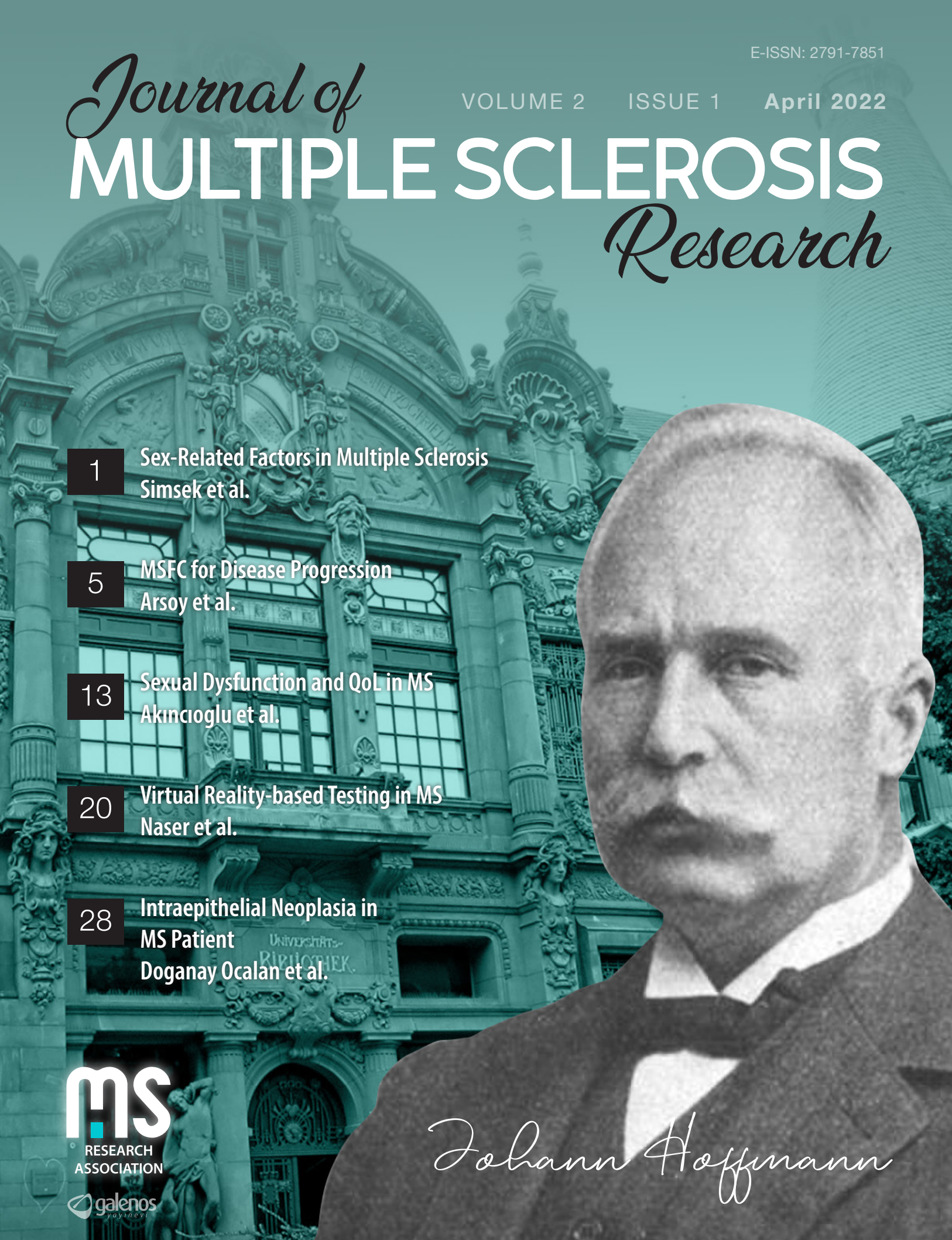
E-ISSN: 2791-7851

VOLUME 2 ISSUE 1 April 2022

Journal of MULTIPLE SCLEROSIS Research



Johann Hoffmann

MS RESEARCH ASSOCIATION

galenos yayınevi

Journal of
MULTIPLE SCLEROSIS
Research

MS ARAŞTIRMALARI DERNEĞİ

galenos yayınevi

Galenos Yayınevi Kurucusu ve Sahibi/ Galenos Publishing House Owner and Publisher
Derya Mor
Erkan Mor

Genel Yayın Koordinatörü/Publication Coordinator
Burak Sever

Web Koordinatörleri/Web Coordinators
Fuat Hocalar
Turgay Akpınar

Grafik Departmanı/Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülay Saday
Gülşah Özgül

Finans Koordinatörü/Finance Coordinator
Sevinç Çakmak
Emre Kurtulmuş

Proje Koordinatörleri/Project Coordinators
Aysel Balta
Duygu Yıldırm
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu
Sümeyye Karadağ

Araştırma&Geliştirme/Research&Development
Nihan Karamanlı
Melisa Yiğitoğlu

Dijital Pazarlama Uzmanı/ Digital Marketing Specialist
Ümit Topluoğlu

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Telefon/Phone: +90 (212) 621 99 25
Faks/Fax: +90 (212) 621 99 27
E-posta/E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Yayıncı Sertifika No:** 14521

Online Yayınlanma Tarihi/Online Publication Date: Nisan 2022/April 2022

E-ISSN: 2791-7851

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

Journal of MULTIPLE SCLEROSIS Research

MS ARAŞTIRMALARI DERNEĞİ

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.

Processing of articles and publication are free of charge. No fee is requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available through the journal's web page.

The editorial processes are designed in accordance with the guidelines of international organizations such as the International Council of Medical Journal Editors (ICMJE) (http://www.icmje.org) and the Committee on Publication Ethics (COPE) (http://publicationethics.org).

All manuscripts should be submitted through the journal's web page at www.jmsres.com. Instructions for authors, technical information, and other necessary forms can be accessed over this web page. Authors are responsible for all contents of their manuscript.

The mission of the *Journal of Multiple Sclerosis Research* is to provide practical, timely, and relevant clinical and basic science information to all health professionals and researchers working in the field of multiple sclerosis.

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.

Open Access Policy

The *Journal of Multiple Sclerosis Research* provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

The Open Access Policy is based on the rules of the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/). "Open access" to peer-reviewed research literature means that it is freely available on the Internet, permitting any user access to the link with the full text of articles to read, download, copy, distribute, print, search, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose without financial, legal, or technical barriers, other than those inseparable from gaining access to the Internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over their work's integrity and the right to be properly acknowledged and cited.

Address for Correspondence

Organization: Multiple Sclerosis Research Association

Address: Korutürk Mah. V. Hüseyin Öğütçen Cad. No: 45/B D: 8 Balçova/İzmir

Phone: (0232) 484 74 80

E-mail: info@msarastirmalaridernegi.com

Issuing Body

Galenos Yayınevi Tic. Ltd. Şti.

Molla Gürani Mah. Kaçamak Sok. No: 21, 34093, Fındıkzade, İstanbul, Türkiye

Phone: +90 212 621 99 25

Fax: +90 212 621 99 27

E-mail: info@galenos.com.tr

Copyright Notice

Material Disclaimer

The author(s) is (are) responsible for the articles published in the *Journal of Multiple Sclerosis Research*. The Editor, Editorial Board, and Publisher do not accept any responsibility for the articles.

Journal of MULTIPLE SCLEROSIS Research

MS ARAŞTIRMALARI DERNEĞİ

INSTRUCTIONS TO AUTHORS

Journal of Multiple Sclerosis Research is the official open access scientific publication organ of the Multiple Sclerosis Research Association, with English as the journal's publication language.

Journal of Multiple Sclerosis Research does not charge any fee for article submission or processing and publication. Also, manuscript writers are not paid by any means for their manuscripts.

The journal should be abbreviated as "J Mult Scler Res" when referenced.

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.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org).

Editorial Process

The manuscript submission and editorial review process are as follows:

After receiving each manuscript, a checklist is completed by the editorial assistant. The editorial assistant checks that each manuscript contains all required components and adheres to the author guidelines, after which time it will be forwarded to the editor in chief. Following the editor in chief's evaluation, each manuscript is forwarded to the associate editor, who assigns reviewers. The selected reviewers (at least three) will generally review all manuscripts based on their relevant expertise. The associate editor could also be assigned as a reviewer along with the reviewers. After the reviewing process, all manuscripts are evaluated in the editorial board meeting.

The Review Process

This journal applies double-blind review, which means that the reviewers cover both the reviewer and the author identifications throughout the review process.

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).

Journal of MULTIPLE SCLEROSIS Research

MS ARAŞTIRMALARI DERNEĞİ

INSTRUCTIONS TO AUTHORS

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.

Manuscript Format and Style

Writing rules

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

a. Title

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

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

d. Copyright Transfer Form and Authorship Contribution Form

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

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.

Word Count: The word count does not include the abstract, references, or figure/table legends. The word count must be noted on the title page, along with the number of figures and tables. Original articles should be less than 3000 words and include no more than six figures, tables and 50 references.

Tables and figures: All tables and figures must be placed after the text and must be labelled.

Data Sharing Policies: Data sharing policies concern the minimal dataset that supports the central findings of a published study. Generated data should be publicly available and cited in accordance with the journal guidelines. Authors must inform the journal about the tables and figures created.

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

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

Journal of MULTIPLE SCLEROSIS Research

MS ARAŞTIRMALARI DERNEĞİ

INSTRUCTIONS TO AUTHORS

Original articles should have the following sections:

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

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

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

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

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

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

Conclusion: The conclusion of the study should be highlighted.

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

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

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

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

4. Images: Authors can submit for consideration an illustration and photos that are interesting, instructive, and visually attractive, along with a few lines of explanatory text and references. No abstract, discussion, or conclusion is required, but a brief title should be included.

5. Letters to the Editor: A letter to the editor (sometimes abbreviated LTTE or LTE) is a letter sent to a publication about issues of concern from its readers. In academic publishing, letters to the editor of an academic journal are usually open post-publication reviews of a paper, often critical of some aspects of the original paper. For letters to the editor, no abstract is required, but a brief title should be included.

6. Invited Review Article: Invited review articles are comprehensive analyses of specific topics in medicine, which are written upon invitation due to extensive experience and publications of authors on their view of the subjects. All invited review articles will also undergo peer review prior to acceptance.

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.

Tables, Graphics, Figures, and Images

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.

Authorship

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

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

Contributor's Statement

All submissions should contain a contributor's statement page. Each manuscript should contain substantial contributions to idea and design, acquisition of data, or analysis and interpretation of findings. All persons designated as an author should qualify for authorship, and all those that qualify should be listed. Each author should have participated sufficiently in the work to take responsibility for appropriate portions of the text.

Acknowledgement

The support received from individuals, organizations, grants, corporations, and any other source should be acknowledged. For work involving a biomedical product or potential product partially or wholly supported by corporate funding, a note stating "This study was financially supported (in part) with funds provided by (company name) to (authors' initials)" must be included. Grant support, if received, needs to be stated and the specific granting institutions' names and grant numbers provided when applicable.

Authors are expected to disclose on the title page any commercial or other associations that might pose a conflict of interest in connection with the submitted manuscript. All funding sources that supported the work and the institutional and/or corporate affiliations of the authors should be acknowledged on the title page.

Ethics

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

INSTRUCTIONS TO AUTHORS

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.

Noncompliance with scientific accuracy is not in accord with scientific ethics.

Plagiarism Detection

Plagiarism is a serious problem, and the most common ethical issue afflicting medical writing.

Journal of Multiple Sclerosis Research does not allow any form of plagiarism. In accordance with our journal policy, submitted manuscripts are screened with plagiarism software to detect instances of overlapping and similar text (iThenticate) at least two times (during the evaluation process and after acceptance).

Conditions of Publication

All authors are required to affirm the following statements before their manuscript is considered:

Submission is considered on the condition that papers are previously unpublished and are not offered simultaneously elsewhere, that all authors have read and approved the content, that authors have declared all competing interests, and that the work has been conducted under internationally accepted ethical standards after relevant ethical review.

All authors are responsible for the manuscript's content.

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

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

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

Abbreviations and Symbols

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.

Subscription Information

Multiple Sclerosis Research Association

Korutürk Mah. V. Hüseyin Öğütçen Cad. No: 45/B D: 8 Balçova/İzmir

Phone: (0232) 484 74 80

Online Submission:

Web page: jmsres.com

E-mail: info@jmsres.com

Correspondence

All correspondence should be directed to the journal's editorial.

Editor in chief: Prof. Dr. Serkan OZAKBAS

Journal of MULTIPLE SCLEROSIS Research

MS ARAŞTIRMALARI DERNEĞİ

PEER REVIEW

Editorial policies of the journal adhere to the rules advised by the Council of Science Editors and are reflected in uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication (http://www.icmje.org/).

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

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

Ethics

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

The approval of the Ethics Committee, statement on the adherence to international guidelines, and patient's informed consent should be indicated in the "Materials and Methods" section. These are also required for case reports whenever data/media used could reveal the identity of the patient. The declaration of a conflict of interest between authors and institutions and acknowledgment of any financial or material support and aid is mandatory for submission of the manuscript. Relevant statements should be written at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists among reviewers, authors, and institutions.

We disapprove unethical practices such as plagiarism, fabrication, duplication, and salamisation, as well as efforts to influence the review process with practices such as gifting authorship, inappropriate acknowledgments, and references. Additionally, authors must respect participants' right to privacy. Moreover, short abstracts published in congress books that do not exceed 400 words, present preliminary research data, and are presented in an electronic environment are not accepted as pre-published work. Authors in such a situation must declare this status on the first page of the manuscript and in the cover letter. (The Committee on Publication Ethics flowchart is available at: http://publicationethics.org) All responsibility of the published articles belongs to the authors.

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.

Journal of MULTIPLE SCLEROSIS Research

MS ARAŞTIRMALARI DERNEĞİ

CONTENTS

DOI: 10.4274/jmsr.galenos.2022.2022-5-1
Journal of Multiple Sclerosis Research 2022;2(1):1-4

RESEARCH ARTICLE

Effects of Sex-Related Factors on Disability Risk in Women with Multiple Sclerosis

Yasemin Simsek[1], Asiye Tuba Ozdogar[2], Sinem Ozcelik[3], Ulvi Samedzade[3], Taha Aslan[3], on behalf of Multiple Sclerosis Research Group

[1]Multiple Sclerosis Research Association, Izmir, Turkey
[2]Dokuz Eylul University, Graduate School of Health Sciences, Izmir, Turkey
[3]Dokuz Eylul University Faculty of Medicine, Department of Neurology, Izmir, Turkey

Abstract

Objective: It has been reported that estrogen may affect T helper (Th) 1 and Th-2 lymphocytes and the ratio of Th-1 to Th-2, which play an essential role in the immunopathogenesis of multiple sclerosis (MS). Therefore, hormonal changes during transitional periods, such as pregnancy and menopause, may affect the activity of the disease at different phases of the menstrual cycle. This study aimed to determine the association of MS in women with variables, such as menarche age, menstrual order, menopausal age, and disease-related factors, such as disability level and the number of relapses.

Materials and Methods: This descriptive study enrolled 281 women with MS. The participants were evaluated using a simple and short survey by the researchers. A neurologist evaluated the Expanded Disability Status Scale (EDSS) score, the number of attacks, and disease duration.

Results: Sixty-seven (23.8%) of 281 patients had entered menopause. There was no significant difference in the EDSS score of women with MS with or without menopause ($p>0.05$). Sixty patients (21.4%) had children after MS. There was no significant difference between the number of relapses before (1.87±1.46) and after having a child (3.15±3.59) ($p>0.05$). Additionally, the last EDSS score (2.46±2.07) was not different from the EDSS score after having a child (2.35±1.81) ($p>0.05$). It was found that 80.4% of the patients had a regular menstrual cycle, whereas 19.6% of them had an irregular cycle. The EDSS score was significantly higher in women with irregular menstrual cycles than in women with regular menstrual cycles ($p<0.05$). The age at menarche in the study group (13.07) was found to be earlier than the average age at menarche in Turkey (13.3) ($p<0.05$).

Conclusion: This study suggested that menopause and childbearing may not affect disability level or the number of attacks in women with MS. Additionally, women with MS have an earlier age at menarche compared with the general population. Future studies should investigate earlier age at menarche as a possible risk factor in MS.

Keywords: Multiple sclerosis, women, disability, menarche

Introduction

Multiple sclerosis (MS) is a chronic, progressive, demyelinating disease that affects over 2.5 million people worldwide and is more common in young adults aged 20-40 years. The incidence of MS is 2-3 times higher in women than in men (1). Pregnancy is an essential clinical condition in individuals with MS since the age of onset of MS usually coincides with the reproductive period in women. While the woman's immune system is modulated to protect the developing fetus during pregnancy, a remission period is frequently observed for autoimmune diseases due to the effect of hormones during pregnancy (2). It has also been shown that the cure rate is increased in other cell-mediated autoimmune diseases, including psoriasis and rheumatoid arthritis, during pregnancy (3). An increase in estrogens (estradiol, estriol) and progesterone may be responsible for the immunomodulation. These hormones peak in the third trimester of pregnancy, the time when the most significant protection against a disease occurs (4).

Additionally, there are slight changes in other hormones, such as cortisol, during pregnancy. It increases early in pregnancy, is

Address for Correspondence: Asiye Tuba Ozdogar, Dokuz Eylul University, Graduate School of Health Sciences, Izmir, Turkey
E-mail: asiye.tuba.ozdogar@gmail.com **ORCID-ID:** orcid.org/0000-0003-0043-9374
Received: 26.05.2022 **Accepted:** 29.05.2022

short-lived, and contributes less to protection against disease in the last trimester of pregnancy. Estrogen is neuroprotective in various neurological disease models and plays a role in normal cognitive development, and this is assumed to be evolutionary. It is advantageous for a pregnancy factor to be both immunomodulatory and neuroprotective because these properties enable the fetus to survive as an allogeneic and protect the developing brain. It may also be an ideal mechanism to protect the fetus in mothers with MS (5). Additionally, decades of observation have shown that women with MS have fewer attacks during pregnancy, but there is an increase in postpartum relapses later. Clinical observations highlight the fact that the onset of MS in women occurs after delivery. Therefore, pregnancy, childbirth, and the postpartum period are turning points for women with MS (6).

In a study that followed up 227 women with MS prospectively, a 70% decrease in the attack rates was shown in the third trimester of pregnancy. In the same study, the rate of attacks in the postpartum period was higher than that before pregnancy. It has been shown that during the following postpartum year, the frequency of attacks decreased, and the attack rate returned to that of the prepregnancy period (7).

The effect of the last trimester of pregnancy on the increase in postpartum attacks or permanent disability accumulation has been a controversial issue. While short-term studies that followed up patients for ≤2 years showed that pregnancy does not affect disability, long-term studies have shown that multiple pregnancies in women with MS cause less disability and/or prolong the time taken to reach a certain level of disability (8-10).

Other turning points for women with MS are menarche age and menopause. Azimi et al. (11) conducted a systematic review to define the role of age at menarche in MS and found that the risk of MS was negatively correlated with age at menarche (11). In contrast, Zuluaga et al. (12) investigated the effects of menarche on the risk of developing MS and found that there was no relationship between age at menarche and the risk of developing MS (12).

Therefore, this study aimed to determine the association of MS in women with menarche age, menstrual order, menopausal age, and disease-related factors such as disability level and the number of attacks. The results of this study will contribute to the literature and provide a different perspective on the effects of sex-related factors on the course of the disease in women with MS.

Materials and Methods

Participants and Procedures

This study was conducted in the MS Center of Dokuz Eylul University Hospital, Izmir, Turkey. The research protocol was approved by the Dokuz Eylul University Ethics Committee (decision number: 2021/28-02, date:13.10.2021). Written consent was obtained from all participants before the assessment.

The eligibility criteria were diagnosis of definite MS according to current diagnostic criteria, age >18 years, and being a woman. The exclusion criterion included women unable to follow instructions.

Outcome Measures

Information, such as age, MS diagnosis year, and disease course of the patients, were obtained from the records in iMed7.0.

Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS) is the most widely used scale for assessing disability in patients with MS. EDSS scoring is based on the neurological examination of the seven functional systems and the patient's ambulation status. Functional systems are ordered as pyramidal, cerebellar, brainstem, sensory, bladder and intestinal, visual, and cerebral. The total score ranges from 0 to 10 (13).

Semistructured Interview

It consisted of 10 questions investigating the age at menarche, presence of menopause, age at menopause, menstrual cycle, and course of the disease in women with MS before, during, and after pregnancy. A nurse who was an expert in MS performed the semistructured interviews.

Sample Sizes

It is recommended to include at least 10% of the total population in descriptive studies (14). There are ~2000 registered women with MS in the MS Center of Dokuz Eylul University Hospital. Therefore, the smallest sample size to be included in the study was planned as 200.

Statistics Analyses

Data were analyzed using the IBM SPSS (version 24.0. Armonk, NY: IBM Corp) program. Kolmogorov-Smirnov/Shapiro-Wilk tests and analysis of graphs were used to determine whether the data were normally distributed. Since the variables did not show a normal distribution, all analyzes were performed with nonparametric methods. Descriptive analyses were presented as percentages and median (interquartile range). Mann-Whitney U test was used to analyze differences between groups for continuous variables.

Results

Most of the participants had a relapsing-remitting disease course (86.8%). The median EDSS score of the participants was 2.0 (range between 0 and 7) (Table 1). Sixty-seven (23.8%) of 281 patients had entered menopause. There was no significant difference in the EDSS score of pwMS with or without menopause ($p>0.05$). Sixty patients (21.4%) had children after

Table 1. Demographic and clinical characteristics of the participants (n=281)	
Age (years)	38.0 (31.0-48.0)
Age at menarche	13.0 (12.0-14.0)
Age at menopause	46.5 (43.0-50.0)
EDSS score	2.0 (1.0-3.5)
Disease duration (years)	8.0 (4.0-14.0)
Number of attacks	3.0 (2.0-5.0)
Disease course	
Relapsing-remitting MS	244 (86.8%)
Secondary-progressive MS	32 (11.4%)
Primer-progressive MS	5 (1.8%)

EDSS: Expanded disability status scale, MS: Multiple sclerosis

MS. There was no significant difference between the number of relapses before (1.87±1.46) and after having a child (3.15±3.59) (p>0.05). Additionally, the last EDSS score (2.46±2.07) was not different from the EDSS score after having a child (2.35±1.81) (p>0.05). According to Adalı and Koç's (15) study, the mean age at menarche was 13.3 in Turkey (15). When comparing the mean age at menarche among women with and without MS in Turkey, a significant difference was found (13.3 versus 13.07) (p=0.007).

It was found that 80.4% of the patients had a regular menstrual cycle, while 19.6% of them had an irregular cycle. The EDSS score was significantly higher in women with irregular menstrual cycles than in women with regular menstruation cycles (p<0.05). The detailed information is presented in Table 2.

Discussion

This study was conducted to describe the effects of sex-related factors on disability in women with MS. Our result showed that the average age at menarche was significantly different in women with MS compared to the general population. Additionally, the women with MS who had irregular menstrual cycles had higher EDSS scores than their regular counterparts. However, there were no significant differences between pwMS with or without menopause in terms of clinical characteristics.

There is no consensus related to the effects of earlier age at menarche on the disease course of MS. Antonovsky et al. (16) compared the age at menarche between women with MS and healthy controls and found no significant difference in terms of the average age of menarche. However, the study was conducted in Israel, and participants consisted of a mixed population, which could affect menstruation due to the heterogeneous genetic background (16). Besides, Zuluaga et al. (12) included 501 female pwMS with a clinically isolated syndrome and assessed the age at menarche as a risk of clinically definite MS. They reported that menarche is not a risk factor for MS (12). A recent systematic review demonstrated that late age at menarche might have a protective effect on MS onset. However, the authors highlighted that the mechanism should be investigated in future studies (17). The present study showed that women with MS had an earlier age at menarche than the average age in Turkey. We speculated that earlier age at menarche led to increased estrogen exposure, which may have affected the occurrence of MS. Additionally, women with irregular menstrual cycles had higher disability levels. These findings also support the fact that hormonal instability could be an influential factor in the progression of MS. Moreover, there was no relationship between menopause, childbearing, and clinical characteristics of MS. This could improve the management of the pregnancy period by neurologists in our clinic. When patients decided to have a child, whole process running with the neurologists and the best time is determine together.

Study Limitations

This study has some limitations. First, we did not include healthy controls to compare the menstruated periods, which could provide detailed information. Second, we used a self-reported method to evaluate the sex-related factors. This method has the disadvantage of being subject to memory bias, especially regarding the age at menarche. Using objective methods to assess hormonal levels may help in understanding the biological mechanisms. Third, the results of the present study cannot be generalized. Therefore, further multicenter studies need to be conducted.

Table 2. Comparison of clinical outcomes according to the menstrual cycle					
	Menstrual cycle (n=214)				
	Regular (n=171)		Irregular (n=43)		
	Median	IQR	Median	IQR	p
EDSS	1.5	1.0-2.0	2.25	1.0-5.5	**0.001***
Disease duration (years)	6.0	3.0-12.0	6.5	3.0-10.25	0.294
Number of attacks	3.0	2.0-5.0	2.5	2.0-4.0	0.746

*Statistically significant. IQR: Interquartile range, EDSS: Expanded Disability Status Scale

Conclusion

This study suggested that menopause and childbearing may not affect the disability level or the number of attacks in women with MS. However, women with MS have an earlier age at menarche, which could be linked to an increased risk of MS or an earlier age at MS symptom onset.

Ethics

Ethics Committee Approval: The research protocol was approved by the Dokuz Eylul University Ethics Committee (decision number: 2021/28-02, date:13.10.2021).

Informed Consent: Written consent was obtained from all participants before the assessment.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: The Authors declare no conflict of Interest.

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

References

1. University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle, 1993.
2. Voskuhl R, Momtazee C. Pregnancy: Effect on Multiple Sclerosis, Treatment Considerations, and Breastfeeding. Neurotherapeutics 2017;14:974-984.
3. Whitacre CC, Reingold SC, O'Looney PA, Blankenhorn E, Brinley F, Collier E, Duquette P, Fox H, Giesser B, Gilmore W, Lahita R, Nelson JL, Reiss C, Riskind P, Voskuhl R. A gender gap in autoimmunity. Science 1999;283:1277-1278.
4. Arevalo MA, Santos-Galindo M, Bellini MJ, Azcoitia I, Garcia-Segura LM. Actions of estrogens on glial cells: Implications for neuroprotection. Biochim Biophy Acta 2010;1800:1106-1112.
5. Spence RD, Voskuhl RR. Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. Front Neuroendocrinol 2012;33:105-115.
6. Nguyen AL, Eastaugh A, van der Walt A, Jokubaitis VG. Pregnancy and multiple sclerosis: Clinical effects across the lifespan. Autoimmun Rev 2019;18:102360.
7. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Eng J Med 1998;339:285-291.
8. D'Hooghe M B, Haentjens P, Nagels G, D'Hooghe T, De Keyser J. Menarche, oral contraceptives, pregnancy and progression of disability in relapsing onset and progressive onset multiple sclerosis. J Neurol 2012;259:855-861.
9. Masera S, Cavalla P, Prosperini L, Mattioda A, Mancinelli CR, Superti G, Chiavazza C, Vercellino M, Pinessi L, Pozzilli C. Parity is associated with a longer time to reach irreversible disability milestones in women with multiple sclerosis. Mult Scler 2015;21:1291-1297.
10. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. Brain 1995;118:253-261.
11. Azimi A, Hanaei S, Sahraian MA, Mohammadifar M, Ramagopalan SV, Ghajarzadeh M. Age at menarche and risk of multiple sclerosis (MS): a systematic review and meta-analysis. BMC Neurol. 2019;19:286.
12. Zuluaga MI, Otero-Romero S, Rovira A, Perez-Hoyos S, Arrambide G, Negrotto L, Galán I, Río J, Comabella M, Nos C, Arévalo MJ, Vidal-Jordana A, Castilló J, Rodríguez B, Midaglia L, Mulero P, Mitjana R, Auger C, Sastre-Garriga J, Montalban X, Tintoré M. Menarche, pregnancies, and breastfeeding do not modify long-term prognosis in multiple sclerosis. Neurology 2019;92:e1507-e1516.
13. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-5142.
14. Lemeshow S, Hosmer D, Klar J, Lwanga S. Sağlık araştırmalarında örneklem büyüklüğünün yeterliliği. Çeviren: S Oğuz Kayaalp Hacettepe-TAŞ Kitabevi, Ankara, 2000.
15. Adalı T, Koç I. Menarcheal age in Turkey: secular trend and socio-demographic correlates. Ann Hum Biol 2011;38:345-353.
16. Antonovsky A, Leibowitz U, Medalie JM, Smith HA, Halpern L, Alter M. Epidemiological study of multiple sclerosis in Israel: Part III Multiple sclerosis and socio-economic status. J Neurol Neurosurg Psychiatry 1967;30:1-6.
17. Jiang X, Olsson T, Alfredsson L. Age at Menarche and Risk of Multiple Sclerosis: Current Progress from Epidemiological Investigations. Front Immunol 2018;9:2600.

DOI: 10.4274/jmsr.galenos.2022.2022-3-1
Journal of Multiple Sclerosis Research 2022;2(1):5-12

RESEARCH ARTICLE

The Multiple Sclerosis Functional Composite (MSFC) for Determining Disease Progression: A Methodological Study

Erdil Arsoy, Nesrin Bulut, Simay Pamuk, Recai Türkoğlu

Istanbul Haydarpasa Numune Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey

Abstract

Objective: The methods used in monitoring the progression of multiple sclerosis (MS) and evaluating the effectiveness of disease-modifying treatments are insufficient. Data obtained from the expanded disability status scale (EDSS), annual relapse rate, or magnetic resonance imaging methods lead to the understanding of symptoms such as cognitive involvement only in the late disease phase. Therefore, this study aimed to compare the relationship between a tool that also evaluated cognitive involvement, such as the multiple sclerosis functional composite (MSFC), which is not widely used in every MS clinic, and a traditional method such as the EDSS.

Materials and Methods: A total of 121 patients with relapsing-remitting MS [female, n=82 (67.8%); male, n=39 (32.2%)] were included in the study. Three (baseline, year 1, and year 2)-year changes in the EDSS scores of these patients within 1 year were visually categorized as both ≥0.5 or ≥1.0. Changes in MSFC components were recorded numerically. The relationship between the changes in 1 year and the EDSS categories was analyzed by repeated-measures analysis of variance (ANOVA). P values <0.05 were considered significant.

Results: According to the results of repeated measures ANOVA, timed 25-foot walk (T25-FW) values were significantly correlated with EDSS changes of ≥1.0 point between both baseline to year 1 [F (1,118) = 6.532; p=0.012] and year 1 to year 2 [F (1,118)=10.222; p=0.002]. When the 3-year change between the baseline and year 2 was considered, the paced auditory serial addition test (PASAT) 3" was found to be significantly correlated with EDSS changes of ≥1.0 points [F (2,118) = 4.204; p=0.043].

Conclusion: MSFC results demonstrated disease progression in line with the EDSS categories designed for the study. T25-FW is effective in predicting changes of ≥1.0 points in the EDSS at 1-year intervals. The PASAT 3" was effective in predicting changes of ≥0.5 points and ≥1.0 points, considering the 2-year change. Accordingly, MSFC components can be used in clinics as an alternative method to determine the treatment endpoint and to monitor cognitive involvement.

Keywords: Multiple sclerosis functional composite, evidence of disease activity, Expanded Disability Status Scale, Paced Auditory Serial Addition Test

Introduction

Multiple sclerosis (MS) is a heterogeneous disease with various challenges in monitoring patients during clinical practice and evaluating the results of their pharmacological interventions. In addition, new disease-modifying therapy options have recently increased in the treatment of the disease, and the concept of "no evidence of disease activity" (NEDA) has become a significant MS progression concept (1).

To date, many different evaluation methods have been developed for disease progression and follow-up. Of these, Kurtzke's (2) expanded disability status scale (EDSS) has been the most widely used method for assessing disease progression in MS clinics for the past 50 years. Similarly, the annual relapse rate (ARR), which is useful for determining regression in the relapsing MS and testing the efficacy of new anti-inflammatory drugs in phase 3 studies, has been widely used together with EDSS in disease follow-up since the 1990s (3). Besides EDSS and ARR, magnetic resonance imaging (MRI) is one of the most common methods of evaluating disease progression and treatment efficacy. Giovannoni et al. (4) highlighted the usefulness of MRI for both fluid-attenuated inversion recovery, T2, and Gd+ T1. If the patient has an increase in Gd+ T1 lesions that will indicate

Address for Correspondence: Erdil Arsoy,Istanbul Haydarpasa Numune Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey
E-mail: erdilarsoy@gmail.com **ORCID-ID:** orcid.org/000-0002-9290-9478
Received: 13.05.2022 **Accepted:** 24.05.2022

a subclinical recurrence and disease progression, changing treatment could be an option.

Moreover, recent developments in imaging methods and in the biomedical field reveal the unparalleled situations between NEDA-3 (EDSS, ARR, and lesion activity on MRI) and progression, especially in cognition. The insufficiency of NEDA components in evaluating cognitive involvement has brought different assessment tools and batteries such as the multiple sclerosis functional composite (MSFC), brief repeatable battery of neuropsychology (BRB-N), (5) and brief international cognitive assessment for MS (BICAMS) (6) to the agenda. According to a meta-analysis by Meyer-Moock et al. (7), in which they included a total of 50 EDSS and 9 MSFC studies, the use of MSFC as disability level and treatment endpoint is recommended as a quantitative assessment tool for cognitive functions. Although MSFC is criticized as the primary or secondary treatment endpoint, it appears to be used in different drug phase studies (8). However, the use of EDSS and MSFC as endpoints should not disregard factors such as limited inter-rater reliability, application of standard protocols, and learning. Specifically, one of the most important handicaps of MSFC is the learning effect seen in the paced auditory serial addition test (PASAT) and the nine-hole peg test (9HPT). According to Rudick et al. (9), MSFC was also correlated with deterioration due to gray matter, white matter, and whole-brain atrophy observed over 6 years. In this study, the 4-year gray matter atrophy rates were parallel to MSFC, but not significantly correlated with EDSS.

Thus, the present study aimed to examine the association of disability, determined according to different EDSS changes, with the MSFC subtotal and total scores over time. This can ensure the consistency between the existing evaluation tools and the creation of alternative evaluation methods.

Materials and Methods

Patient Selection

Initially, 121 patients with relapsing-remitting MS followed in the Multiple Sclerosis Unit of the University of Health Sciences Haydarpasa Numune Training Hospital were considered for the study. Patients with RRMS who had a disease duration of at least 2 years, aged <50 years, had an EDSS score of ≤4, had no relapse in the last 6 months, and had no inflammatory or psychiatric disease other than MS were included in the study. The retrospective data of the patients who did not sign the informed consent form were not evaluated.

Disease Activity Data Conversion

Disease activity was determined visually in Excel in two ways. Within the scope of the study, EDSS changes were recorded from baseline to year 1 and from year 1 to year 2, taking into account ≥0.5 and ≥1 score ranges. If the EDSS score increased by 0.5 and ≥1 point within a year, it was determined as "increased disease activity (IDA)." Similarly, if the EDSS score decreased, it was determined as "decreased disease activity (DDA)." If there was no change in the EDSS score within 1 year, it was defined as "stable disease activity (SDA)." The relationship between sequential disease activities and 1-year recurrent dominant, non-dominant upper extremity, lower extremity, cognition, and MSFC overall score data were included in the analysis.

Calculation of the Overall MSFC Score

According to Fischer et al. (10), the patient's scores on the lower, upper extremity, and cognitive subtests were calculated according to the following formula:

- Z_{leg} = (Mean T25-FW-9.5353)/11.4058

- Z_{arm} = [Mean (1/9HPT)-0.0439]/0.0101

- Z_{cog} = (PASAT3"-45.0311)/12.0771

In the above formula, 9.5353 is the "mean reference cohort of T25-FW," and 11.4058 is the "standard deviation reference cohort of T25-FW." The reference cohorts for 9 HPT and PASAT 3" were also determined by Fischer et al. (10). The composite score was obtained by taking the arithmetic average of the Z values calculated according to the above formulas:

- $Z_{MSFC} = (Z_{arm} - Z_{leg} + Z_{cog})/3$

Statistical Analysis

As a result of the analysis made with the G* Power 3.1 (11), 168 participants should be included in the study; however, only 121 participants were included because a sufficient number could not be reached due to the aforementioned reasons. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Variables were expressed as apercentage and mean ± standard deviation. Age, number of relapses, disease duration, and age of disease onset were evaluated as both numerical and ordinal data. The ratio of ordinal or nominal data to each other was evaluated using the chi-square test. Changes in dominant (9HPT-D), non-dominant upper extremity (9HPT-ND), lower extremity (T25-FW), multi-tasking skills (PASAT 3"), and overall MSFC scores over 2 years were analyzed using the one-way repeated-measures ANOVA. The two-way repeated-measures ANOVA test was applied to evaluate the effect of ordinal variables such as age and number of relapses on repeated measures over time. Those with a p value <0.05 were considered significant.

Results

Demographic Features of the Patients

In this study, the mean age of the 121 patients with RRMS [female, n=82 (67.8%); male, n=39 (32.2%)] was 37.92±9.10 [minimum (min)=20, maximum (max)=50] years, and the mean age of onset was 28.81±8.50 (min=10, max=46) years. When the clinical features of the patients were examined, the disease

duration was 9.14±5.99 (min=2, max=28), and the number of relapses was 5.57±3.80 (min=2, max=20) (Table 1).

Relationship Between Clinical Features and Disease Activity

Ordinal variables such as age, sex, education level, number of relapses, disease duration, age of disease onset, first disease symptom, presence of Gd+ T1 and T2 hyperintense lesions, and 0.5 and 1.0 changes in the EDSS level were evaluated separately by the chi-square method. Hence, variables other than the presence of lesion were not associated with the progression determined using EDSS (p>0.05).

In addition, a significant correlation was found between disease progression determined using an EDSS change of 0.5 and the presence of T2 hyperintense lesions [$\chi 2$ (2, N=121) =11.581; p=0.003]. Specifically, a significant correlation was noted between 0.5 EDSS changes in disease progression of patients with ≥9 T2 hyperintense lesions.

Another similar significant relationship was observed between disease progression determined using an EDSS change of 1.0 and the presence of Gd+ T1 lesions [$\chi 2$ (2, N=121)=6.367; p=0.041]. The results of the chi-square test indicated that the fixed disease activity and presence of Gd+ T1 lesion were highly correlated.

Relationship Between Disease Activity and Possible Assessment Methods

Changes in MSFC and its four components (9HPT/D, 9HPT/ND, timed 25-foot walk [T25-FW], and PASAT 3") over 1 year were measured by repeated-measures ANOVA. Accordingly, changes in 9HPT/D, 9HPT/ND, and PASAT 3" results between baseline and year 1, year 1 and year 2, and baseline and year 2 were not significant when considering both EDSS ≥0.5 and ≥ 0.1 (p>0.05).

Considering the ≥0.5 changes in EDSS, only the timed 25-foot walk change between baseline and year 1 was significant [$F_{\text{Timed 25-Foot Walk}}(1,118) = 6.532$; p=0.012] (Table 2, Figure 1). However, this change was not significantly distributed among the groups (p>0.05).

Similarly, the timed 25-foot walk scores between year 1 and year 2 were significant when evaluated considering the change in EDSS value of ≥1.0 [$F_{\text{T25-FW}}(1,118) = 10.222$; p=0.002] (Table 3). When the significance of the distribution was evaluated between the groups, this change was significant [$F_{\text{T25-FW*disease activity(≥1.0)}}(2,118)=5.523$; p=0.005] (Figure 1). However, according to the post-hoc test results, it could not be observed from which groups the difference originated (p>0.05).

In the evaluation of cognitive functions, the PASAT 3" results changed significantly, which was valid for both half-point [$F_{\text{PASAT 3"}}(1,118)=5.849$; p=0.017] and 1-point [$F_{\text{PASAT 3"}}(2,118) = 4.204$; p=0.043] changes (Table 4, Figure 2). Still, this change was not significantly distributed between the groups. In the case where the EDSS change is ≥1.0, the change in the MSFC overall score between year 1 and year 2 is significant at the trend level [$F_{\text{MSFC}}(1,118) = 3.068$; p=0.082] (Table 3). However, this change was not significantly distributed among the groups (p>0.05).

Relation of Significant MSFC Components and Clinical Factors

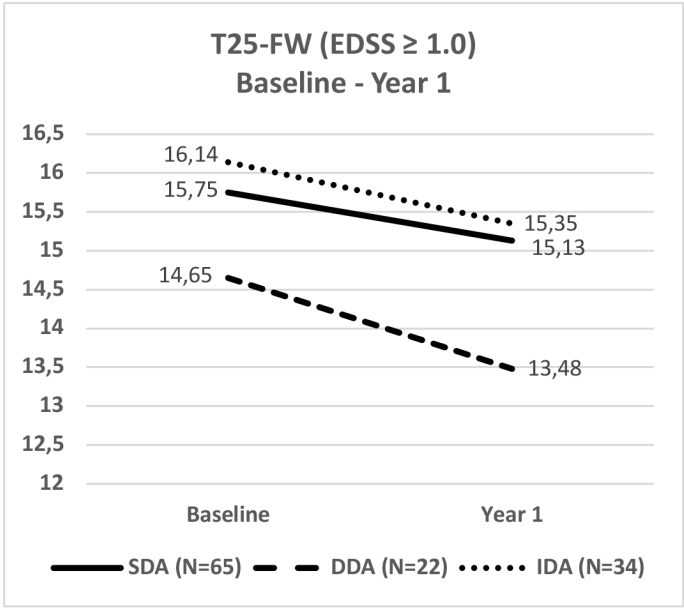
In the evaluations made with two-way repeated-measures ANOVA, no relationship was found between clinical factors and recurrent MSFC components (p>0.05).

Discussion

The primary aim of this study is to evaluate whether there is a relationship between the disability levels recorded over 1- and

Table 1. Demographic features of the patients

		N	%
Age	**<29**	32	26.4
	30-39	33	27.3
	40-49	38	31.4
	>50	18	14.9
Gender	**Female**	82	67.8
	Male	39	32.2
Education	**Elementary/ middle school**	32	26.4
	High school	38	31.4
	Undergraduate/ graduate	51	42.1
Number of relapse	**<4**	44	36.4
	4–6	43	35.5
	>6	34	28.1
Disease duration	**<5**	26	21.5
	5-10	57	47.1
	>10	38	31.4
Age of onset	**<20**	16	13.2
	20-24	31	25.6
	25-29	23	19.0
	30-34	15	12.4
	35-39	15	12.4
	>40	21	17.4
First symptom	**Supratentorial**	31	25.6
	Optic pathway	29	24.0
	Cerebellum	32	26.4
	Spinal cord	29	24.0
Gd+ T1 lesions	**–**	97	80.2
	+	24	19.8
T2 hyperintense lesions	**3-8**	25	20.7
	9+	96	79.3



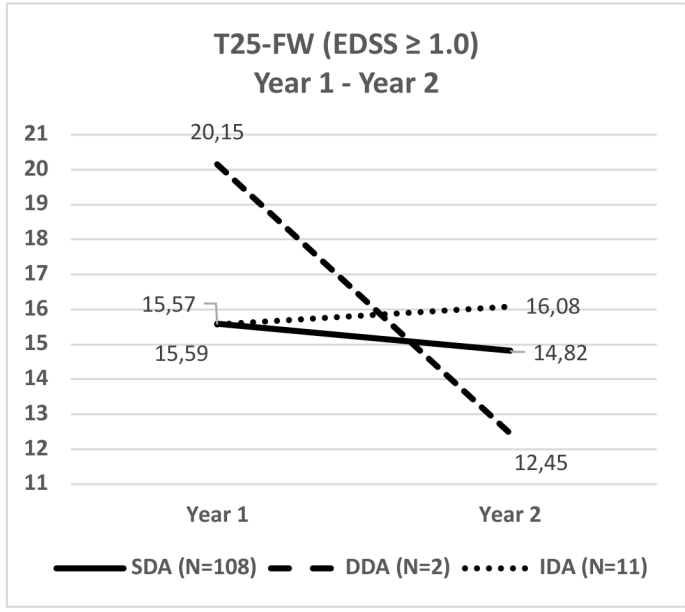
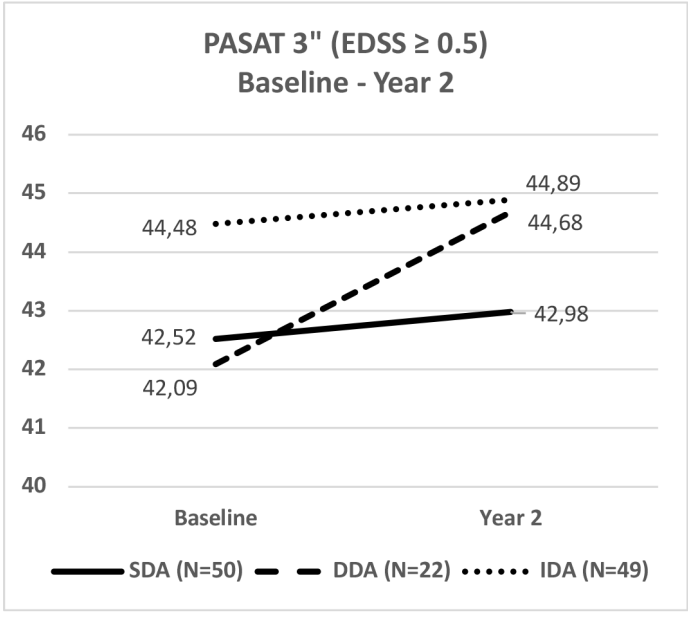


Figure 1. T25-FW Change Over Time According to EDSS
EDDS: Expanded disability status



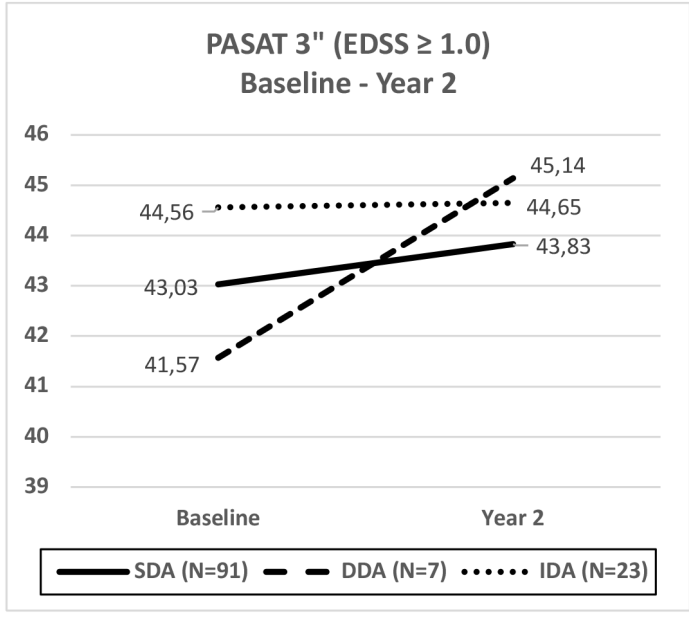


Figure 2. PASAT 3" Change Over Time According to EDSS
EDDS: Expanded disability status

2-year periods and the MSFC components. Within the scope of the study, MSFC components were analyzed considering both 0.5 and 1.0 point changes over two time periods. Therefore, EDSS changes of ≥0.5 were not associated with any MSFC component. However, a change of ≥1.0 in disability over 1 year is consistent with the change in the T25-FW test. In addition, the level of disability is significantly correlated with the change of 0.5 and ≥1.0 observed in 2 years from the PASAT 3." According to these results, lower extremity evaluations made in 1 year and cognitive evaluations made in 2 years may be useful in determining the disability levels and "evidence of disease activity" of patients.

Unlike existing studies, we described the changes in EDSS scores as increasing (IDA), decreasing (DDA), and stable (SDA) forms, not numerically. Existing studies have considered EDSS scores as numerical (12) or basal limits (13,14). During our literature review, we only encountered two studies (15) that are similar to our research method. Since EDSS is an ordinal variable, it was not used numerically in the study, and it was taken into account as 0.5- and 1.0-point changes. In addition, our study covers disability or functionality assessments for 3 years and is similar to Kragt's dissertation in terms of the components and duration it examined. Kragt (15) evaluated the relationship between EDSS, Guy's Neurological Disability Scale (GNDS), and MSFC

Table 2. Changes in MSFC components between baseline and year 1 according to the stages of progression											
		EDSS ≥0.5						EDSS ≥1.0			
	N	Baseline	Year 1	F	p		N	Baseline	Year 1	F	p
		Mean (SD)	Mean (SD)					Mean (SD)	Mean (SD)		
SDA	63	21.89 (4.64)	22.20 (3.87)	1.257	0.265	SDA	65	21.01 (3.91)	21.83 (3.74)	1.607	0.207
DDA	20	22.67 (5.01)	21.48 (3.47)			DDA	22	21.56 (3.22)	22.21 (4.16)		
IDA	38	21.88 (4.31)	21.58 (3.15)			IDA	34	21.85 (3.19)	22.59 (3.88)		
9 HPT/D											
SDA	63	24.78 (8.68)	23.74 (4.72)	1.037	0.311	SDA	65	23.32 (4.60)	23.20 (4.55)	2.442	0.121
DDA	20	23.02 (5.95)	22.62 (3.57)			DDA	22	23.25 (4.44)	24.49 (5.49)		
IDA	38	22.69 (3.57)	22.22 (3.19)			IDA	34	22.50 (2.88)	23.05 (4.64)		
9 HPT/ND											
SDA	63	15.78 (3.61)	15.30 (2.80)	1.213	0.273	SDA	65	15.75 (3.91)	15.13 (4.15)	6.532	**0.012**
DDA	20	14.76 (2.95)	14.94 (2.69)			DDA	22	14.65 (3.44)	13.48 (2.47)		
IDA	38	15.11 (2.86)	16.63 (4.90)			IDA	34	16.14 (3.07)	15.35 (3.16)		
Timed 25-foot walk											
SDA	63	43.30 (11.29)	43.04 (11.43)	2.661	0.105	SDA	65	41.98 (11.47)	42.36 (11.13)	0.532	0.467
DDA	20	42.25 (12.79)	43.20 (11.37)			DDA	22	45.31 (9.35)	45.54 (9.91)		
IDA	38	43.65 (9.25)	45.28 (9.35)			IDA	34	46.20 (9.86)	46.35 (10.73)		
PASAT 3"											
SDA	63	0.045 (0.48)	0.033 (0.46)	1.440	0.233	SDA	65	0.016 (0.43)	0.046 (0.43)	0.005	0.945
DDA	20	0.041 (0.43)	0.096 (0.39)			DDA	22	0.140 (0.46)	0.114 (0.43)		
IDA	38	0.085 (0.36)	0.131 (0.36)			IDA	34	0.143 (0.36)	0.135 (0.40)		
MSFC Overall											

MSFC: Multiple sclerosis functional composite, EDDS: Expanded disability status, DDA: Decreased disease activity, SD: Standard deviation

scores in patients with secondary progressive MS and designed the changes in EDSS values as 0.5 and 1.0. Unlike our study, the study of Kragt (15) found a consistent relationship between EDSS and MSFC components only in the upper extremity. This situation was seen only in patients with severe disability (EDSS ≥6.0) with a 0.5-point EDSS change. The study of Coles et al. (16), using the EDSS method, is closely related to our study and similar in terms of progression level. In the study in which the effects of alemtuzumab and interferon beta 1-a were evaluated in patients with early-stage MS, the patients were evaluated in the 1st, 12th, and 24th months, and 1.0- and 1.5-point changes in EDSS scores were taken into account. Since MSFC results were not used in this study, they are similar to our study only in terms of method.

The association between MSFC components and disability is mostly seen in drug efficacy studies. Only methodically similar, Ozakbas et al. (14) evaluated the effect of methylprednisolone in 30 days, although the research durations were different. Accordingly, T25-FW, one of the MSFC components, was found to be the strongest test to correlate with EDSS scores. These results are also in line with the work of Patzold et al. (17). Unlike our study, the MSFC component, which evaluated the upper extremities, also significantly separated the groups, which included a 20-day treatment period. The weakest aspect of our study is the effect of the drugs used by the patients. These data were not included in the study because the drugs used vary, and they may affect the results negatively. However, none of the study patients received acute-relapse (corticosteroid) treatment during follow-up.

In a study in which EDSS scores differed from our study (≤5.5, 6.0-7.0, and >7.5) and lesion burden and MSFC Z score were compared, the precision of different assessment algorithms was evaluated (18). Basically, it aimed to measure the relative precision of progression in patients grouped according to different lesion burdens. Accordingly, MSFC was found to be more effective in observing an increase in T2-hyperintense lesions than EDSS. As seen in Section 3.2., these results are inconsistent with our study. The burden of Gd+ T1 lesions, especially T2 hyperintense lesion burden, was not significantly associated with MSFC scores, but with 0.5-point changes in EDSS.

In the study, the PASAT 3" was the MSFC component that was significant with both EDSS changes. The PASAT 3," which

Table 3. Changes in MSFC components between year 1 and year 2 according to the stages of progression

	EDSS ≥ 0.5						EDSS ≥ 1.0				
	N	Year 1st Mean (SD)	Year 2nd Mean (SD)	F	p	N	Year 1st Mean (SD)	Year 2nd Mean (SD)	F	p
SDA	96	22.06 (4.54)	21.92 (3.65)	0.138	0.711	108	21.76 (3.65)	21.94 (3.91)	0.248	0.619
DDA	9	22.38 (4.26)	21.73 (3.40)			2	22.90 (4.80)	20.30 (1.27)		
IDA	16	21.52 (2.79)	21.76 (3.45)			11	22.93 (2.58)	24.13 (2.78)		
9 HPT/D										
SDA	96	24.31 (7.70)	23.31 (4.35)	0.002	0 .967	108	23.07 (4.17)	23.45 (4.70)	0.873	0.352
DDA	9	21.85 (3.15)	23.73 (3.54)			2	22.60 (7.91)	19.25 (3.46)		
IDA	16	22.08 (2.85)	21.31 (2.65)			11	23.18 (3.68)	23.57 (5.33)		
9 HPT/ND										
SDA	96	15.55 (3.53)	15.45 (3.35)	2.085	0.151	108	15.59 (3.56)	14.82 (3.70)	10.222	**0.002**
DDA	9	15.24 (2.07)	14.87 (2.69)			2	20.15 (9.12)	12.45 (0.07)		
IDA	16	14.63 (2.10)	17.35 (5.08)			11	15.57 (3.00)	16.08 (3.47)		
Timed 25-Foot walk										
SDA	96	42.87 (10.94)	43.30 (11.10)	1.446	0.232	108	43.92 (10.91)	44.15 (11.00)	0.181	0.671
DDA	9	42.66 (11.88)	43.88 (9.47)			2	37.50 (17.67)	37.50 (17.67)		
IDA	16	45.75 (10.31)	46.56 (9.52)			11	43.45 (8.89)	44.36 (9.23)		
PASAT 3"										
SDA	96	0.036 (0.45)	0.058 (0.44)	0.036	0.849	108	0.085 (0.41)	0.091 (0.43)	3.068	0.082
DDA	9	0.072 (0.42)	0.064 (0.32)			2	-0.157 (1.04)	0.126 (0.69)		
IDA	16	0.173 (0.38)	0.179 (0.29)			11	0.014 (0.37)	0.000 (0.39)		
MSFC Overall										

MSFC: Multiple sclerosis functional composite, EDDS: Expanded disability status, DDA: Decreased disease activity, SD: Standard deviation

measures information processing speed or multiprocessing skills, was found to be compatible with disease progression. This is significant in terms of reviewing classical methods (such as EDSS and GNDS) that are inadequate in assessing cognitive progress. Different studies also support that the PASAT 2" or 3" is important in determining cognitive findings (18,19). In addition, studies have found that different tools such as the Symbol Digit Modalities Test (SDMT), which measures information-processing speed, are more useful than the PASAT in longitudinal evaluations (20-21). Drake et al. (22) conducted disease prediction research with different MSFC components including SDMT and PASAT 3" on 400 patients with MS and 100 controls. Accordingly, the change in the PASAT 3" score between baseline and follow-up was more significant. In addition to their usefulness in understanding disease progression, SDMT and PASAT have limitations, such as the learning effect. Sonder et al. (23) analyzed the reliability of SDMT and PASAT 3" over time. As a result of the test-retest, SDMT was found to be more reliable over time than the PASAT 3," and there was a significant ceiling and learning effect in the PASAT 3." As seen in Figure 2, the EDSS change of 0.5 observed in 2 years in the PASAT 3" appears to be a learning effect. In addition, although the score increase in patients with DDA at 1.0 EDSS change appears to be above the learning effect, it would be useful to control these results with an advanced analysis method.

In line with these results and the literature, 9HPT-D/ND, which evaluates the upper extremities, and MSFC Z score, which evaluates all activities, were not sufficient to predict disease progression. Specifically, PASAT 3" scores were found to be effective in comprehending 0.5-point changes. Cognitive impairment (CI) in MS is insidious and shows only severe losses in routine neurological examinations such as the standardized minimental test (24). Since the evaluation of CI in EDSS scoring is subjective, it may not be detected clinically. For this reason, it would be useful to observe cognitive involvement by expanding assessment tools such as MSFC.

Study Limitations

Comparative evaluations with the current SDMT could not be obtained in the study. This is because not every patient has SDMT scores during this period. Adding studies such as volumetric-based morphometry (VBM) to the study, where we can determine the location of Gd+ T1 and T2 hyperintense lesions rather than the number, will strengthen the research. We could not benefit from these data because we had standardized MR images. In addition, it is possible to add the effect of

Table 4. Changes in MSFC components between baseline and year 2 according to the stages of progression

		EDSS ≥ 0.5						EDSS ≥ 1.0			
	N	Baseline	Year 2	F	p		N	Baseline	Year 2	F	p
		Mean (SD)	Mean (SD)					Mean (SD)	Mean (SD)		
SDA	50	21.37 (4.16)	21.21 (3.44)			**SDA**	91	21.77 (4.17)	21.79 (3.68)		
DDA	22	23.45 (5.91)	23.16 (4.43)	0.004	0.947	**DDA**	7	24.75 (7.08)	22.34 (4.08)	0.522	0.472
IDA	49	22.04 (3.48)	22.56 (3.82)			**IDA**	23	22.16 (3.73)	23.30 (4.32)		
9 HPT/D											
SDA	50	24.63 (9.17)	23.01 (4.87)			**SDA**	91	23.98 (7.37)	23.35 (4.97)		
DDA	22	24.56 (6.47)	24.58 (4.86)	0.269	0.605	**DDA**	7	24.82 (9.35)	23.31 (3.36)	0.242	0.623
IDA	49	22.69 (4.15)	23.25 (4.57)			**IDA**	23	22.96 (4.71)	23.60 (4.32)		
9 HPT/ND											
SDA	50	16.03 (3.70)	14.96 (3.77)			**SDA**	91	15.54 (3.49)	14.66 (3.77)		
DDA	22	14.77 (3.12)	13.77 (2.54)	2.518	0.115	**DDA**	7	15.62 (2.91)	14.77 (2.50)	0.148	0.701
IDA	49	15.04 (2.83)	15.34 (3.93)			**IDA**	23	14.79 (2.49)	15.88 (3.51)		
Timed 25-Foot Walk											
SDA	50	42.52 (11.74)	42.98 (12.05)			**SDA**	91	43.03 (11.12)	43.83 (11.43)		
DDA	22	42.09 (12.88)	44.68 (11.58)	5.849	**0.017**	**DDA**	7	41.57 (13.36)	45.14 (9.82)	4.204	**0.043**
IDA	49	44.48 (8.94)	44.89 (9.32)			**IDA**	**23**	**44.56 (9.41)**	**44.65 (9.16)**		
PASAT 3″											
SDA	50	0.038 (0.48)	0.095 (0.49)			**SDA**	91	0.053 (0.44)	**0.093 (0.45)**		
DDA	22	-0.016 (0.47)	0.047 (0.42)	1.638	0.203	**DDA**	7	-0.063 (0.49)	0.098 (0.37)	1.345	0.248
IDA	49	0.109 (0.37)	0.087 (0.36)			**IDA**	23	0.106 (0.39)	0.040 (0.36)		
MSFC Overall											

MSFC: Multiple sclerosis functional composite, EDDS: Expanded disability status, DDA: Decreased disease activity, SD: Standard deviation

research drugs, but since we did not have drug-free values of the patients, these data would only negatively affect the results.

Conclusion

T25-FW, which evaluates the lower extremities, and PASAT 3″ results, which evaluate the multiprocessing capacity, are thought to indicate disease progression, consistent with EDSS. While the T25-FW is useful in predicting 1.0-point changes in EDSS, the PASAT 3″ can be used as an effective examination method in terms of both 0.5- and 1.0-point changes. These results also suggest that both the PASAT 3″ and T25-FW test may be a possible treatment endpoint or NEDA.

Ethics

Ethics Committee Approval: The research protocol was approved by University of Health Sciences Turkey Hamidiye Scientific Research Ethics Committee (decision number: 22/15, date: 14.01.2021)

Informed Consent: The retrospective data of the patients who did not sign the informed consent form were not evaluated.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.T., Concept: E.A., N.B., S.P., R.T., Design: E.A., R.T., Data Collection or Processing: E.A., N.B., S.P., R.T., Analysis or Interpretation: E.A., Literature Search: E.A., R.T., Writing: E.A.

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

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

References

1. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of No Evidence of Disease Activity in a 7-Year Longitudinal Multiple Sclerosis Cohort. JAMA Neurol 2015;72:152-158.
2. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444-1453.
3. Lublin FD. Disease activity free status in MS. Mult Scler Relat Disord 2012;1:6-7.
4. Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis ? Mult Scler Relat Disord 2015;4:329-333.
5. Damasceno A, Damasceno BP, Cendes F. Subclinical MRI disease activity influences cognitive performance in MS patients. Mult Scler Relat Disord 2015;4:137-143.

6. Ozakbas S, Cinar BP, Yigit P, Kosehasanogullari G. "No evidence of disease activity – cognition" in relapsing-remitting multiple sclerosis: recommendation for an extensive assessment of disease activity (P4.389). Neurology Apr 2017;88:P4.389.
7. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol 2014;14:58.
8. Giovannoni G, Cohen JA, Coles AJ, Hartung H, Havrdova E, Selmaj KW, Margolin DH, Lake SL, Kaup SM, Panzara MA, Compston DAS. Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients. Neurology 2016;87:1985-1992.
9. Rudick RA, Lee J-C, Nakamura K, Fisher E. Gray Matter Atrophy Correlates With MS Disability Progression Measured with MSFC But Not EDSS. J Neurol Sci 2010;282:106-111.
10. Fischer J, Rudick R, Cutter G, Reingold S. The Multiple Sclerosis Functional Composite measure (MSFC): an integrated approach to MS clinical outcome assessment. Mult Scler. 1999;5:244-250.
11. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-191.
12. Kalkers NF, de Groot V, Lazeron RH, Killestein J, Adèr HJ, Barkhof F, Lankhorst GJ, Polman CH. MS functional composite: relation to disease phenotype and disability strata. Neurology 2000;54:1233-1239.
13. Miller DM, Rudick RA, Cutter G, Baier M, Fischer JS. Clinical Significance of the Multiple Sclerosis Functional Composite. Arch Neurol. 2000;57:1319-1324.
14. Ozakbas S, Cagiran I, Ormeci B, Idiman E. Correlations between multiple sclerosis functional composite , expanded disability status scale and health-related quality of life during and after treatment of relapses in patients with multiple sclerosis. J Neurol Sci 2004;218:3-7.
15. Kragt JJ. Measuring disease progression in MS: do patients' and physicians' perspectives match? Vrije Universiteit Amsterdam; 2010.
16. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, Norris K, Tandon PK. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359:1786-801.
17. Patzold T, Schwengelbeck M, Ossege L-M, Malin J-P, Sindern E. Changes of the MS functional composite and EDSS during and after treatment of relapses with methylprednisolone in patients with multiple sclerosis. Acta Neurol Scand 2002;105:164-168.
18. Hobart J, Kalkers N, Barkhof F, Uitdehaag B, Polman C, Thompson A. Outcome measures for multiple sclerosis clinical trials: relative measurement precision of the Expanded Disability Status Scale and Multiple Sclerosis Functional Composite. Mult Scler 2016;10:41-46.
19. Rosti E, Hamalainen P, Koivisto K, Hokkanen L. The PASAT performance among patients with multiple sclerosis : analyses of responding patterns using different scoring methods. Mult Scler 2006;12:586-593.
20. Coo H, Hopman W, Edgar C, McBride E, Brunet D. The Paced Auditory Serial Addition Test: to what extent is it performed as instructed , and is it associated with disease course? Mult Scler 2015;11:85-89.
21. Brochet B, Deloire MSA, Bonnet M, Ouallet JC, Petry KG, Dousset V. Should SDMT substitute for PASAT in MSFC ? A 5-year longitudinal study. Mult Scler 2008;14:1242-1249.
22. Drake A, Morrow S, Hojnacki D, Munschauer F, Benedict R. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test. Mult Scler 2010;16:228-237.
23. Sonder JM, Burggraaff J, Knol DL, Polman CH, Uitdehaag BMJ. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. Mult Scler J 2014;20:481-488.
24. Beatty WW, Goodkin DE. Screening for Cognitive Impairment in Multiple Sclerosis An Evaluation of the Mini-Mental State Examination. Arch Neurol 1990;47:297-301.

DOI: 10.4274/jmsr.galenos.2022.2022-1-3
Journal of Multiple Sclerosis Research 2022;2(1):13-19

RESEARCH ARTICLE

Effects of Sexual Dysfunction, Fatigue, and Depression on the Quality of Life of Women with Multiple Sclerosis

Selin Akıncioglu[1], Nurgul Gungor Tavsanlı[2], Hatice Mavioglu[3]

[1]Manisa Celal Bayar University Health Science Institute, Manisa, Turkey
[2]Manisa Celal Bayar University Faculty of Health Science, Department of Midwifery, Division of Internal Medicine Nursing, Manisa, Turkey
[3]Manisa Celal Bayar University Faculty of Medicine, Department of Neurology, Manisa, Turkey

Abstract

Objective: This study aimed to assess the effects of sexual dysfunction, fatigue, and depression of women with multiple sclerosis (MS) on their quality of life (QoL).

Materials and Methods: The study included 30 women with MS, and 60 healthy women who presented to the outpatient clinics of Hafsa Sultan Hospital, Celal Bayar University, with simple complaints without a chronic disease. The sociodemographic form, fatigue severity scale (FSS), Arizona sexual experiences scale (ASES), Beck Depression scale (BDS), and Health-Related QoL Short Form-36 (SF-36) were administered to the patients with MS and patients in the control group. While patients with MS were assigned to the experimental group, other patients were assigned to the control group.

Results: In both groups, the mean age of the patients was 34 (minimum=24, maximum=40) years. A significant statistical difference was found between the two groups in terms of the mean scores they obtained from the FSS ($p<0.05$). In our study, the mean scores of the participants in the experimental and control groups obtained from the overall BDS were 16.00±7.96 and 2.10±2.62, respectively. Of the participants in the experimental group, 9 experienced moderate depression and 2 had severe depression. Of the participants, 29 women in the experimental group and 10 women in the control group had sexual dysfunction. In terms of the mean scores they obtained from the ASES, a significant difference was found between the participants in the experimental and control groups ($p<0.01$).

Conclusion: Women with MS had higher levels of fatigue, sexual dysfunction, and depression than did the healthy controls, which explains the decrease in their QoL. The comparison of the participants in both groups in terms of their QoL revealed that the women with MS had a lower level of QoL than did the women in the control group.

Keywords: Multiple sclerosis, fatigue, depression, sexual dysfunction, quality of life

Introduction

Multiple sclerosis (MS) is a disease in which multiple demyelination plaques involving the central nervous system develop focally and diffusely and is characterized with remission and exacerbations. It is 1.5 times more common in women (1). Neuropathic complications, depression, fatigue, sexual dysfunction (SD), and cognitive changes in MS affect the quality of life (QoL) of patients with MS (2).

The incidence rate of at least one of the SD symptoms in MS is approximately 84% in men and 85% in women, and the most common SD symptoms are decreased sexual demand, sexual desire problems, decrease in orgasm, or inability to have orgasms (3,4). In patients with MS, SD is classified into three groups: (1) primary SD, which is considered a direct result of MS, (2) secondary SD, which is caused by other symptoms of MS that reduce sexual function, and (3) tertiary SD, which influences sexual life in relation to psychological, emotional, social, and cultural factors (5). Sexual problems are not comfortably talked about in our society. Nurses can attempt to identify and prevent sexual problems. Thus, nurses should consider patients' sexual habits in the pre-disease period to determine sexual problems and thus assess whether there is a problem

Address for Correspondence: Nurgul Gungor Tavsanlı, Manisa Celal Bayar University Faculty of Health Science, Midwifery Department, Internal Medicine Nursing, Manisa, Turkey **E-mail:** nurgul.gungor@hotmail.com **ORCID-ID:** orcid.org/0000-0002-1831-2171
Received: 07.02.2022 **Accepted:** 06.03.2022

and if they receive medical treatment for their problems. Nurses can investigate the causes of patients' sexual problems, plan appropriate interventions, and provide them guidance to solve the problems (6).

Psychiatric disorders are frequently observed in the course of MS disease. One of the highly common psychiatric problems in patients with MS is depression (7). General causes of depression are as follows: cognitive, mental, and functional impairments noticed by patients with insight (catastrophic anxiety), insufficient assessment of stimuli from the environment, inability to overcome events, social losses, loneliness, or problems associated with physical diseases that accompany dementia (8).

MS has adverse effects on the QoL of patients and their families and affects young people mostly. Because MS is more common in young people, it causes loss of productivity, decrease in QoL, and a serious burden. In studies that compared the relationship between QoL and health in patients with MS and patients with other chronic medical-neurological diseases, the QoL scores were lower in the former group than those in the latter group (9). In addition to medical treatment, training and counseling services play an important role in controlling the disease. Midwives and nurses, who are responsible for the physical, cognitive, and mental wellbeing of patients, can help improve the QoL in patients through training and counseling services they provide to patients (10). Studies have suggested that SD, fatigue, and depression are the most important factors that negatively affect the QoL in patients with MS (9,10).

SD, fatigue, and depression, which are among the irreversible problems of women with MS, negatively affect their QoL (11). Therefore, detecting SD problems in the routine follow-ups of women with MS, making measurements to evaluate fatigue, depression, and QoL, and using them in clinical settings will generate positive changes on the disease course in women with MS.

In this study, we aimed to determine the effects of SD, fatigue, and depression on the QoL of women with MS. Therefore, by comparing the SD, fatigue, depression, and QoL of women with MS with those of healthy women, the problems of women with MS will be more clearly identified.

Materials and Methods

This cross-sectional and case-control study included 60 healthy women and 30 women diagnosed with MS according to McDonald's diagnostic criteria and monitored in the neurology clinic of a medical center in the west of Turkey between April 1, 2015, and September 30, 2015.

Female outpatients with MS who underwent treatment during the first 6 months of 2015 in the neurology clinic of a medical center were monitored. The simple random sampling method was used for sample selection.

The control group consisted of 60 volunteer women who presented to the outpatient clinics of the internal diseases department of a university hospital between April 1, 2015, and September 30, 2015, had similar characteristics (such as age, educational level, marital status, working status, and health insurance), met the inclusion criteria, did not have a neurological disease, gave informed consent, and had simple complaints but no chronic diseases. The participants were informed about the aim of the study and further assessments before they were invited to take part in the study. Of them, those who accepted to participate in the study were evaluated in terms of their suitability for the study and inclusion criteria.

Data Collection

In this study, the sociodemographic form, Arizona sexual experiences scale (ASES), fatigue severity scale (FSS), Beck Depression scale (BDS), and Health-Related QoL Short Form-36 (SF-36) were used to collect the study data. The participants spend 30-35 min to the fill in the forms.

Sociodemographic Form: The form was used to question the characteristics of the participants such as age, sex, bodyweight, height, education level, marital status, number of children, social insurance, working status, MS history, disease type, and whether they had undergone physiotherapy and rehabilitation therapy. Then, the obtained data were recorded (1-11).

ASES: This scale, which was developed to quickly and easily scan and detect the problems patients experience in their sexual life, consists of five items. Responses given to the items are rated on a six-point Likert-type scale. The ASES has two separate forms for women and men (2,12). Of the participants, those whose ASES scores were ≥11 were considered highly likely to have SD. The increase in the score is directly associated with the severity of the pathology (or "the higher the score is the more severe the pathology is") (2).

FSS: The FSS includes nine items. The maximum possible score to be obtained from each item is seven: the higher the score, the higher the fatigue level. The scale is used to question the state of fatigue in the last 1 month, including the day it is filled in. The participants scored each item on a scale ranging from 1 (strongly disagree) to 7 (strongly agree). The lowest and highest possible scores to be obtained from the overall scale are 9 and 63, respectively. The sum of the mean scores of the nine items yields the overall FSS score: the higher the mean score, the greater the severity of fatigue. Patients whose FSS score is <4 are considered "not fatigued," and patients with a fatigue intensity scale score of >4 are considered "fatigued" (3).

BDS: It is a self-report scale developed to assess emotional, cognitive, somatic, and motivational components of depression. The scale consists of 21 items: two items are allocated to emotions, 11 items to cognitive functions, 2 items to behaviors, 5 items to bodily symptoms, and 1 item to

interpersonal symptoms. The minimum and maximum possible scores are 0 and 3 for each item, and 0 and 63 for the overall BDS, respectively. The scores 0-9 refer to minimal depression or absence of depression; 10-18, mild depression; 19-29, moderate depression; and 30-63, severe depression (3,4,5).

SF-36: This scale was developed by Ware and Sherbourne (6), consists of 36 items, and provides extensive measurement of eight dimensions. The responder must take into account the last 4 weeks while replying the questions. The score is calculated not for the overall scale but for each dimension separately, ranging from 0 to 100: 0 refers to bad health, whereas 100 refers to good health (7).

Expanded Disability Status Scale (EDSS): The EDSS is frequently used to evaluate a neurological disorder together with disability, based on the interview between the patient with MS and physician, and the neurological examination of the patient. It consists of 20 steps between 0 and 10, where 0 is normal and 10 means death due to MS. The EDSS steps are determined with a neurological examination. A numerical increase in EDSS indicates a bad MS course. The EDSS rating relies on the ambulation status and the neurological examination of the eight functional systems (FS) (8,9).

Statistical Analysis

In the data analysis, the SPSS 15.00 for Windows software was used. The Kolmogorov-Smirnov test was used to identify whether the data were normally distributed. The independent samples t-test, correlation analysis, and chi-square tests were used for the comparison of the two groups. The p value <0.050 was considered significant at a confidence interval of 95. A correlation coefficient of 0.00-0.30 indicates negligible correlation; 0.30-0.50, low positive/negative correlation; 0.50-0.70, moderate positive/negative correlation; 0.70-0.90, high positive/negative correlation; and 0.90-1.00, very high positive/negative correlation (3,7).

Ethical Considerations

This study was conducted in the neurology clinic of a medical center. The study was approved by the Ethical Commission of University of Health Sciences Turkey, Faculty of Medicine was obtained (decision number: 140, date: 25.03.2015).

Results

No significant difference was found between the participants in the experimental and control groups in terms of their sociodemographic characteristics, such as education, marital status, working status, and social insurance (p<0.01) (Table 1).

Of the participants with MS, 90% (n=27) had relapsing-remitting multiple sclerosis (RRMS) which manifests itself with attacks, 10% (n=3) had SPMS, 6.70% (n=2) had a family history of MS, and 93.30% (n=28) had no family history of MS. The minimum and maximum scores that the participants obtained from the EDSS were 0 and 7, respectively, whereas their mean EDSS score was ≤3.0, which indicated that they had sufficient physical capacity to perform their usual activities and roles of daily living (8,9) (Table 2).

The mean ASES scores were 19.53±5.46 and 8.28±3.21 in the experimental group and control group, respectively. In this study, 29 women in the experimental group and 10 women in the control group scored ≥11 points from the ASES. While 29 women in the experimental group were sexually dysfunctional, 10 women in the control group had SD. According to their ASES scores, a significant difference was found between the experimental and control groups (p<0.01) (Table 3).

While an FSS of <4 indicate that the person is not fatigued, an FSS score of ≥4 indicates a fatigued state. In our study, the FSS score of 27 participants in the experimental group and 4 in the control was ≥4, which indicated that they suffered from fatigue. A significant difference was found between the two groups with regard to their FSS scores (p<0.01) (Table 3).

In our study, the mean overall BDS scores of the participants in the experimental and control groups were 16.00±7.96 and 2.10±2.62, respectively. Of the women in the experimental group, 6 had depression or minimal depression, 13 (43.30%) had mild depression, 9 (30.00%) had moderate depression, and 2 (6.70%) had severe depression. In the control group, 58 women were not depressed or were minimally depressed. A significant difference was found between the two groups in terms of their BDS scores (p<0.05) (Table 3).

The comparison of the experimental and control groups in terms of their mean SF-36 QoL scores revealed that the control group obtained higher scores from the physical function n(t=-7.01, p<0.01), role difficulty (t=-8.60, p<0.01), general health (t=-8.49, p<0,01), energy vitality (t=-10.94, p≤0.01), social function (t=-12.02, p<0.01), role difficulty emotional (t=-5.53, p<0.01), and mental health (t=-6.16, p<0.01) sub-dimensions of the SF-36 than did the experimental group. As for the pain sub-dimension, the experimental group obtained significantly higher scores than did the control group (t=44.53, p<0.01) (Table 4).

In the women with MS, a moderately significant correlation was noted between the mean scores that they obtained from the overall ASES and the physical function sub-dimension of the SF 36 (rs=-0.37*, p<0.043). A weak relationship was noted between the mean overall ASES scores and score regarding role difficulties (rs=-0.041, p=0.830), pain (rs=-0.239, p<0.203), general health (rs=-0.182, p<0.336), energy (rs=0.152, p=0.422), and social function (rs=0.152, p=0.422), and average significant relationship (p>0.05) with the emotional (rs=0.351, p=0.057) and mental health (rs=-0.327, p=0.077) sub-dimensions of the SF-36 (Table 5).

Table 1. Participants' sociodemographic characteristics

Sociodemographic characteristics		Case group		Control group			
		N	%	N	%	x^2	p
Age group	<34 age	9	30	20	33.3	11,377	0.00
	>35 age	21	70	40	66.7		
Educational level	Writer-reader	1	3.30	2	3.30	35,600	0.00
	Primer school	14	46.70	28	46.70		
	High school	6	20.00	12	20.00		
	University	9	30.00	18	30.00		
Marital status	Married	30	100	60	100	34,844	0.00
	Single	0	0	0	0		
Work status	Working	7	23.30	10	16.70	34,844	0.00
	Not working	23	76.70	50	83.30		
Health insurance	Yes	28	93.30	59	98.30	78,400	0.00
	No	2	6.70	1	1.70		

*Chi-square test

As the SD scores of the women with MS decreased, their mean score for the physical function sub-dimension of the SF-36 increased, which was an expected outcome (Table 5).

A weak relationship was found between the mean scores that they obtained from the overall FSS and those from the role difficulties (rs=-0.022, p=0.908), physical function (rs=-0.201, p=0.288), pain (rs=-0.145, p=0.444), energy (rs=-0.249, p=0.185), social function (rs=-0.191, p=0.313), and mental health (rs=-0.190, p=0.314), and average insignificant relationship (p>0.05) with the general health (p=0.352, rs=-0.176) and emotional (rs=0.351, p=0.057) sub-dimensions of the SF-36 (Table 5).

In women with MS, a negative average relationship was found between the mean scores that they obtained from the overall BDS and the pain sub-dimension of the SF-36 (rs=-0.393*, p=0.032). As depression scores increased in women with MS, their score for the pain sub-dimension of the QoL decreased. Depression experienced by women with MS increased their pain tolerance and caused them to feel more pain (Table 5).

A weak relationship was note dbetween the mean scores that they obtained from the overall BDSS and from the physical function(rs=-0.074, p=0.698), role difficulty (rs=-0.241, p=0.200), general health (rs=-0.239, p=0.204), social function (rs=-0.035, p=0.852), and emotional (rs=0.160, p=0.398) and moderate insignificant relationship (p>0.05) with energy (rs=-0.258, p=0.168) and mental health (rs=-0.282, p=0.131) sub-dimensions of the SF-36 (Table 5).

Table 2. EDSS scores and MS types of patients with MS

		N	%
MS types	RRMS	27	90.00
	SPMS	3	10.00
History of MS in their family	Yes	2	6.70
	No	28	93.30
EDSS scores		**N**	**%**
0		9	30.0
1.5		2	6.70
2.0		4	13.30
2.5		1	3.30
3.0		5	16.70
4.0		2	6.70
5.0		1	3.30
5.5		1	3.30
6.0		4	13.30
7.0		1	3.30

EDSS: Expanded disability status scale, MS: Multiple sclerosis

Discussion

The RRMS rate was 82% in the study of Bertado et al. (10), 85.4% in the study of Sorgun and Yücesan (11), and 69.8% in the study of Nazari et al. (12). Disabilities in patients with MS may have a significant negative effect on their QoL, fatigue, and sexual function. Disabilities in patients with MS have been investigated in several studies. In studies conducted by Arpacı et al. (13) and Solaro et al. (14), the level of disability assessed by the EDSS score was 2.8 and 3.3, respectively. In our study, the mean EDSS score was similar to those determined in the aforementioned studies (10-14).

SD, which is a common problem in patients with MS, is often overlooked because people refrain from talking about it (15). In their study conducted in 137 patients with MS, Lew-Starowicz and Rola (16) reported that only 2.2% of the physicians questioned sexual functions of the patients. SD is observed in

Table 3. Comparison of ASES, FSS total scores, and BDS scores of the case and control groups

ASES total scores	Case groups		Control groups		Total		t	p	x^2
	N	%	N	%	N	%			
≤10	1	3.30	50	83.30	51	56.70	-12.28	0.00*	26.3**
≥11	29	96.70	10	16.70	39	43.30			
FSS total scores	**Case groups**		**Control groups**		**Total**		**t**	**p**	**x^2**
	N	**%**	**N**	**%**	**N**	**%**			
≤3.9	3	10.00	56	93.30	**59**	65.60	-13.78	0.00*	61.50**
≥4.0	27	30.00	4	6.70	31	34.40			

BDI scores	Case groups		Control groups		Total		p	x^2
	N	%	N	%	N	%		
0-9 none/minimal depression	6	20.00	58	96.70	64	71.10	0.00	57.73**
10-18 mild depression	13*	43.30*	2	3.30	15	16.70		
19-29 moderate depression	9*	30.00*	0	0.00	9	10.00		
30-63 severe depression	2	6.70	0	0.00	2	2.20		

*Independent sample T **Chi-square test

ASES: Arizona sexual experiences scale, FSS: Fatigue severity scale, BDS: Beck depression scale, BDI: Beck depression inventory

Table 4. Comparison of SF-36 sub-domain scores of the case and control groups

SF-36 sub-domains scores	Group	N	Mean	SD	T	p
Physical function	**Case** **Control**	30 60	57.66 93.08	27.02 20.00	**-7.01**	**0.00***
Role difficulty	**Case** **Control**	30 60	34.16 92.50	36.83 26.56	**-8.60**	**0.00***
Pain	**Case** **Control**	30 60	87.33 2.66	8.27 8.60	44.53	0.00*
General health	**Case** **Control**	30 60	34.00 51.73	6.94 10.30	**-8.49**	**0.00***
Energy vitality	**Case** **Control**	30 60	34.33 62.25	6.39 13.19	**-10.94**	**0.00***
Social function	**Case** **Control**	30 60	29.16 61.45	15.85 9.57	**-12.02**	**0.00***
Role difficulty emotional	**Case** **Control**	30 60	36.66 65.00	36.46 11.35	**-5.53**	**0.00***
Mental health	**Case** **Control**	30 60	52.00 65.73	5.84 11.46	**-6.16**	**0.00***

*Independent Sample T, SD: Standard deviation

30-80% of the patients with MS and has a strong negative effect on the QoL (16,17). Questioning SD in patients with MS can improve their QoL (18). Education and counseling to patients can help solve hidden problems such as SD and improve their QoL (19). In several studies, SD is a widespread problem in women with MS (20,21). The findings of these studies are consistent with those of our study. In Marita's study, patients with MS had sexual problems more than did healthy people (22). Although fatigue is a widespread symptom in patients with MS, it is often overlooked or undervalued because of its subjective nature. Its treatment is rather complex. Fatigue is more common in patients with MS than in healthy adults or in individuals with other diseases and affects their activities of daily living, causing loss of energy and motivation (23,24). Members of a health team should motivate individuals with MS to manage fatigue, maintain good relationships with other people, organize life, and use their energy correctly (25).

MS is a neurological disorder in which psychiatric symptoms such as depression are frequently observed (25). Depression is more widespread in patients with MS than it is in patients with other chronic neurological disorders. Many factors such

as fatigue, sleep disorders, and movement limitation can affect depression in patients with MS (26). Therefore, although depression is frequently observed in patients with MS, it is difficult to recognize and diagnose it. MS has been reported to reduce the QoL by disrupting the emotional wellbeing of patients, affecting their social life (25,26). In 2005, the Goldman Consensus group stated that depression was an important factor in reducing the QoL along with cognitive impairment (27). In several studies, depression is reported as common in patients with MS and to affect their QoL (28,29). In the present study, the SF-36 QoL scale was used, and the QoL score was low in patients with MS suffering depression (28-30). In another study, Nourbakhsh et al. (30) assessed the QoL with SF-36 and found that QoL was negatively affected in patients with MS suffering depression (30). In our study, a significant relationship was noted between SF-36 QoL scale and depression level in women with MS. Domingo et al. (31) and Bartnik et al. (32) also reported a relationship between depression and SD (31,32). Factors such as depression and fatigue can decrease sexual desire, vaginal lubrication, and genital sensitivity (33). Usually, depression is neglected in the treatment process of patients with MS; thus, psychological problems of these people should be tackled through a multidisciplinary approach (34).

Study Limitations

The results are applicable only to those who presented to a neurology clinic for follow-up; thus, they cannot be generalized to all people with MS. A statistical limitation is that the study was conducted with 30 women with MS. Patients are admitted to the MS outpatient clinic in the hospital where the study was conducted once a week, and because only female patients were included in the study, it was conducted with 30 women with MS. Therefore, our sample does not represent people with all MS subtypes.

Conclusion

In this study, we investigated the effects of SD, fatigue, and depression on the QoL of women with MS and determined that people with MS had higher levels of fatigue, SD, and depression than did healthy controls, which may have decreased their QoL. We also determined that SD, fatigue, and depression affected the QoL in healthy women negatively, but less frequently than in women with MS. The comparison of the two groups revealed that the level of QoL was significantly lower in participants with MS than it was in participants in the control group.

Ethics

Ethics Committee Approval: This study was conducted in the neurology clinic of a medical center. The study was approved by the Ethical Commission of University of Health Sciences Turkey, Faculty of Medicine, was obtained (decision number: 140, date: 25.03.2015).

Informed Consent: Written consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Table 5. Relationship between SF-36 sub-dimensions of MS patients and Arizona sexual lives scale, fatigue severity scale, and Beck depression scale scores

SF-36 Sub-fields	ASES	FSS	BDS
Physical function	**r_s=-0.372* p=0.043**	r_s=-0.201 p=0.288	r_s=-0.074 p=0.698
Role difficulty	r_s=-0.041 p=0.830	r_s=-0.022 p=0.908	r_s=-0.241 p=0.200
Pain	r_s=-0.239 p=0.203	r_s=-0.145 p=0.444	**r_s=-0.393* p=0.032**
General health	r_s=-0.182 p=0.336	p=0.352 r_s=-0.176	r_s=-0.239 p=0.204
Energy/vitality	r_s=0.152 p=0.422	r_s=-0.249 p=0.185	r_s=-0.258 p=0.168
Social function	r_s=-0.157 p=0.409	r_s=-0.191 p=0.313	r_s=-0.035 p=0.852
Emotional	r_s=0.351 p=0.057	r_s=0.351 p=0.057	r_s=0.160 p=0.398
Mental health	r_s=-0.327 p=0.077	r_s=-0.190 p=0.314	r_s=-0.282 p=0.131

*The correlation is significant at the p<0.05 level. MS: Multiple sclerosis ASES: Arizona sexual experiences scale, FSS: Fatigue severity scale, BDS: Beck depression scale, BDI: Beck depression inventory

Authorship Contributions

Surgical and Medical Practices: S.A., H.M., Concept: N.G.T., H.M., Design: S.A., N.G.T., H.M., Data Collection or Processing: S.A., N.G.T., H.M., Analysis or Interpretation: S.A., N.G.T., H.M., Literature Search: S.A., N.G.T., Writing: S.A.

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

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

References

1. Göksel Karatepe A, Kaya T, Günaydn R, Demirhan A, Ce P, Gedizlioğlu M. Quality of life in patients with multiple sclerosis: the impact of depression, fatigue, and disability. Int J Rehabil. Res 2011;34:290-298.
2. Soykan, A. The reliability and validity of Arizona Sexual Experiences Scale in Turkish ESRD patients undergoing hemodialysis. Int J Import Res 2004;16:531-534.
3. Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, Karabudak R. The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. Int J Rehabil Res 2007;30:81-85.
4. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-571.

5. Hisli Sahin N. The validity and reliability of Beck depression inventory for university students. Turkish Journal of Psychology 1989;7:3-13.
6. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.
7. Koçyiğit H, Aydemir Ö, Güler F, Ölmez N, Memis A. Reliability and Validity of the Turkish Version of the Short Form-36 (SF36). İlaç ve Tedavi Dergisi 1999;12:102-106.
8. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444-1452.
9. Özakbas S. Evaluation of Disability in Multiple Sclerosis. Archives of Neuropsychiatry 2008;45:6-9.
10. Bertado-Cortés B, Villamil-Osorio L, Carrera-Pineda R, Martínez-Cortés C, Guerrero-Cantera J. Clinical and demographic characteristics of patients with multiple sclerosis. Rev Med Inst Mex Seguro Soc 2016;54:S186-190.
11. Sorgun HM, Yücesan C. Headache and Functional System Involvement in Multiple Sclerosis. J Ankara Univ Fac Med 2011;64:81-85.
12. Nazari F, Shaygannejad V, Sichani MM, Mansourian M, Hajhashemi V. Sexual dysfunction in women with multiple sclerosis: prevalence and impact on quality of life. BMC Urol 2020;20:15.
13. Arpaci E, Unal EH, Gulpek D, Pınar CE, Turkoglu Akbay S, Gedizlioglu M, Mete L. Sexual Dysfunction in Multiple Sclerosis Patients. Jounal of Neurological Sciences 2011; 28:71-78.
14. Solaro C, Trabucco E, Signori A, Martinelli V, Radaelli M, Centonze D, Rossi S, Grasso MG, Clemenzi A, Bonavita S, D'Ambrosio A, Patti F, D'Amico E, Cruccu G, Truini A. Depressive symptoms correlate with disability and disease course in multiple sclerosis patients: an ıtalian multi-center study using the Beck depression inventory. PLoS One 2016;15;11:e0160261.
15. Kisic-Tepavcevic D, Pekmezovic T, Trajkovic G, Stojsavljevic N, Dujmovic I, Mesaros S, Drulovic J. Sexual dysfunction in multiple sclerosis: A 6-year follow-up study. J Neurol Sci. 2015;358:317-323.
16. Lew-Starowicz M, Rola R. Prevalence of sexual dysfunctions among women with multiple sclerosis. Sex Disabil 2013;31:141-153.
17. Schmidt EZ, Hofmann P, Niederwieser G, Kapfhammer HP, Bonelli RM. Sexuality in multiple sclerosis. J Neural Transm (Vienna). 2005;112:1201-1211.
18. Haliloglu S, İcagasıoglu H, Baklacıoglu HS, Yumusakhuylu Y, Atlıg RS, Demirhan E, Işık N. Relationship between functional status and quality of life in multiple sclerosis. Göztepe Tıp Dergisi 2009;24:129-133. Available from: https://jag.journalagent.com/medeniyet/pdfs/MEDJ_24_3_129_133.pdf
19. Lefebvre S, Simonin L. Improving the sexual QoL of people with multiple sclerosis. Rev Infirm 2016;222:21-23.
20. Silva RA, Olival GS, Stievano LP, Toller VB, Jordy SS, Eloi M, Tilbery CP. Validation and cross-cultural adaptation of sexual dysfunction modified scale in multiple sclerosis for Brazilian population. Arq Neuropsiquiatr 2015;73:681-687.
21. Terzi M, Kocamanoglu B, Güz H, Onara M, Sahin AR. Sexual dysfunction in multiple sclerosis patients. J. Exp. Clin. Med. 2009;26:81-85.
22. McCabe MP. Relationship functioning and sexuality among people with multiple sclerosis. J Sex Res 2002;39:302-309.
23. Kaya T, Karatepe GA, Demirhan A, Günaydın R, Gedizlioğlu M, Ortan P. Fatigue and Related Factors in Patients With Multiple Sclerosis. Journal of Neurological Sciences 2009;26:190-197.
24. Krupp LB. Fatigue in multiple sclerosis: definition, pathophysiology and treatment. CNS Drugs 2003;17:225-234.
25. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nat Rev Neurol 2014;10:507-517.
26. Brenner F, Piehl P. Fatigue and depression in multiple sclerosis: pharmacological and non- pharmacological interventions. Acta Neurol Scand 2016;134:47-54.
27. Ensari I, Motl RW, McAuley E, Mullen SP, Feinstein A. Patterns and predictors of naturally occurring change in depressive symptoms over a 30-month period in multiple sclerosis. Mult Scler 2014;20:602-609.
28. Mohammadi K, Rahnama P, Montazeri A. Prevalence and risk factors for depression in women with multiple sclerosis: a study from Iran. Ann Gen Psychiatry 2015;22:14-29.
29. Gumus H, Akpınar Z, Yılmaz H. The effects of multiple sclerosis on female sexuality: Controlled study. J Sex Med 2014;11:481-485.
30. Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict QoLin patients with early multiple sclerosis: a longitudinal study. Eur J Neurol. 2016;23:1482-1486.
31. Domingo S, Kinzy T, Thompson N, Gales S, Stone L, Sullivan A. Factors associated with sexual dysfunction in individuals with multiple sclerosis: implications for assessment and treatment. Int J MS Care 2018:20:191-197.
32. Bartnik P, Wielgoś A, Kacperczyk J, Pisarz K, Szymusik I, Podlecka-Piętowska A, Zakrzewska-Pniewska B, Wielgoś M. Sexual dysfunction in female patients with relapsing-remitting multiple sclerosis. Brain Behav 2017:7:e00699.
33. Hösl KM, Deutsch M, Wang R, Roy S, Winder K, Niklewski G, Lee D-H, Linker RA, Hilz MJ. Sexual dysfunction seems to trigger depression in female multiple sclerosis patients. Eur Neurol 2018:80:34-41.
34. Zavoreo I, Gržinčić T, Preksavec M, Madžar T, Bašić Kes V. Sexual dysfunction and incidence of depression in multiple sclerosis patients. Acta Clin Croat 2016:55:402-406.

DOI: 10.4274/jmsr.galenos.2022.2022-4-1
Journal of Multiple Sclerosis Research 2022;2(1):20-27

RESEARCH ARTICLE

Designing Virtual Reality-based Testing and Rehabilitation Software for People with Multiple Sclerosis

Iman Naser[1], Mehmet Hilal Ozcanhan[1], Ergi Kaya[2], Asiye Tuba Ozdogar[3]

[1]Dokuz Eylul University Faculty of Engineering, Department of Computer Engineering, Izmir, Turkey
[2]Dokuz Eylul University Faculty of Medicine, Department of Neurology, Izmir, Turkey
[3]Dokuz Eylul University, Graduate School of Health Sciences, Izmir, Turkey

Abstract

Objective: Physical disability is a fact of some neurologic disorders, such as multiple sclerosis. One of the treatments for such disability is routine physical exercises, or "rehabilitation". However, rehabilitation in hospitals is often unattractive to patients. Another difficulty is objectively assessing the final effect of rehabilitation on disabilities, as assessment often depends on the subjective opinion of the physician. In the present study, we offer exergaming rehabilitation at home (telerehabilitation) and an objective method for measuring the physical performance of people with multiple sclerosis using a virtual reality tool to assist the decision of whether improvement, no change, or deterioration in the patient's health status has occurred.

Materials and Methods: Telerehabilitation is provided by custom-made exergames specifically designed for patients with upper extremity disabilities. Our performance measurement method records the time taken by a patient to finish a physical test and measures the angles of interest between predetermined upper extremities. The measurements are recorded and saved for future determinations of patient progress. Thus, improvement-deterioration-no change decisions can depend less on subjective opinions. Preliminary performance experimentation was conducted before and after participants played our virtual reality exergames.

Results: The results reveal that our method is capable of measuring angles with an error margin of 6.44%. The accuracy of our method is 86.00%. The sensitivity, i.e., ability to detect improvements in patient performance, of our method is higher at 88.24%. The specificity, i.e., correct determination of no change in performance, is lower at 82.25%. The time taken to finish a physical test could not be evaluated due to a lack of real patients in our engineering laboratories.

Conclusion: The impact of our telerehabilitation exergaming solution on patient performance requires prolonged use by patients and future analysis of accumulated medical opinions. Our proposal is the first step toward exergaming and digital performance determination.

Keywords: Virtual reality, telerehabilitation, multiple sclerosis, upper extremities, Kinect, performance measurement

Introduction

As a result of a neurological disorder, people with multiple sclerosis (MS, pwMS) suffer from motor impairment affecting their everyday activities, defined as a physical disability (1). Approximately 66% of pwMS suffer from upper extremity dysfunction (2). One of the treatments for upper extremity dysfunction is rehabilitation, or physical education (3). As the first step of the rehabilitation process, the disability level of pwMS is determined through a set of physical tests (4). The main goal of the tests is to observe the body functions and decide the degree of capability of executing specific movements. At the end of the examination a physician assigns a disability score to pwMS. Following a score assignment, an individual and convenient rehabilitation program is designed for the patient (5). Informative rehabilitation sessions take place at hospitals under the supervision of professional healthcare personnel. Afterwards, the patient is expected to follow the advised rehabilitation program at home. However, during the coronavirus disease 2019 (COVID-19) pandemic, patients are not recommended to re-visit hospitals for rehabilitation, to avoid COVID-19

Address for Correspondence: Asiye Tuba Ozdogar, Dokuz Eylul University, Graduate School of Health Sciences, Izmir, Turkey
E-mail: asiye.tuba.ozdogar@gmail.com **ORCID-ID:** orcid.org/0000-0002-5781-3497
Received: 26.05.2022 **Accepted:** 01.06.2022

transmission. Unfortunately, it is frequently reported that patients lose interest and fail to follow their programs, due to various personal reasons. A lack of telerehabilitation system substructures in developing countries such as Turkey also adversely affects the implementation of rehabilitation programs (6).

The most common and global measurement of disability is the expanded disability status scale (EDSS) (7). However, since the EDSS does not include upper extremity and cognitive function assessment, the MS functional composite was developed (8). Unfortunately, the mutual disadvantage of those methods is that the score determined for pwMS may differ from one physician to another. Consequently, the difference in the assigned scores may result in inconsistent rehabilitation programs and ultimately cause loss of interest in rehabilitation and physical activities by pwMS, resulting in no physical improvement. Such an outcome is the most undesired by all parties involved.

While the patients discontinue long-term traditional rehabilitation programs, interest in virtual reality (VR) for passing time is on the rise. VR also offers the opportunity to receive task-oriented training by merging exercise and gaming into the exergames technology (9). Moreover, VR exergaming has also been suggested for rehabilitation as a more motivational method for pwMS treatment. Many previous studies utilized the Microsoft Kinect™ camera (Kinect) for VR rehabilitation applications. Some authors have developed Kinect-based games to help patients exercise and improve their body's motor movements (10). The games were designed to help the player train specific muscles or parts of the body. For instance, while one game targeted the upper extremities, another targeted the whole body. In another work, a framework was developed using Kinect to help evaluate gait in pwMS (11). It was concluded that Kinect is a feasible tool for clinical assessment. Other studies also approved the validity of using the Kinect for limb dysfunction assessment. For example, Cai et al. (12) showed that Kinect is a reliable tool for functional upper extremity assessment. In a recent review, researchers discussed the gaming platforms used for measuring clinical outcomes, such as upper extremity movement assessment (13). The paper demonstrates the high precision and accuracy of Kinect in objective disability assessment.

In present work, we aimed to help physicians in two ways, using a state-of-the-art VR technology:

1. Overcome the problem of discontinued patient rehabilitation,
2. Provide help in assessing physical disability using engineering methods.

In the first phase, we developed an exergaming software specifically targeting pwMS. The pwMS executes some house chores using the developed VR software, instead of playing games intended for healthy people. In the second phase, we developed a software program using the same tool for measuring the time taken by a patient to finish a physical test and the angles of interest (AoI) between some nodes of the upper body extremities. Thus, disability assessment will become more objective, by using our computerized physical performance measurements.

Materials and Methods

Our telerehabilitation VR applications consist of custom-made exergaming software that runs on a personal computer (PC) with a Kinect connected to it. Both the exergaming scenarios and the performance measurements of the pwMS have been implemented using the same tool. This study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (decision number: 2022/14-02, date: 13.04.2022). An informed consent form was obtained from all participants.

Participants

Exergames were attempted by multiple healthy people in their homes, but because of the COVID-19 pandemic, performance measurement tests were carried out with one healthy control person in an engineering laboratory in order to limit the contact with many people. As a future study, clinical tests with more participants are needed to obtain better results from the performance measurement software.

Procedure

The scenarios were planned in three separate meetings by a team consisting of computer engineers, doctors, and physiotherapists. In the first meeting, 16 scenarios, including kitchen activities, were determined by doctors and physiotherapists. In the second meeting, the team discussed all scenarios, and they decided to merge some of those. The last version of the exergames, which comprises 13 scenarios, was completed in the third meeting. The following activities were included: opening the door, wearing a kitchen apron, choosing and memorizing a recipe, selecting items from the fridge, cleaning and dishwashing, cooking, and eating.

Materials

Our work involves both hardware and software. We designed and programmed the software on a Microsoft Windows™ operating system with Windows Presentation Foundation (WPF) and the C# programming language. In addition, we included the Microsoft.Kinect.dll library, which provides Kinect-related functionality. The materials used are given below:

Hardware

- PC with Gen Intel® Core™ i5-1135G7, 8 GB RAM and Intel Iris® Xe Graphics card,
- Microsoft Kinect™ V2,
- Conversion adapter for direct connection to a PC.

Software

- Microsoft Windows 10 Operating System™,

- Visual Studio™ 2019,

- C# Net and WPF,

- Kinect software development kit and library,

- Vitruvius package of utility programs (14).

However, the hardware is not invariant. Other VR tools such as Kinect Azure™, Intel RealSense™, or other brands can be used with the same developed algorithms. Microsoft initially produced the Kinect Xbox One for motion capture and gaming. Unlike Kinect for Windows, it cannot directly connect to the PC and needs an additional external power adapter, as shown in Figure 1. Hence, Xbox can be replaced by a PC, making software development and testing on the same computer possible. The developed software can be adapted to run on Xbox One or other Xbox versions.

Method

In the first phase of our work, a household chore scenario is reflected on the PC monitor. The pwMS is requested to complete a chore using the hands, rather than a remote controller. The Kinect tracks the hand movements of the pwMS, as it is equipped with an infra-red (IR) emitter, a red-green-blue camera, and an IR depth sensor as shown in Figure 2. The specially designed dotted light pattern emitted by the IR emitter is not visible to the human eye. The IR depth sensor captures the reflected light pattern from the objects in front of it. Figure 3 shows the IR dotted light pattern emitted by the Kinect IR sensor toward a 3D object. The CMOS sensor captures the pattern, and the time of flight of each dot reflected from the 3D object is recorded. The information is used to create a depth map of the objects in front of the Kinect (10). Hence, the positions of human body parts are determined by the calculated distance of each reflection (15).

The user interfaces of the exergaming and performance measurement software are shown in Figure 4, 5, respectively.

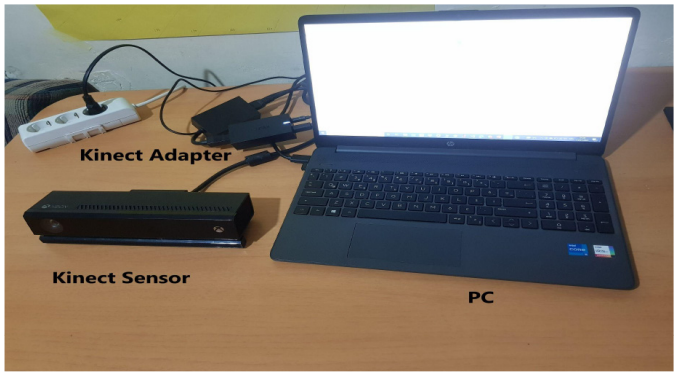


Figure 1. A Diagram of the Kinect connection to a PC

PC: Personal computer

The household chore exergames are determined by the physicians working on the project team. The scenarios start with verbal instructions. The pwMS is given a task to finish. For example, the pwMS is asked to open a jar and empty the contents into a bowl, as in Figure 4. The camera view shows the pwMS role-player performing the chore. The finished chores are assigned a point to motivate the player. The patient must finish within a predetermined period. The test is timed using

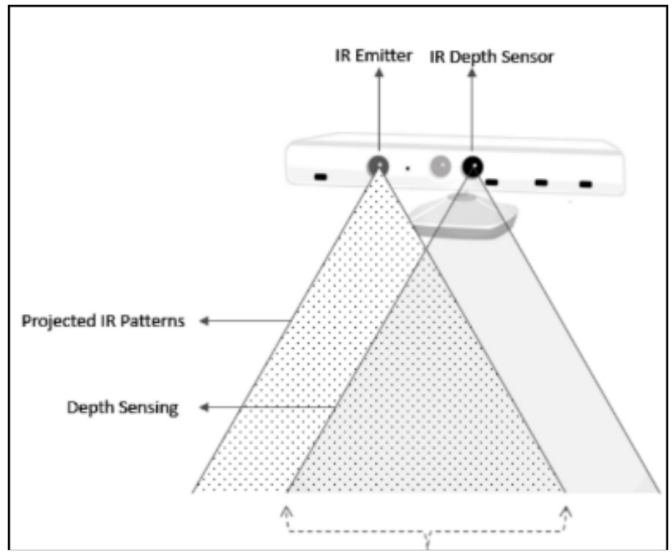


Figure 2. The overall depth sensing principle (15)

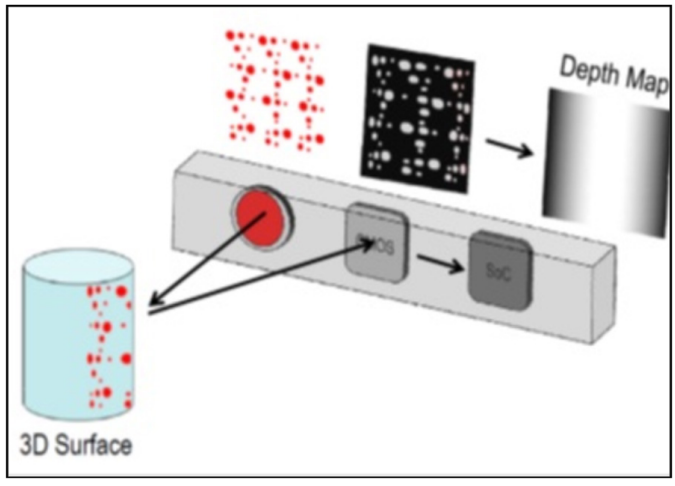


Figure 3. The working principle of Kinect (10)

Table 1. Node numbers forming the AoI

AoI	Node 1	Middle node	Node 3	Color
Θ1	2	3	4	Green
Θ2	2	11	12	Blue
Θ3	3	4	5	Red
Θ4	11	12	13	Brown

AoI: Angles of interest

the system clock. Hence, the physical speed of the pwMS is measured. The performance measurement interface contains a set of buttons for choosing a test. After making a choice, the pwMS is verbally instructed about the test. Then, the Kinect is activated, and tracking of the pwMS is started.

The labeled pwMS skeleton and the AoI to be measured for the chosen test are displayed on the monitor. Four colored and numbered rectangles on the upper right corner show the values of the AoI measured. Table 1 gives the location of the AoI. The interface also displays the real system time and the chronometer, which display the time passed since the start of the test. Hence, the pwMS's physical capability/disability and the time taken are measured. The overall result is recorded as a triplet, (Θ1, Θ3, time) and (Θ2, Θ4, time), in the PC database.

Preliminary performance measurement experimentation has been carried out. The tests were carried out before and after 10 physical training sessions with the custom-made VR scenarios. The subject is asked to take a position in front of the Kinect during testing. The subject's distance from the Kinect is optimized by moving the subject toward or away (according to body size), until the best region of interest frame is obtained. It is usually recommended to position the pwMS at a distance

Figure 4. Our custom-made VR scenario for opening a jar
VR: Virtual reality

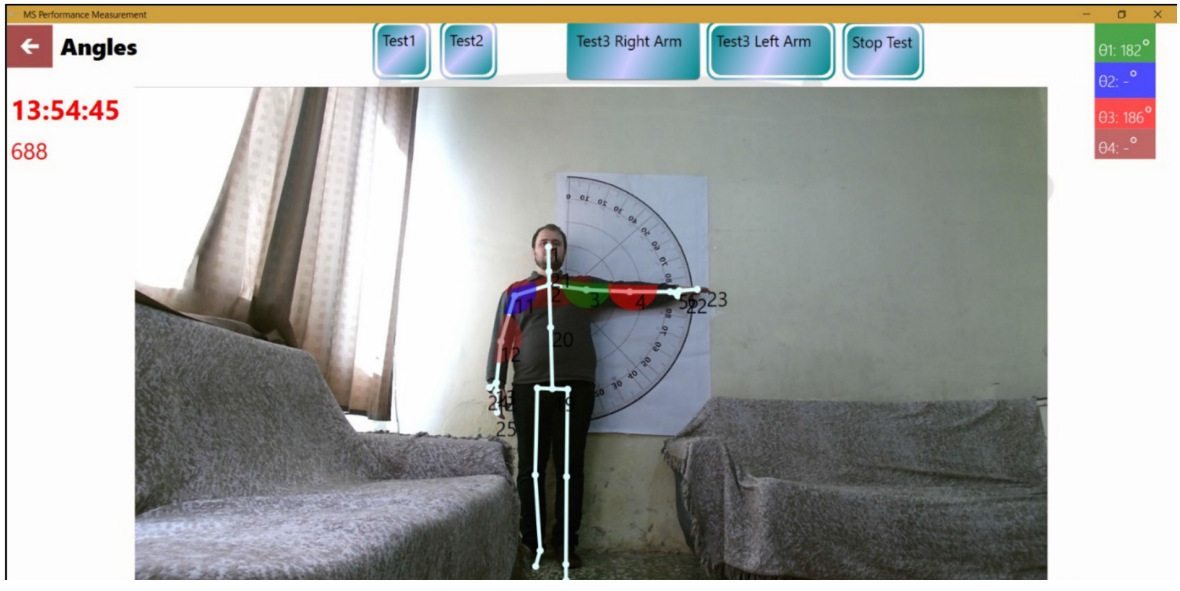


Figure 5. Our AoI performance measurement software screen
AoI: Angles of interest

of 1.5-4 m away from the Kinect (16). The determined optimal distance is used in every test, for each subject. During testing, the following steps are carried out:

1. The subject is instructed to stand at the baseline with both arms resting at their sides,
2. The physician selects the desired test by clicking on the planned test button,
3. When the button is pressed, the participant is instructed by a by pre-recorded voice to execute a sequence of actions,
4. Recording of the subject movements starts five seconds before the end of the instructions,
5. While the subject performs the physical activities, the AoI and the time are shown on the computer screen and recorded into a file,
6. The subject finishes the test by placing both arms at their sides as in the start position,
7. The test automatically stops at its conclusion.

There is no need to synchronize the start or end of the test. The first change in the AoI detects the moment when the subject starts to move. Conversely, the moment the subject ends the test is detected by the unchanging AoI. The Kinect tracks 25 nodes on the subject's skeleton during the test. The numbering of the nodes has been defined in previous works as in Figure 6 (17).

Each AoI is determined by three nodes. For example, angle Θ1 of the left shoulder in Figure 6 is determined by nodes 2, 3, and 4. In the "Test3 Left Arm" experiment, angles Θ1 and Θ3 are recorded, as shown in Figure 7. The angles Θ2 and Θ4 are recorded in the "Test3 Right Arm" experiment.

Results

VR exergaming scenarios are approved by a medical committee before being made available to pwMS. There are a total of 13 scenarios, and each one is continuously perfected according to the physician's comments. The first evaluations indicate that VR exergaming in the form of house chores is feasible. Furthermore, exergaming at home appears as a promising means of limiting hospital rehabilitation visits of pwMS.

All AoI measurements are saved in a file as shown in Figure 8, with a timestamp for later comparison with previous results. The file is closed at the end of the test. Figure 8 shows the angle value, and the time it was recorded. The angle readings are matched with the actual angle values marked on the paper protractor behind the player's arm, as in Figure 5. The percent error in determining the AoI is calculated using equation (1):

$$\text{Error} = \frac{|(\text{Actual Value} - \text{Measured Value})|}{\text{Actual Value}} \times 100 \quad (1)$$

The mean error in measuring AoI in 50 different tests is 6.44%. The mean error in measuring the time taken to finish a test is less than 1%. However, this is not a valid estimate as the experiment subjects are not patients but healthy people.

Discussion

Our study proposes VR-based rehabilitation and performance assessment software for pwMS. In the first phase, a custom-made telerehabilitation exergaming software is implemented, using Microsoft Kinect. The pwMS are offered to play a game of complete series of scenarios, mimicking house chores. The developed scenarios are designed and approved by a team of physicians. In the second phase, we propose a method to measure the time taken to complete a task and the AoI of pwMS. AoI and task-timing values are recorded in a file using the Kinect tool, to help determine improvement, no change, or deterioration in the disability condition of the pwMS. The preliminary results show that the exergaming method is feasible in pwMS telerehabilitation. Notably, the number of hospital visits by the pwMS for rehabilitation can be reduced by the opportunity to exergame at home. The measurement of AoI with an average error of 6.44% and no valid timing measurement was not found satisfactory. Therefore, we sorted the measurements to mimic making the decision of whether a patient's physical state has improved or has not changed. Changes less than 5 degrees (5°) were not noticeable by a physician observer. Therefore, to decide that the patient

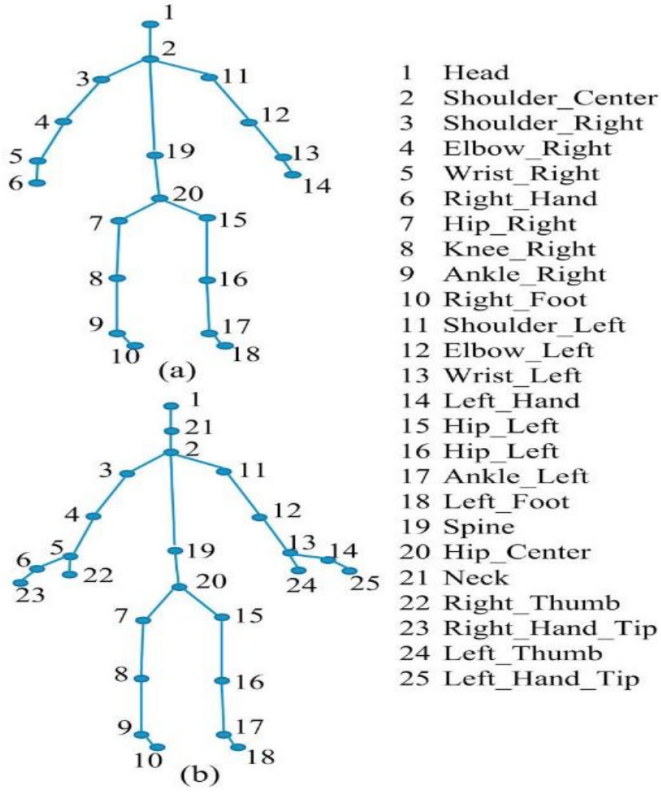


Figure 6. Kinect skeleton nodes numbering (17)

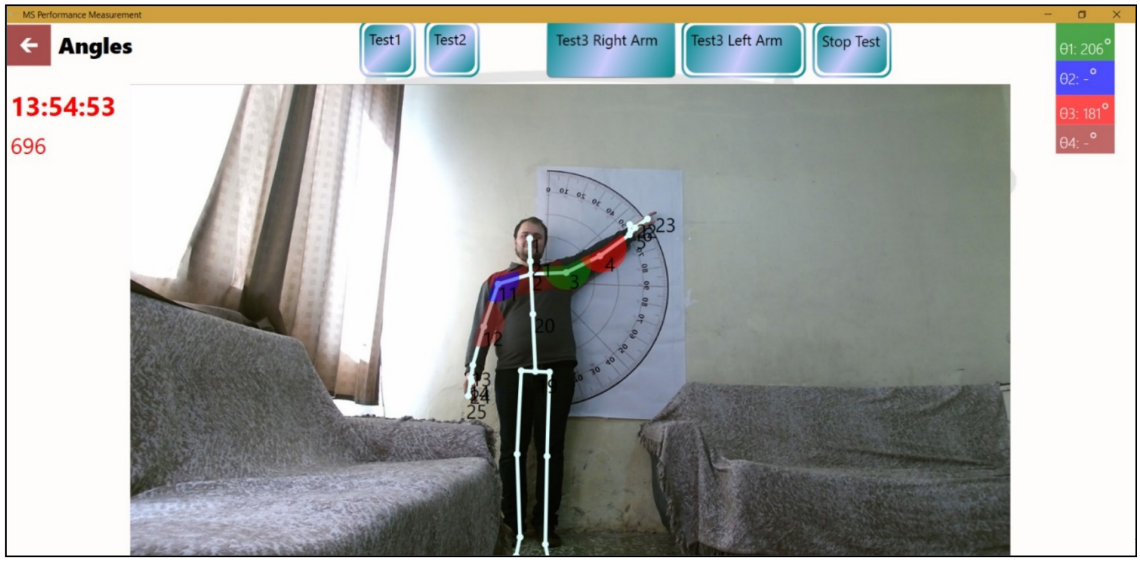
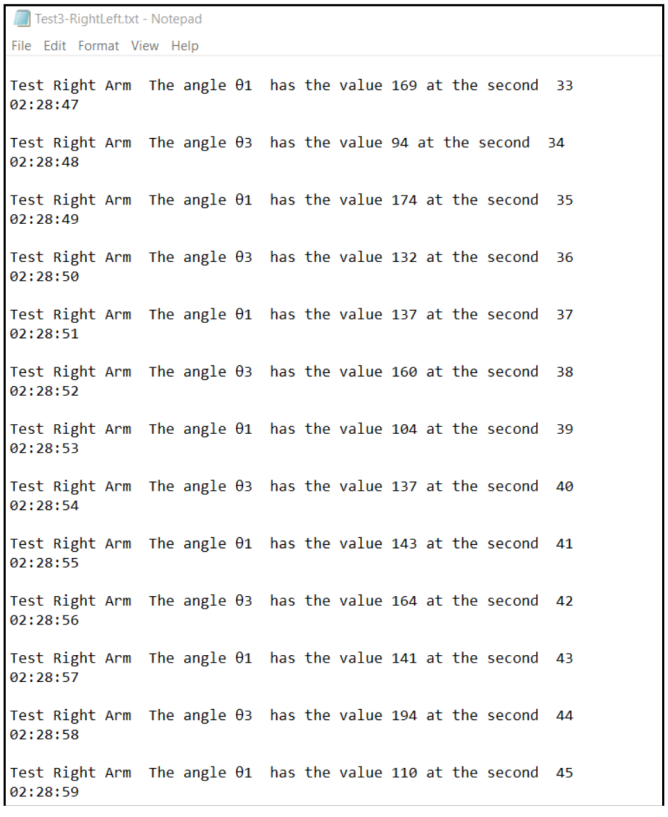


Figure 7. "Test3 Left Arm" experiment and angle-timing measurements

had "improved", a change larger than 5° in AoI measurement by the software was accepted. Otherwise, the patient was considered as "not improved". The improved or not improved decision was also made by an observer, independent of the software. In total, 50 tests were made to calculate the accuracy, sensitivity, and specificity of our software. For statistical calculations, true positive (TP), true negative (TN), false positive (FP), and false negative (FN) classifications were made as follows:


Test3-RightLeft.txt - Notepad

File Edit Format View Help

```
Test Right Arm  The angle θ1  has the value 169 at the second  33
02:28:47

Test Right Arm  The angle θ3  has the value 94 at the second  34
02:28:48

Test Right Arm  The angle θ1  has the value 174 at the second  35
02:28:49

Test Right Arm  The angle θ3  has the value 132 at the second  36
02:28:50

Test Right Arm  The angle θ1  has the value 137 at the second  37
02:28:51

Test Right Arm  The angle θ3  has the value 160 at the second  38
02:28:52

Test Right Arm  The angle θ1  has the value 104 at the second  39
02:28:53

Test Right Arm  The angle θ3  has the value 137 at the second  40
02:28:54

Test Right Arm  The angle θ1  has the value 143 at the second  41
02:28:55

Test Right Arm  The angle θ3  has the value 164 at the second  42
02:28:56

Test Right Arm  The angle θ1  has the value 141 at the second  43
02:28:57

Test Right Arm  The angle θ3  has the value 194 at the second  44
02:28:58

Test Right Arm  The angle θ1  has the value 110 at the second  45
02:28:59
```

Figure 8. Screenshot for saved values

TP: Patient improved according to observer, and software also predicted improvement.

TN: Patient not improved according to observer, and software also predicted no improvement.

FP: Patient improved according to observer, but software predicted no improvement.

FN: Patient not improved according to observer, but software predicted improvement.

The testing results are summarized in Table 2. Out of 50 tests, our solution correctly detected 30 cases of improved patient performances. Thirteen cases of no performance improvement were also correctly detected. However, six cases of performance improvement and four cases of no performance improvement were incorrectly predicted.

The accuracy of our proposed method is its ability to determine the actual improvement in patient performances correctly. The universal equation for accuracy is:

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN} \text{ x } 100 \qquad (2)$$

The ability to detect an improvement in patient performance correctly gives the sensitivity of our proposed method. The accepted equation for sensitivity is given in (3).

$$\text{Sensitivity} = \frac{TP}{TP+FN} \text{ x } 100 \qquad (3)$$

Another important parameter is the specificity, which demonstrates the ability of the method used to correctly

Table 2. Test results of our proposed method

		Predicted improvement	
		Negative	Positive
Actual improvement	Negative (-)	True negatives=13	False positives=3
	Positive (+)	False negatives=4	True positives=30

Table 3. Performance results

Measurement	Performance criteria			
	Accuracy	Sensitivity	Specificity	Percentage of error
Achievement	86.00	88.24	82.25	6.44

determine no improvement in patient performance. The specificity equation is:

$$\text{Specificity} = \frac{TN}{TN+FP} \text{ x } 100 \qquad (4)$$

The calculated accuracy, sensitivity, and specificity of our proposed method are tabulated in Table 3. The accuracy of our method is 86.00%, and the sensitivity is higher at 88.24%. It is obvious that our method is superior at detecting improvements in patient performances. The specificity, i.e., correct determination of no improvement in performance, is lower at 82.25%. Nevertheless, these results come as no surprise, since the experiments were carried out in engineering laboratories and not in a hospital environment.

This study has some limitations. First, due to the COVID-19 pandemic, performance measurement tests and exergames were attempted on a limited pool of healthy controls. Second, we did not compare the results of measurements performed using the Kinect tool with real-time measurements.

Conclusion

The use of VR technology has been proposed for rehabilitation and physical performance determination in pwMS. The average error in determining AoI is 6.44%. The accuracy, i.e., correct determination of improvement or lack of improvement in patient performance, of our method is 86.00%. The sensitivity, i.e., ability to detect improvement in patient performance, is higher at 88.24%. The specificity, i.e., correct determination of no improvement in patient performance is lower at 82.25%. The successful measurement of the time taken to finish a physical test could not be evaluated due to the lack of real patients in our engineering laboratories.

The results are promising for obtaining objective clinical decisions about the physical performances of pwMS. Clinical work is needed to decrease the error, increase the accuracy and determine the task completion time. Future work also involves devising machine learning methods for interpreting collected pwMS performance data.

Ethics

Ethics Committee Approval: This study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (decision number: 2022/14-02, date: 13.04.2022).

Informed Consent: The informed consent form was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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

Acknowledgments: The authors acknowledge the Multiple Sclerosis Research Association-Izmir for assistance during the recruitment of the study.

References:

1. Burridge J, Alt Murphy M, Buurke J, Feys P, Keller T, Klamroth-Marganska V, Lamers I, McNicholas L, Prange G, Tarkka I, Timmermans A, Hughes AM. A Systematic Review of International Clinical Guidelines for Rehabilitation of People With Neurological Conditions: What Recommendations Are Made for Upper Limb Assessment? Front Neurol 2019;10:567.
2. Bertoni R, Lamers I, Chen CC, Feys P, Cattaneo D. Unilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis. Mult Scler 2015;21:1566-1574.
3. Donzé C, Massot C. Rehabilitation in multiple sclerosis in 2021. Presse Med 2021;50:104066.
4. Lamers I, Kelchtermans S, Baert I, Feys P. Upper limb assessment in multiple sclerosis: a systematic review of outcome measures and their psychometric properties. Arc Phy Med Rehabil 2014;95:1184-1200.
5. Sutliff MH, Bennett SE, Bobryk P, Halper J, Saslow LA, Skutnik LT, Smith C, Zackowski K, Jones DE. Rehabilitation in multiple sclerosis: Commentary on the recent AAN systematic review. Neurol Clin Pract 2016;6:475-479.
6. Srivastava A, Swaminathan A, Chockalingam M, Srinivasan MK, Surya N, Ray P, Hegde PS, Akkunje PS, Kamble S, Chitnis S, Kamalakannan S, Ganvir S, Shah U; Indian Federation of Neurorehabilitation (IFNR) Research Task Force.

Tele-Neurorehabilitation During the COVID-19 Pandemic: Implications for Practice in Low- and Middle-Income Countries. Front Neurol 2021;12:667925.

7. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-1452.
8. Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, Syndulko K, Weinshenker BG, Antel JP, Confavreux C, Ellison GW, Lublin F, Miller AE, Rao SM, Reingold S, Thompson A, Willoughby E. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999;122:871-882.
9. Taylor MJ, Griffin M. The use of gaming technology for rehabilitation in people with multiple sclerosis. Mult Scler 2015;21:355-371.
10. J. Fong, J. Gorman, Z. Panzarino, S. Topper and S. Weill, "Motion control gaming with Kinect", 2016, [online] Available: https://soe.rutgers.edu/sites/default/files/imce/pdfs/gset-2016/MotionControlGamingfinalpaper.pdf.
11. Gholami F, Trojan DA, Kovecses J, Haddad WM, Gholami B. A Microsoft Kinect-Based Point-of-Care Gait Assessment Framework for Multiple Sclerosis Patients. IEEE J Biomed Health Inform. 2017;21:1376-1385.
12. Cai L, Ma Y, Xiong S, Zhang Y. Validity and Reliability of Upper Limb Functional Assessment Using the Microsoft Kinect V2 Sensor. Appl Bionics Biomech 2019;2019:7175240.
13. Pöhlmann ST, Harkness EF, Taylor CJ, Astley SM. Evaluation of Kinect 3D Sensor for Healthcare Imaging. J Med Biol Eng 2016;36:857-870.
14. Vangos Pterneas, Lightbuzz [internet]. New York, U.S.A . 2016 Aug. [cited 2022 March 21]. Available from: https://github.com/LightBuzz/Vitruvius.
15. Abhijit. J Understandıng the Kinect Device. In: Abhijit. J, editor. Kinect for Windows SDK Programming Guide. UK: Packt Publishing; 2012.p.11-14.
16. Cai L, Liu D, Ma Y. Placement Recommendations for Single Kinect-Based Motion Capture System in Unilateral Dynamic Motion Analysis. Healthcare (Basel) 2021;9:1076.
17. Naveenkumar M, Domnic S.Vector Quantization based Pairwise Joint Distance Maps (VQ-PJDM) for 3D Action Recognition. Procedia Computer Science 2018;133:27-36.

DOI: 10.4274/jmsr.galenos.2022.2022-3-2
Journal of Multiple Sclerosis Research 2022;2(1):28-30

CASE REPORT

HPV-associated Anal and Genital Intraepithelial Neoplasia After Using Fingolimod in the Treatment of Relapsing-remitting Multiple Sclerosis: A Case Report

Melis Doganay Ocalan[1], Gulin Morkavuk[1], Asli Yarci Gursoy[2], Suleyman Ozdemir[3], Alev Leventoglu[1]

[1]Ufuk University Faculty of Medicine, Department of Neurology, Ankara, Turkey
[2]Ufuk University Faculty of Medicine, Department of Gynecology and Obstetrics, Ankara, Turkey
[3]Ufuk University, Faculty of Medicine, Department of General Surgery, Ankara, Turkey

Abstract

Multiple sclerosis (MS) is a chronic, autoimmune, neurodegenerative disease of the central nervous system, with inflammation and loss of myelin in axons. Fingolimod is the first oral disease-modifying agent approved for the treatment of relapsing-remitting MS. Here we aimed to present a patient with MS who developed human papillomavirus (HPV)-associated anal and genital intraepithelial neoplasia while on fingolimod treatment. A 19-year-old female patient presented with the complaint of diplopia. The diagnosis of MS was made based on imaging and cerebrospinal fluid results. She was treated first with beta-interferon 1a, then methotrexate, and finally fingolimod. While the patient was being followed without attack under fingolimod treatment, HPV-associated genital, and further, anal warts developed. This is a rare case that developed both cervical dysplasia and anal Condyloma acuminatum due to the HPV that developed after fingolimod treatment in a patient with MS. In conclusion, fingolimod treatment increases the risk of cervical HPV infection and related cancer in patients with MS.

Keywords: Multiple sclerosis, relapsing-remitting, fingolimod, HPV, cervical dysplasia

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, neurodegenerative disease of the central nervous system. Various immunomodulatory treatment strategies are available, which differently affect the immunological settings in MS pathology. Today, early initiation of disease-modifying therapies (DMT) is beneficial over the long term, resulting in a significant disability reduction. Fingolimod is the first oral immunomodulatory agent that has recently been used for the treatment of relapsing-remitting MS (RRMS) and is a functional S1P analog that acts as an antagonist to S1P receptors (1). After oral administration, the molecule undergoes phosphorylation and binds to the S1P receptor, thereby internalizing and degrading the receptor. Lymphocytes are separated from the lymphoid tissue due to S1P activation, and fingolimod secondary decreases the circulating lymphocyte levels in the absence of this activation (1). Reported side effects include symptomatic bradycardia, macular edema, and liver dysfunction. Rare neoplasms while on fingolimod treatment, such as melanoma, uterine leiomyoma, Bowen's disease, breast cancer, Kaposi's sarcoma, and thyroid cancer, have been reported in case reports (2). Human papillomavirus (HPV) infection can be cleared from the body through the immune system. However, it can cause permanent infections in people whose immune response is insufficient. Additionally, persistent infections are also associated with high-risk oncogenic HPV-related cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancers (3). Herein, we will discuss the young female patient with MS treated with fingolimod and known HPV with varying degrees of cervical, vulvar, and anal dysplasia.

Case Report

Our female patient was diagnosed with RRMS aged 19-years-old, after presenting with a diplopia complaint. Her neurological

Address for Correspondence: Gulin Morkavuk, Ufuk University Faculty of Medicine, Department of Neurology, Ankara, Turkey
Phone: +90 505 508 82 56 **E-mail:** drgcmor@yahoo.com **ORCID-ID:** orcid.org/0000-0001-7522-8585
Received: 31.03.2022 **Accepted:** 03.05.2022

examination revealed a 4/5 muscle strength in the right lower extremity, normal sensory examination, hyperactive deep tendon reflexes, and bilateral extensor plantar response. Cranial and cervical spine magnetic resonance imaging showed lesions typical of inflammatory demyelination. The cerebrospinal fluid analysis showed Type-2 oligoclonal bands. She was commenced on a first-line DMT in the form of subcutaneous beta-interferon 1a that lasted for 2 years. Further, she was treated with methotrexate and pulse methylprednisolone IV every month (both together) between 2012 and 2014. Unfortunately, she continued to have relapses; thus, escalation to fingolimod was initiated in 2014. Her lymphocyte count before starting treatment was 1.8×10^9/L and her varicella-zoster virus immunoglobulin G was positive. At the 3-month followup, she had become lymphopenic, as expected, with a lymphocyte count of 0.5×10^9/L. During the 6 years following the fingolimod administration, she was relapse-free and without significant disability (EDSS=1.5). Additionally, lymphocyte values ranged between 0.3×10^9/L and 0.6×10^9/L. However, when she reached 30 years, she developed genital warts that responded to cryotherapy treatment and were periodically assessed by a dermatologist and gynecologist. Additionally, a few months later, she developed anal warts. Her general surgeon resected the lesions twice but she stayed on fingolimod. The gynecological examination detected multiple millimetric condylomas in the vulvar region. A cervical smear was taken for the first time and an HPV vaccine was recommended. The cytological examination was reported as "low-grade squamous intraepithelial lesion" and HPV screening was positive for high-risk HPV types other than 16 and 18. Colposcopic examination revealed multiple suspicious lesions, and cervical biopsies, including endocervical curettage were held. Histopathological examination was reported as "high-grade squamous intraepithelial lesion" at 3 locations without endocervical involvement. The patient was treated with a loop electrosurgical excision procedure, and the histopathological examination of the conization specimen was reported as cervical intraepithelial neoplasia (grade 2) at multiple locations with disease-free surgical margins. Anal inspection at the same session revealed perianal condilomatous lesions, which all were excised and histopathologically reported as anal intraepithelial neoplasia I.

Fingolimod was discontinued and all lesions resolved within a month. One month after drug discontinuation, a new attack developed with sudden vision loss and right hemiparesis. She was treated with intravenous methylprednisolone for 10 days. Approximately 2 months after the fingolimod cessation, the patient started natalizumab therapy while maintaining a stable neurological condition and had no further wart recurrence since natalizumab is a humanized monoclonal antibody that inhibits the passage of activated T-cells, B-cells, and monocytes across the blood-brain barrier and has no effect on peripheral lymphocyte count.

Written and informed consent was obtained from the patient for publication of this case report.

Discussion

HPV is the most common sexually transmitted disease worldwide. The broad majority of sexually active males and females are affected at some point in their lives (4). The immune system has a fundamental role in the spontaneous recovery phase, and immunosuppressive drugs may be the major risk factors for persistent HPV infection. Generally, HPV infections are cleared by the host immune system within 1-2 years in the majority of cases. Only 10-15% of cases develop persistent infection leading to cancer, if not managed and treated appropriately and promptly (5). Scientific data about the effect of fingolimod treatment on HPV infection is unavailable; however, a few cases were reported in the literature regarding the possible promoting effects of fingolimod on HPV reactivation and genital dysplasia (3). However, a case series of 16 patients with no previous HPV infection who developed HPV lesions after starting fingolimod was published in 2021. Of these patients, 6 discontinued fingolimod, and the HPV vaccine was administered (6). The other mentioned cases were on fingolimod treatment for ~17-58 months and did not respond to conventional treatments for benign/malign warts until the drug dose was modulated or discontinued (3). Our case had been receiving fingolimod treatment for 72 months at the time of diagnosis and the dose was not modulated due to its high effectiveness on MS.

Despite the strong immunomodulatory effects of fingolimod, it was not associated with significantly increased other infections in phase III clinical studies, except for varicella-zoster and herpes simplex virus (1,7). Additionally, the increased cutaneous malignancy rates are thought to be associated with fingolimod, and dermatological examination is recommended before treatment initiation (8).

The exact mechanism of action of fingolimod in patients with MS is unknown, by interacting with S1P receptors, it prevents the release of lymphocytes from lymphocyte tissue (8). S1P inhibition leads to cancer cell growth, nutrients and oxygen supplication for tumor formation, and process regulation, such as inflammation that triggers neovascularization (7). Concerns regarding the use of fingolimod increased due to the risk of prolonged lymphopenia and associated infections (1). The proper functioning of the immune system prevents HPV infection from becoming permanent. Herein, the role of T and B lymphocytes is great. The decreased lymphocyte count during fingolimod treatment may not provide the necessary immune response during HPV infection. Therefore, we think that the infection may become permanent and turn into neoplasia in this case (5).

The effect of fingolimod on cellular immunity, which is favorable for MS treatment might be an emerging risk factor for high-risk females with positive HP that deserves further attention. HPV infection, previous gynecological history, and screening test evaluation might have value before starting up fingolimod treatment (3). Primary prevention through HPV vaccination reduces the frequency of HPV-related neoplasms (9).

Conclusion

Therefore, studies have shown that immunosuppressant drugs can increase the risk of cancer in patients with MS. We wanted to contribute to the literature with this case of cancer, which we think is caused by the effect of fingolimod. We think that cervical screening, pap smear, gynecological examination, and HPV vaccination programs before fingolimod treatment in patients with MS are important. However, more research is needed to better understand the risks and other known risk factors regarding the duration and type of immune therapy in females with autoimmune disease.

Ethics

Informed Consent: Written and informed consent was obtained from the patient for publication of this case report.

Authorship Contributions

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

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

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

References

1. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, Pelletier J, Capra R, Gallo P, Izquierdo G, Tiel-Wilck K, de Vera A, Jin J, Stites T, Wu S, Aradhye S, Kappos L; TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402-415.
2. Mahajan KR, Ko JS, Tetzlaff MT, Hudgens CW, Billings SD, Cohen JA. Merkel cell carcinoma with fingolimod treatment for multiple sclerosis: A case report. Mult Scler Relat Disord 2017;17:12-14.
3. Triplett J, Kermode AG, Corbett A, Reddel SW. Warts and all: Fingolimod and unusual HPV-associated lesions. Mult Scler. 2019;25:1547-1550.
4. Jaafar N, Zeineddine M, Massouh J, Yamout BI. Skin warts during fingolimod treatment in patients with multipl sclerosis. Mult Scler Relat Disord 2019;36:101437.
5. Jee B, Yadav R, Pankaj S, Shahi SK. Immunology of HPV-mediated cervical cancer: current understanding. Int Rev Immunol 2021;40:359-378.
6. Mhanna E, Nouchi A, Louapre C, De Paz R, Heinzlef O, Bodini B, Assouad R, Chochon F, Lubetzki C, Papeix C, Pourcher V, Maillart E. Human papillomavirus lesions in 16 MS patients treated with fingolimod: Outcomes and vaccination. Mult Scler 2021;27:1794-1798.
7. Cohen JA, Arnold DL, Comi G, Bar-Or A, Gujrathi S, Hartung JP, Cravets M, Olson A, Frohna PA, Selmaj KW; RADIANCE Study Group. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial. Lancet Neurol 2016;15:373-381.
8. Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 2010;33:91-101.
9. Berman TA, Schiller JT. Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases. Cancer 2017;123:2219-2229.