	0.183	**0.008**	0.117	**0.010**

[a]Adjusted for EDSS, Significant p-values are presented in bold. BMI: Body mass index, T25FW: Timed 25-foot walk, 6MWT: 6 minute walk test, TUG: Timed up and go test, MSWS-12: 12-item Multiple sclerosis walking scale

and 59.3% of men were classified as overweight and obese (22). Obesity frequency seems similar in men; however, women with MS have less frequency than the general population.

A recently published review on the comorbidities in MS emphasized that obesity and overweight are associated with longer diagnostic delays, more rapid disability progression, and increased cardiac risk (23). Additionally, Marck et al. (24) showed that overweight and obese people with MS reported a worse quality of life in terms of mental and physical health than those with normal weight. Considering the high prevalence and adverse impact of obesity on the course of MS, patient care, physiological status, and systemic and pulmonary complications, evaluating obesity in MS is of worth (25,26).

Similarly, Kalron (11) examined the obesity in people with MS using 24.7 kg/m^2 as a cut-off value and found that the obese group walked slower and had shorter step lengths, wider step width, and prolonged double support period than non-obese subjects. Additionally, the obese group had shorter distances and poor balance performance on clinical measures. However, no significant differences were found between the groups in MSWS-12 and static postural control assessment that was evaluated with Zebris FDM-T Treadmill. They hypothesized that obesity could have negatively affected the dynamic activities, such as gait, rather than static balance activities (11). This study used the TUG test to evaluate the dynamic balance. Therefore, our results also support this hypothesis.

Furthermore, Pilutti et al. (10) investigated the effects of weight on several mobility parameters, such as gait kinematics and self-reported walking impairment, by classifying the participants into four groups as normal weight, overweight, and obese classes 1 and 2. No significant relationship was found between the weight status and mobility assessments (10). The "obese class 2" group was not included in our study because no BMI value of >35.0 kg/m^2 was recorded. Therefore, walking endurance and balance control was significantly affected in overweight and obese groups compared to non-obese people with MS. However, walking speed and perceived walking impairment were not significantly different between normal and obese groups. Using two classification methods to determine obesity could be the main reason for conflicting results. The low prevalence of obesity in our MS population according to the WHO classification could also add to this discrepancy.

Our study revealed a 1.0 mean EDSS score. However, Liparoti et al. (27) showed that walking impairments could arise from the presence of cognitive impairment, fatigue, and depression in people with MS without any clinically detectable walking abnormalities. Additionally, Ayan et al. (28) reported that people with MS with the absence of clinical disability have a low balance and gait performance compared to the healthy controls. Moon et al. (29) investigated the walking changes in people with MS with minimal disability and compared it with healthy controls using a temporal-spatial gait analysis (GAITRite system). They revealed that walking speed, step features (e.g., length and width), and double support time were affected people with MS with minimal disability compared to the controls (29). This finding makes us think that walking impairments and balance problems can occur even in people with lower levels of disability, and higher BMI could be one of the risk factors.

Furthermore, studies that investigate the effects of obesity in the general population reported possible compensator alterations of gait mechanics, such as decreased walking speed, prolate double support, and stance times, in the obese and overweight subjects (30). Manawat and Shweta (31) compared obese people with non-obese to determine the relationship between the BMI and 6MWT and revealed that increases in BMI induce decreases in 6MWT performance. Likewise, a negative correlation was detected between the BMI and 6MWT, whereas a positive correlation between the BMI and walking speed, perceived walking impairment, and balance control.

In the clinic aspect, many studies have investigated the effects of different types of exercise modalities to improve walking and balance; however, little is known about the management of obesity that could positively affect walking and balance

performance (32,33). Mokhtarzade et al. (34) reported that elevated body composition might adversely influence the progression, course, and treatment in the MS progression, which is directly related to gait and balance. Additionally, Pilutti et al. (35) provided some evidence about the efficacy of 6-month internet-delivered physical activity behavioral intervention on body composition. A systematic review demonstrated that aerobic and strength exercises are the essential parts of dealing with obesity in the general population; however, even the most effective intensity and type of exercise are still unclear (36). Therefore, body composition should be considered when prescribing exercise for walking impairment and balance problems in people with MS.

Strengths of this research include the large sample size that increases the study's power and the low level of disability of participants that eliminated other factors that affect walking and balance in MS. The study has limitations in the used measurement methods. BMI used to identify obesity is cost effective and convenient to use. However, it does not provide information about people's adiposity. Clinical measurement technics were used for walking and balance assessment. Laboratory-based measurement could provide more detailed information on the characteristics of walking and balance. Another limitation is the absence of a healthy control group, which could help us understand the differences in walking that arise from obesity that are specific to people with MS.

Conclusion

This study revealed that people who are overweight and obese with MS have less walking speed, walking endurance, perceived walking impairment, and balance control than non-obese counterparts regardless of the BMI classification method. Moreover, we speculate that being overweight and obese could be important factors affecting walking and balance in people with mild disability in MS. Future studies can provide answers to the management of obesity via exercise programs to improve walking and balance control in people with MS.

Acknowledgments

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Ethics

Ethics Committee Approval: The study and approved by the Dokuz Eylul University Ethics Committee (approval number: 2021/12-34 and protocol number: 2959-GOA).

Informed Consent: Written consent was obtained from all participants.

Authorship Contributions

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

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CASE REPORT

Subdural Hemorrhage Mimicking Relapse in a Patient with Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system, which is more common in young adults and can present with various clinical manifestations. The emerging neurological findings in the course of MS are often considered as relapses; however, neurological deterioration may have other treatable causes than relapses. No data are indicated in the increased frequency of the overall hemorrhagic stroke in individuals with MS, thus the coexistence of MS and subdural hematoma has been rarely reported. This study presents a 49-year-old male patient with a subdural hematoma that mimics a relapse. Recently emerging neurological symptoms in the course of MS frequently indicate a new demyelination event; however, emerging neurological symptoms may have other treatable causes besides relapse, especially in the presence of red flags such as headaches.

Keywords: Demyelinating disorder, multiple sclerosis, subdural chronic hematoma

Introduction

Multiple sclerosis (MS) is a chronic and persistent inflammatory demyelinating disease of the central nervous system that is pathologically characterized by areas of inflammation, demyelination, axonal loss, and gliosis (1). Recently developing neurological symptoms are often considered as a new active demyelination episode in the course of relapsing-remitting MS, without infection or fever (2). Accurate identification of the demyelinating attack in the patient's history or objective detection by examination is critical in MS diagnosis and treatment. Red flags were defined, such as headache, acute or subacute cognitive impairment, and steroid unresponsive neurological deficit, which represent an atypical relapse (3). A distinction of the relapse mimics from true demyelination episodes requires expertise and rigorous clinical judgment. The most common disorders that are mistaken with MS are reported to be functional neurological disorders and migraine (4). Additionally, cerebrovascular disorders may mimic relapse, and subdural hemorrhage (SDH) is a surgically treatable cause of neurological deterioration in persons with MS (pwMS). Reported herein is a case of SDH that mimics relapse, which is initially treated with high-dose methylprednisolone.

Case Report

A 49-year-old male patient was admitted to our clinic 10 years ago with dizziness and gait impairment. The patient was diagnosed with MS based on physical examination, neuroimaging (Figure 1), and cerebrospinal fluid examination. After his diagnosis, he was treated with interferon β 1 b; however, he experienced approximately two relapses annually, which are mainly motor and cerebellar functions. In the fourth year of treatment, he was admitted again with gait impairment complaints. The physical examination revealed bilateral 3/5 muscle strength on the lower extremity and 4/5 on the bilateral upper extremity. Further, deep tendon reflexes were generalized hyperactive, and the bilateral Babinski sign was positive. The expanded disability status scale score was 3. This new neurological function loss was evaluated as an attack and intravenous methylprednisolone treatment was initiated. However, despite the 3-day course of pulse steroid treatment, the patient's clinical findings did not improve. Additionally, he began to experience mild to moderate

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headache that was not previously present. Brain magnetic resonance imaging was performed because of the red flags for neurological deterioration, which revealed a bilateral subacute SDH (Figure 2).

SDH was successfully treated with bilateral burr-hole (Figure 3). The patient reached the previous neurological stage after the operation. During the 6-year follow-up period after SDH, SDH was not observed again; however, the secondary progression of MS continued. The treatment was first shifted to fingolimod and subsequently to ocrelizumab upon progression.

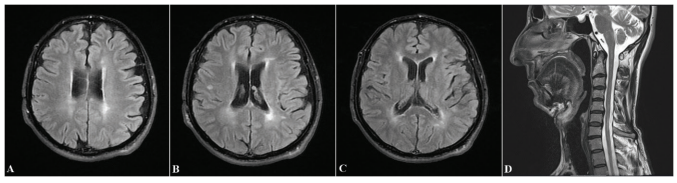

Figure 1. A, B, C. Periventricular, subcortical, and deep white matter hyperintense lesions are seen on the fluid-attenuated inversion recovery (FLAIR) images. D. T2-weighted images reveal hyperintense lesions and a slight volume loss of the cervical spinal cord

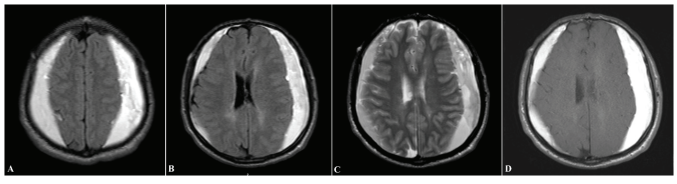

Figure 2. A, B, C. FLAIR and T2-weighted images reveal hyperintense signal in the subdural space with slight hypointense areas. D. T1-weighted images reveal hyperintense signal in the subdural space. Additionally, effacement is observed in both lateral ventricles, which is more prominent on the left side

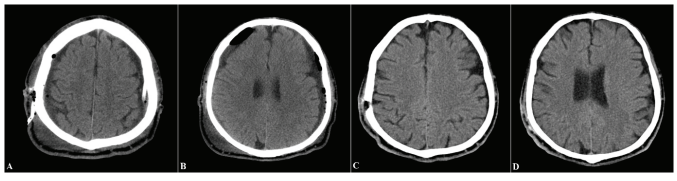

Figure 3. A, B. Early postoperative computed tomography (CT) images reveal air intensities in the subdural space with an indwelling drain. C, D. CT images one month after operation reveal complete improvement in the subdural hemorrhage

Discussion

To our best knowledge, this is the fourth case of SDH ever reported in a pwMS. SDH is a common disease characterized by the abnormal collection of blood products in the subdural space (5). Individuals with MS may clinically present with monofocal or multifocal symptoms. Typical symptoms of MS include unilateral optic neuritis, focal supratentorial syndrome, focal brainstem or cerebellar syndrome, partial myelopathy with atypical presentations being bilateral optic neuritis, complete ophthalmoplegia, complete myelopathy, encephalopathy, headache, altered consciousness, meningismus, or isolated fatigue (2). The first case of SDH in a pwMS was reported by Harding (6) who experienced SDH associated with a lumbar puncture. In addition, Magro et al. (7) reported bilateral subacute subdural hematoma following implantation of intrathecal drug delivery device in a pwMS. The first study about spontaneous SDH was published by Flohil et al. (8) who described two cases of unilateral SDH without trauma or headache. As in our case, they were initially misinterpreted as a relapse because of the MS history of patients.

The risk of SDH in pwMS can be explained by several possible mechanisms. Brain atrophy is a well-known risk factor for SDH (5). In addition, stretching the bridge veins secondary to brain volume loss, which inevitably arises in the course of the disease, may increase the risk of SDH in MS. Moreover, interferon β 1 b treatment was reported to affect the platelet count and function causing a tendency to bleed (9). In an early report, Pakulski et al. (10) reported severe vaginal bleeding probably associated with interferon β 1 b. Subsequently, Perlman and DiMarco (11) reported postmenopausal bleeding in a pwMS receiving interferon β 1 b probably due to elevated estrogen levels with unknown mechanisms. Although pwMS were reported to have an increased risk of developing any type of stroke compared with the general population, increased frequency of hemorrhagic stroke compared to matched controls were not found (12). Contrarily, PwMS have increased balance issues and are more likely to fall, which may lead to head trauma (5). The risk of developing SDH in a pwMS appears to have increased for several reasons, but few reports are available in the literature.

This discordance suggests the underdiagnosis of SDH in pwMS. In addition, the elevated risk of falling due to the loss of balance and vision in pwMS increases the risk of SDH.

Consequently, the third case with spontaneous SDH and first bilateral SDH in pwMS was presented in this study to attract attention to a treatable cause of relapse mimic. Recently emerging neurological symptoms in the course of MS frequently point to a new demyelination event; however, neurological deterioration should be kept in mind to also have different reversible causes, such as SDH, especially in the presence of red flags, such as headache and unresponsiveness to steroid treatment.

Ethics

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: M.F.Y, M.F.G., M.M., Concept: M.F.Y, M.F.G., Design: M.F.Y., M.M., Data Collection or Processing: M.F.Y., M.M., Analysis or Interpretation: M.F.Y., M.A., Literature Search: M.F.Y., M.A., Writing: M.F.Y., M.A.

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

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