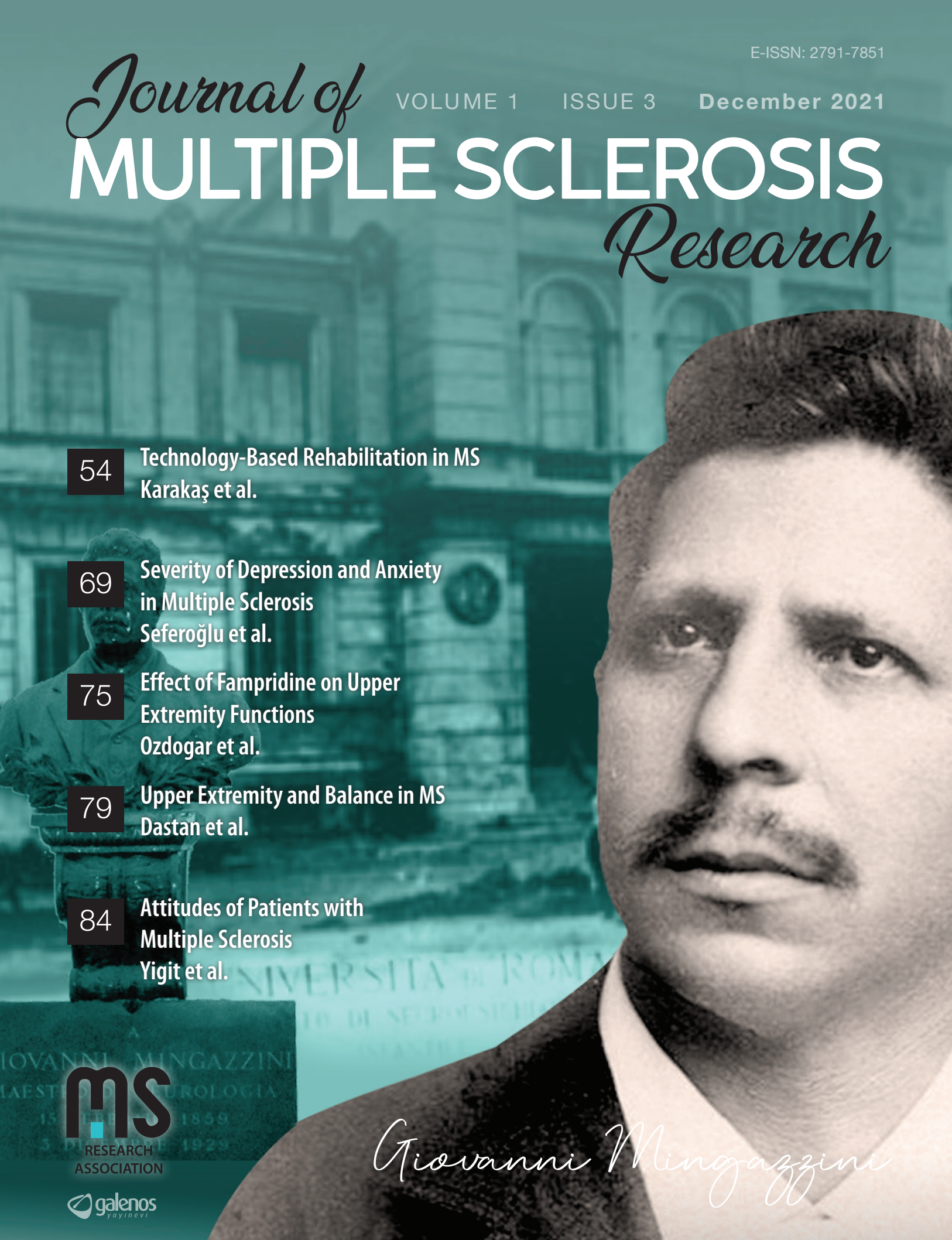
E-ISSN: 2791-7851

Journal of MULTIPLE SCLEROSIS Research

VOLUME 1 ISSUE 3 December 2021



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Faks/Fax: +90 (212) 621 99 27
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Web: www.galenos.com.tr **Yayıncı Sertifika No:** 14521

Online Yayınlanma Tarihi/Online Publication Date: Aralık 2021/December 2021

E-ISSN: 2791-7851

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

Journal of MULTIPLE SCLEROSIS Research

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ABOUT US

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

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

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.

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

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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

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

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

Preparation of Manuscript

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

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

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

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

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

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

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

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

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

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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.

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

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

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.

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

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

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

Abstract

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

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

Materials and Methods: Important methods should be written respectively.

Results: Important findings and results should be provided here.

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

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

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

1. Original Articles:

An article is considered original research if;

- It is the report of a study written by the researchers who actually did the study.
- The researchers describe their hypothesis or research question and the purpose of the study.
- The researchers detail their research methods.
- The results of the research are reported.
- The researchers interpret their results and discuss possible implications.

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

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Original articles should have the following sections:

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

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

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

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

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

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

Conclusion: The conclusion of the study should be highlighted.

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

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

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

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

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

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

Examples of References

1. List All Authors

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

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

2. Organization as Author

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

3. Complete Book

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

4. Chapter in Book

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

5. Abstract

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

6. Letter to the Editor

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

7. Supplement

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

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

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

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

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

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

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

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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.

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

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

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All authors are responsible for the manuscript's content.

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

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

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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.

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

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Ethics

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

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.

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CONTENTS

DOI: 10.4274/jmsr.galenos.2021.2021-10-3
Journal of Multiple Sclerosis Research 2021;1(3):54-68

REVIEW

Technology-Based Rehabilitation in People with Multiple Sclerosis: A Narrative Review

Hilal Karakas[1], Barbara Seebacher[2,3], Turhan Kahraman[4*]

[1]Izmir Katip Celebi University, Graduate School of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey
[2]Medical University of Innsbruck, Clinical Department of Neurology, Innsbruck, Austria
[3]Rehab Centre Muenster, Department of Rehabilitation Research, Muenster, Austria
[4]Izmir Katip Celebi University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey

Abstract

With the overall progress of technology, developing technological approaches has become an integral part of modern society, and using advanced technology in rehabilitation has gained increasing importance. This narrative review discusses the role of technology-based rehabilitation in people with multiple sclerosis by presenting the evidence, advantages, and disadvantages of robotic rehabilitation, virtual reality training applications, telerehabilitation, and movement analysis systems. Technological systems used in rehabilitation are based on motor learning principles by providing task-specific and highly repetitive activities. Current scientific evidence emphasizes that significant gains in ambulation and upper extremity function can be achieved with technological approaches. The use of technological approaches in multiple sclerosis rehabilitation, despite being challenging in terms of cost and accessibility, is promising and has enormous potential for the future. However, although the evidence supports the use of technological systems in multiple sclerosis rehabilitation, well-designed studies with a larger sample size are needed.

Keywords: Multiple sclerosis, biomedical technology, robotics, virtual reality, telerehabilitation, remote sensing technology

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammatory demyelination and axonal damage (1). MS is typically diagnosed between the ages of 20 and 30 years (1). Since MS is a disease that can affect many regions of the central nervous system, it causes many symptoms such as motor, sensory, visual, and autonomic disorders, impairs physical and cognitive functions in people with MS (pwMS), and negatively affects the quality of life and employment (1,2). Rehabilitation practices, including physiotherapy, are one of the most frequently used treatment options for managing symptoms in pwMS. Technological advancement has created new possibilities for neurorehabilitation. As with other populations with a chronic disease, it is necessary to identify or develop new assessment and treatment methods for pwMS (3). Along with technological developments, current neurorehabilitation practices focus on the principle of motor learning with high-intensity, repetitive and task-specific exercises (4).

With the development of technological systems and their application to rehabilitation settings, technology-based devices have become usable in daily evaluation and treatment programs. The advantages of technology-based rehabilitation in pwMS are listed as follows:

- The training content provided in technology-based rehabilitation is similar to the tasks individuals frequently encounter in their daily lives. Therefore, technology-based rehabilitation applications are task-specific (4).
- Visual or auditory feedback given in technology-based rehabilitation allows patients to receive information about their task performance (4).

Address for Correspondence: Turhan Kahraman, Izmir Katip Celebi University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey
E-mail: turhan.kahraman@yahoo.com **ORCID-ID:** orcid.org/0000-0002-8776-0664
Received: 26.10.2021 **Accepted:** 27.12.2021

- They increase the duration, intensity, and frequency of the treatments and hence allow them to perform a considerable number of movements (4).

- They increase motivation and enhance active participation in and compliance with the treatment regimen (5).

- This narrative review aims to discuss the role of technology-based rehabilitation in pwMS by presenting the evidence, advantages, and disadvantages of robotic rehabilitation, virtual reality (VR) training applications, telerehabilitation, and movement analysis systems. Table 1 provides an overview of the advantages and disadvantages of technology-based rehabilitation methods compared to traditional rehabilitation, their areas of use, and clinical efficacy.

Effects of Robotic Systems in Technology-Based Rehabilitation for pwMS

In recent years, robotic technology has considerably developed with the availability of new scientific approaches and extensive electro-mechanical components (6). With these developments, "robotic technology" has become usable in the field of rehabilitation (6).

A key feature of robotic rehabilitation is that it induces neuroplastic changes and motor recovery by providing increased functional activity within the sensory-motor network (7). Robotic rehabilitation helps reduce the therapist's physical fatigue. In addition, setting the rehabilitation program according to the patient's needs and providing visualized performance feedback increases patients' motivation. Offering an objective evaluation of the patient's physical performance by using computer-aided evaluation scales are other important advantages of robotic rehabilitation (4). However, robotic systems also have disadvantages such as being expensive and making it difficult to feel the differences during movement because of the decreased therapist-patient interaction.

A literature review was conducted on September 30, 2021, using MEDLINE via PubMed and Google Scholar using the related keywords including "robotic systems", "rehabilitation", "multiple sclerosis", and "randomized controlled trial". Table 2 provides an overview of some selected randomized controlled trials (RCTs) of robotic systems in MS rehabilitation.

In a majority of pwMS, balance and gait are affected. Gunn et al. (8) have reported that as many as 50-80% of pwMS experience

Table 1. Overview of advantages and disadvantages of technology-based rehabilitation methods compared to traditional rehabilitation, their areas of use and clinical efficacy

Advantages	Disadvantages	Area of use	Effectiveness in clinical practice
• Provides repetitive/intensive exercise training • Adaptable to patient condition • Usable in immobile patient • Movements similar to activities of daily living • Delivering engaging/motivating training • Increased safety • Provides rehabilitation at home • Induces neuroplastic changes • Induces motor recovery • Reduces the therapist's physical fatigue • Provides multisensory input and multisensory feedback • Facilitates adaption to different environmental • Saves time for the patients • Enables patients to receive rehabilitation services in an environment that they are comfortable • Close follow-up • Enable assessment in real-world unsupervised environments • Offers an objective assessment • Remote database access	• Expensive equipment • Difficult to feel the differences that occur during movement • Decreased therapist-patient interaction • Requires technical expertise • Difficult limb configuration • Lack of natural interfaces	• Impairment/Function • Balance • Walking functions • Upper extremity functionality • Lower extremity functionality • Quality of life • Fatigue • Disability • Functional mobility	• Improvement in cognitive/motor functions • Improvement in gait and balance performance • Improvement in brain connectivity • Improvement in the quality of life • Reduces in fatigue Offers an objective assessment • Improvement of functionality in daily life

Table 2. An overview of some selected randomized controlled trials of robotic systems in MS rehabilitation

Study	Sample size	Experimental intervention	Control intervention	Duration and frequency	Measured domains	Main results
Androwis et al. (2021) (21)	10 pwMS Robotic xoskeleton assisted exercise rehabilitation (REAER) group: 6 Conventional gait training (CGT) group:4	The exercise consisted of approximately 30 minutes of above-ground walking training using the recommended maximum allowable level of 100% robotic assistance/ session (week 1) at baseline. At the end of the training program, approximately 45 minutes of walking training was continued using the recommended maximum allowable level of 40% robotic assistance/session (week 4).	Focused on mobility, gait, balance, and lower extremity function. Sessions included training on elements of stretching, strengthening, ambulation training, balance training, weight support, transfer training, stepping length and width and weight shift during ambulation.	4 weeks 2 times/ week	Functional mobility, walking endurance, cognitive processing speed, brain connectivity (thalamocortical resting-state functional connectivity based on fMRI)	Compared with CGT, 4-weeks of REAER was associated with large improvements in functional mobility, cognitive processing speed and brain connectivity between the thalamus and ventromedial prefrontal cortex, but not walking endurance. However, increased thalamocortical brain connectivity was associated with improved functional mobility, walking endurance, and cognitive processing speed.
Sconza et al. (2021) (22)	17 pwMS Experimental Group: 8 Control Group: 9	Each training session on the Lokomat lasted 30 min. All participants started with 40% body weight support and an initial treadmill speed of 1.5 km/h. In the following sessions, the training was standardized by increasing the speed of the training and then removing the body weight support. After each Lokomat session, participants performed a 60-minute physiotherapy program that included a general exercise program and gait training.	Each training session was carried on 1 hour and a half. The conventional physiotherapy treatment consisted of a general exercise program and gait training. It consisted of cardiovascular warm-up exercises, muscle stretching exercises, active-assisted or active isometric and isotonic exercises for the main muscles of the trunk and limbs, relaxation exercises, coordination, and static/dynamic balance exercises. Conventional gait therapy included the concept of proprioceptive neuromuscular facilitation, training to walk on different surfaces with or without appropriate walking aids, exercises to restore a correct gait pattern, implementation of residual compensatory strategies, and progressive increase in walking resistance.	5 weeks 5 times/ week	Gait speed, lower limb motor and function skills, gait and balance skills, instrumental kinematic parameters, disability and quality of life	In both groups, it was observed that RAGT was more beneficial than the control treatment on the improvement of activities of daily living, gait parameters, motor abilities and autonomy.

Straudi et al. (2020) (23)	72 PwMS Robot-assisted gait training (RAGT) group: 36 PwMS Conventional therapy (CT) group: 36 PwMS	Robot-assisted walking training, which lasted for about 40 minutes, was performed on the Lokomat treadmill. As the training progressed, adjustments (10% each) in these parameters were done according to the patient's performance.	A total of approximately 40 minutes of assisted walking was performed, placed between 10-minute warm-up and cool-down periods. The patients walked 80 m without resting in the closed straight corridor with walking devices.	4 weeks 3 times/ week	Gait speed, mobility, balance, fatigue, quality of life	This study, performed in a PwMS population, failed to show a greater benefit of RAGT compared to gait training-based CT in terms of walking speed. Similarly, secondary outcomes, including fatigue, quality of life, balance, and mobility, were no more beneficial for RAGT compared to conventional treatment. However, significant improvements of gait speed, walking endurance, balance and quality of life were observed following both treatments.
Gandolfi et al. (2018) (12)	44 PwMS experimental group =23 control group =21.	Patients underwent robot-assisted hand training on an Amadeo. Three different training modes were performed: 1) passive flexion and extension of the fingers (10 min) with continuous passive movement (CPM); 2) active-assisted therapies with functional use of the hand (10 min); 3) interactive therapy via active training with specifically developed virtual therapy games (10 min).	The protocol for upper limb rehabilitation consisted of upper limb mobilization (shoulder girdle, elbow, wrist, and finger joints), facilitation of movements, and active tasks that were chosen out of 15 that are challenging for patients.	5 weeks 2 times/ week	Upper limb activity, Upper limb function, Upper limb performance, The EMG activity of 6 upper limb muscles (deltoid scapular, deltoid clavicular, triceps brachii, biceps brachii, flexor carpi radialis, and extensor carpi radialis), Quality of life, Patient satisfaction with daily activities or social roles	There were no significant between-group differences in outcomes. Electromyography showed relevant changes providing evidence of increased activity in the extensor carpi. The training effects on upper limb activity and function were comparable between the two groups. However, robot-assisted training demonstrated remarkable effects on upper limb use and muscle activity.

Feys et al. (2015) (13)	17 PwMS experimental group: 9 control group group: 8	Training sessions lasted 30 minutes by interacting with the HapticMaster robot in an individualized virtual learning environment. This virtual learning environment allows people to learn and train the skill components necessary during the activities of daily living related to the upper extremity.	Conventional rehabilitation programs consisted of 2 h multidisciplinary treatment per day including 30 min physiotherapy, 30 min occupational therapy, and 60 min group physiotherapy, speech therapy, or psychotherapy.	8 weeks 3 times/ week	Hand grip strength, upper limb activity, upper limb sensorimotor function, active range of motion, movement duration and speed	PwMS commented favorably on the robot-supported virtual learning environment and reported functional training effects in daily life. Robot-measured three-dimensional motion tasks were carried out to make transport and reach motion tasks more efficient in a shorter time. However, observational analyzes of the included cases showed great improvements in upper extremity sensorimotor function in subjects with more significant upper extremity dysfunction but no significant change for any clinical measure in the intervention and control group.

balance disorders and more than 50% of them fall at least once a year. Impaired balance and walking cause fear of falling and decreased dual-task performance in those concerned (8). Studies on robotic-assisted rehabilitation in pwMS primarily have explored its effects on the lower extremities concerning improving the balance and gait parameters. In 2021, 12 RCTs were included in a systematic review that evaluated the effects of robotic systems on balance and walking in pwMS (9). It was stated that wearable exoskeleton-type robots were the most frequently used to improve balance and gait patterns in pwMS (9). When the studies included in the review were examined, it was seen that the treatments applied included 2 to 5 sessions per week, i.e.; overall between 6 and 40 sessions, and the session duration ranged from 40 to 50 minutes (9). The review has reported an increase in walking speed, cadence, and stride length and a decrease in double support stance time in a clinically meaningful way (9). It has further reported improved balance parameters after the robotic rehabilitation and that this improvement was also maintained at a 3-month follow-up (9).

Tremor, coordination disorder, muscle weakness, sensory disorders, and spasticity in the upper extremities seen in pwMS have been found to limit the upper extremity activities (10). Holper et al. (11) reported that 56% of 205 pwMS had disorders in the upper extremity function, and 71% of them had limitations and restrictions in activities and participation requiring the use of hands and arms. Upper extremity rehabilitation includes practices to increase patients' independence in daily life and quality of life. At present, in pwMS, a limited number of robotic systems that are used for upper extremity rehabilitation exist. These devices improve hand and arm function with targeted tasks and reaching movements (12,13). Robots can assist movement in different ways. For example, robots may be chosen to achiev direct action movement or to passively move a limb; they can further provide the user with stimuli and feedback of different modalities used to facilitate a movement (14). Studies investigating the effectiveness of robot-assisted upper limb training in pwMS are scarce, and most of these studies have used a combination with VR (12,13). A systematic review including 30 studies investigated the effects of upper extremity rehabilitation in pwMS (15). Six of the included studies investigated the effectiveness of robot-assisted upper extremity exercises in pwMS (13,16-20). Two studies (17,20) compared the effects of different robot-assisted training. One study (13) compared the robotic rehabilitation group with the control group, which continued their routine treatment, and three studies (16,18,19) only investigated the effects of robotic rehabilitation without a control group. In the studies, the duration of treatment was between 1.5 and 10 weeks, the frequency was between 2 and 5 days a week, and the session duration was between 30 and 60 minutes. It was found that robot-assisted upper extremity training improved body functions and structures, and activity with effect sizes from low to high (15).

All the RCTs listed in Table 2 compare robotic rehabilitation with traditional rehabilitation methods. Robotic-assisted

rehabilitation was applied for 8-25 sessions, and the duration of each session was between 30 and 40 minutes. Two studies found that robotic rehabilitation was more effective than conventional rehabilitation in functional mobility, cognitive processing speed, and brain connectivity improvement of activities of daily living, gait parameters, motor abilities, and autonomy walking speed (21,22). Three studies compared robotic rehabilitation with conventional rehabilitation and found no significant difference in the study outcomes, including gait speed, mobility, balance, fatigue, quality of life, and upper limb-related assessments (12,13,23). The difference between the studies might be due to the difference in the protocols.

Robotic-assisted upper and lower extremity rehabilitation methods effectively improve balance, walking functions, and lower extremity functionality in pwMS. Although these methods seem to have the potential to improve upper extremity functionality, more studies are needed.

Robotic systems should be used in the rehabilitation of pwMS in the clinic. However, the clinical condition of an individual is critical in the selection of the robotic system to be used. The contracted joint cannot complete normal joint movement, which can be problematic when robotic systems are used. Robotic systems used in patients with spasticity should have a mechanism to detect and direct it. The robotic system should provide active-assisted movement when the patient cannot complete the active movement and have active resistance exercise options.

Effects of VR in Technology-Based Rehabilitation for pwMS

VR is defined as a three-dimensional simulation system that allows interaction with an environment constructed by computerized systems, which gives the feeling of moving in the real world (24). The main principles of VR involve creating activity environments suitable for daily life (a), providing multisensory (i.e., visual, somatosensory, and auditory) input (b) and multisensory feedback (c) to facilitate adaption to different environmental conditions and enable learning (25). The advantages of VR rehabilitations are that they are innovative and enjoyable, suitable for different learning styles with realistic scenarios, and simplify complex movements. However, VR rehabilitation also has disadvantages. These disadvantages are often associated with immersive technologies created with head-mounted displays (26). The possible side effects and disadvantages of virtual reality therapy should be explained to the patient, and if any symptoms occur, the therapist should stop the therapy. The most significant disadvantages of virtual reality applications are examined in two categories (27). The first of these is seen as "cybersickness". The cybersickness is due to immersion during virtual reality therapy (28). Cybersickness symptoms include headache, pallor, sweating, dryness of mouth, stomach fullness, nausea, vomiting, eyestrain, disorientation, ataxia, and vertigo (29). The second disadvantageous category of VR is the 'after-effects'. The after-effects symptoms are usually seen due to the subject's adaptation to the sensory and motor needs of the virtual world and the need for time to return to the real world after the virtual reality application (30). Movement disorder, changes in postural control, perceptual-motor disturbances, lethargy, and fatigue are after-effect symptoms (30). In addition, the expensiveness of virtual reality applications and the fact that devices produced with virtual reality technology are not suitable for rehabilitation purposes are among the other disadvantages (26). The role of VR training approaches as a rehabilitation method in pwMS is discussed in the literature. Many studies have stated that interacting with a VR may significantly affect both motor and cognitive functions in pwMS (31-33).

A literature review was conducted to determine RCTs about VR on September 30, 2021, using MEDLINE via PubMed and Google Scholar using the related keywords including "virtual reality", "video-based exergaming", "rehabilitation", "multiple sclerosis", and "randomized controlled trial". Table 3 provides an overview of some selected RCTs that used VR in MS rehabilitation.

A recent systematic review and meta-analysis, including 9 RCTs (424 pwMS), investigated the effects of VR applications used with motor training (34). This review has shown that VR interventions involved a frequency of 8 to 25 sessions, with each session ranging between 10 and 60 minutes (34). It has further been found that virtual reality-based motor training increased balance and quality of life, reduced fatigue, and did not change functional mobility in pwMS compared to conventional rehabilitation programs and routine treatments (34). Ten studies (466 pwMS) were included in another systematic review and meta-analysis examining the effects of VR training applications on walking and balance in pwMS (35). It showed that motor training in VR increased balance, postural control, mobility, and walking ability compared to the control group without intervention (35). Further findings showed a reduction of symptoms such as fatigue and fear of falling (35). The total number of sessions of the included studies ranged from 8 to 48, and training frequency was between 1 and 4 sessions per week, and the training duration varied between 20 and 60 minutes per session (35). These studies concluded that VR training could be as effective as conventional training in improving balance, quality of life, and fatigue, and more effective than no intervention in improving balance and gait in pwMS.

A recent systematic review and meta-analysis including 10 studies investigated the effects of VR applications on upper extremity functions in pwMS (36). The review has confirmed the frequent use of Microsoft Kinect and Nintendo Wii VR programs for motor training interventions in pwMS (36). Results have shown a total duration of virtual reality-based training programs from 1 day to 6 months, and the duration of individual sessions was between 20 and 60 minutes (36). The training content comprised of upper extremity activities such

Table 3. Overview of some selected randomized controlled trials of virtual reality in MS rehabilitation

Study	Sample size	Experimental intervention	Control intervention	Duration and frequency	Measured domains	Main results
Molhemi et al. (2021) (38)	39 PwMS Virtual reality (VR)-based group: 19 Control group: 20	Progressive balance exercises were used using the Xbox360 with Microsoft's Kinect. (35 min.)	The standing exercise included multidirectional stepping and single- and double-leg standing; the walking exercise involved forward, backward, and side walking and weight-shifting exercise; consisted of the lunge, half-squat, leaning, and reaching.	6 weeks 3 times/ week	Limits of stability, balance, functional mobility, walking speed, dual task capacity, fall history	Both VR-based and conventional balance exercises improved balance and mobility in PwMS, while each acted better at improving certain aspects. VR-based training was more effective at improving cognitive-motor function and reducing falls, while conventional exercises provided better directional control.
Ozdogar et al. (2020) (41)	60 PwMS video-based exergaming group:21 conventional rehabilitation group: 19 control group:20	Video-based exergaming group: The video-based exergaming was implemented using a game console. In all games were required core stabilization, balance, and arm and leg function. Conventional rehabilitation group: This program included balance, arm and leg, and core stability exercises. (45 min.)	Control group: During the study period, participants were asked not to participate in a new exercise program if they did not have a previous exercise program.	8 weeks 1 times/ week	Upper extremity functions, cognitive functions, core stability, walking, depression, fatigue, quality of life	There was no significant difference in changes from baseline in study results at 8 weeks between video-based exergaming and conventional rehabilitation groups. Outcomes regarding arm function, cognitive function, most leg function, and balance were significantly improved in the video-based exercise and conventional rehabilitation groups.
Maggio et al. (2020) (39)	60 PwMS semi-immersive virtual reality (VR) training group (EG): 30 control group (CG): 30	The patient performed exercises in a virtual context to stimulate different cognitive areas through a widescreen dynamic interface that responded to the patient's movements with audiovisual feedback. (60 min.)	Conventional cognitive training consisted of a face-to-face approach between patient and therapist in individual sessions. The tasks were presented using a paper-and-pencil method and were designed to encourage specific cognitive skills.	8 weeks 3 times/ week	Cognitive/motor functions, visual perception, visuospatial abilities, short term visual memory, working memory and executive functions, speed of information processing, sustained attention, functional mobility, depression, and quality of life	CG and EG showed significant improvement in mood as well as various cognitive/ motor functions. In EG only, we observed a significant increase in visual perception, visuospatial abilities, short-term visual memory, working memory and executive functions, information processing speed and sustained attention, along with functional mobility.

Cuesta-Gómez et al. (2020) (40)	30 PwMS Experimental group (16) Control group (14)	Received the same conventional motor rehabilitation therapy (45 min) plus Leap Motion Controller (15 min)	Conventional motor rehabilitation based on functional task practice was applied. This practice included shoulder, elbow, wrist, and finger mobilization, strengthening of the upper extremity extensor muscles, and stretching exercises for the upper extremity flexor muscles.	10 weeks 2 times/ week	Upper limb grip muscle strength, coordination, speed of movements, fine and gross dexterity, fatigue, and quality of life.	Significant improvements were observed in the post-treatment assessment for coordination, speed of movement, and fine and coarse upper extremity dexterity in the experimental group compared to the control group. In addition, significant results were found in coordination, speed of movement, fine and coarse follow-up for the more affected side.
Yazgan et al. (2020) (42)	47 PwMS Group I:16 Group II:16 Group III:15	Group I (Nintendo Wii Fit) training protocol consisted of games such as Penguin Slide, Table Tilt, Ski Slalom, Heading and Balance Bubble selected from the Wii Fit Plus balance games section. The game levels and repetitions were determined by the therapists for each patient to standardize the progress of the exercises. (60 min.) The Group II (Balance Trainer) training protocol consisted of Collect Apples, Outline, Rowing Battle, and Motion Evaluation games included in the device software, which allowed patients to perform balance exercises in different directions. (60 min.)	Group III (control group) waitlisted	8 weeks 3 times/ week	Balance, functional mobility, walking speed, fatigue, quality of life	All parameters evaluated in groups I and II showed statistically significant improvement after treatment. Changes in all outcome measures were found to be superior in group I compared with group III. Similarly, all measures except the walking speed were found to be superior in group II compared with group III. Changes in balance and Quality of life were found to be superior in group I compared with group II. In comparison with no intervention, exergaming with Nintendo Wii Fit and Balance Trainer improves balance, increases functionality, reduces fatigue severity, and increases the quality of life in pwMS.

as reaching, grasping, carrying, and organizing the kitchen (36). The review has suggested that VR for the upper extremity in pwMS increased upper extremity muscle strength and function compared to conventional treatment and other upper extremity physiotherapy and rehabilitation approaches (36). Another systematic review has included 10 studies examining the effect of virtual reality-based rehabilitation on motor and cognitive parameters in pwMS and has found that VR reduced the risk of falling and improved balance, postural control, and gait parameters in pwMS (37). In addition, it has been stated that VR optimizes sensory information processing and integration in the brain, increases patients' motivation towards treatment, and facilitates motor learning (37).

VR rehabilitation programs were applied for 8-24 sessions, and each session lasted between 15 and 60 minutes (Table 3). In most studies, VR rehabilitation was compared with conventional rehabilitation (38-41). The results of these studies are different from each other. Molhemi et al. (38) found that VR-based training was more effective than conventional rehabilitation in improving cognitive-motor function and reducing falls, while conventional rehabilitation improved directional control. It can be thought that the reason for this is that VR-based rehabilitation consists of balance training, and conventional rehabilitation consists of training to move in different directions. Cuesta-Gómez et al. (40) found that VR rehabilitation was more effective than conventional training in improving coordination, speed

of movement, and fine and coarse upper extremity dexterity parameters. However, Ozdogar et al. (41) found no significant difference in upper extremity functions, cognitive functions, core stability, walking, depression, fatigue, quality of life between VR and conventional rehabilitation. It can be thought that the differences are due to the different content, duration, and frequency of the applied VR and conventional rehabilitation methods. Yazgan et al. (42) compared the VR rehabilitation with the control group that received no rehabilitation and found that VR rehabilitation provided significant improvements in balance, functional mobility, walking speed, fatigue, and quality of life. Studies have shown that virtual reality-based rehabilitation improved motor and cognitive functions in pwMS, and patients had a positive attitude towards this type of training. Reviews have also reported that there is no consensus on the most effective VR application for rehabilitation in pwMS. In addition, the dose-response relationship of exercises in a VR and gains in motor and cognitive function is not clear. Therefore, more studies are needed to investigate VR applications for rehabilitation in pwMS.

VR applications are promising approaches used to improve rehabilitation processes. Physiotherapists should be informed of these systems and trained about using them to expand VR use in clinical settings. In VR rehabilitation, therapists should prefer games that can recover functional deficiencies and provide a clear and safe recovery to the patient. During rehabilitation, the patient should be constantly observed, and possible side effects should be evaluated throughout the treatment.

Effects of Telerehabilitation in pwMS

There is an increasing interest in developing innovative ways of providing patient-centered, technology-supported MS rehabilitation outside hospital settings, such as telerehabilitation (43,44). Telerehabilitation applications provide rehabilitation services to patients at home, especially exercise training and health behavior-changing approaches such as motivational interviews and social cognitive theory. Patients can access their treatments through video calls, software applications (apps), and online platforms (45,46).

Telerehabilitation provides rehabilitation opportunities for patients who cannot receive rehabilitation services due to the problems such as geographical remoteness, economic constraints, and physical disabilities. In addition, telerehabilitation enables to maintain the continuity of care for patients concerning rehabilitation services. Further advantages of telerehabilitation are that it helps overcome the barrier of patient transportation over long distances and saves time for the patients having to travel to the rehabilitation center or therapists to provide home visits. Finally, telerehabilitation enables patients to receive rehabilitation services in an environment where they are comfortable. However, telerehabilitation-based interventions also have some disadvantages, such as the difficulty of finding the appropriate digital platform and the decrease in the quality of the treatment because of the internet connection problems. In addition, patient-therapist interaction is reduced during telerehabilitation.

Various telerehabilitation systems have been developed and investigated in pwMS (47). A literature review was conducted on September 30, 2021, using the MEDLINE via PubMed and Google Scholar using the related keywords including "telerehabilitation", "multiple sclerosis", and "randomized controlled trial". Table 4 provides an overview of some selected RCTs of telerehabilitation in MS.

A recent systematic review and meta-analysis including 9 studies with a total of 716 pwMS evaluated the effects of telerehabilitation applications on the motor, cognitive, and patient participation parameters (43). The duration of the studies ranged from 6 weeks to 6 months, and telerehabilitation training was delivered using a session duration of 30 minutes and a frequency of twice a week on average (43). The effect of telerehabilitation applications integrated with the patient was large for motor disability, medium for gait and balance, and small for cognitive outcomes (43). They also have a medium effect on depression (43).

Videoconference systems, VR applications, and sensor-based systems are often used for telerehabilitation-based training (33). Hoang et al. (48) provided step training together with a telerehabilitation-based VR application for 12 weeks at home. This study found that the telerehabilitation-based VR training program was usable and safe, and positively affected stepping, standing, balance, coordination, and functional performance (48).

Dennett et al. (5) have investigated the feasibility of a web-based exercise program twice a week for 6 months in pwMS. The patients reported that the applied exercise program increased their physical activity levels, and they felt more motivated and fit after exercises (5). Patients also reported that although it was easy to access the web-based exercises, they would prefer an application that they could download to their mobile devices instead of connecting via a link. They also added that an app would facilitate their access to the exercise program and increase their opportunities to exercise at different places and daytimes, which overall increased their compliance with the exercises (5).

Table 4 provides an overview of some RCTs investigating the effects of telerehabilitation-based intervention methods. Telerehabilitation-based interventions last for 16-52 sessions. Tarakci et al. (49) compared the effects of supervised exercise and telerehabilitation and they found that telerehabilitation can improve health-related quality of life and activities of daily living, yet, supervised exercises can be more beneficial regarding

Table 4. Overview of some selected randomized controlled trials of telerehabilitation in MS rehabilitation

Study	Sample size	Experimental intervention	Control intervention	Duration and frequency	Measured domains	Main results
Tarakci et al. (2021) (49)	30 PwMS Group 1 (Controlled Exercise Group): 15 Group 2 (Telerehabilitation Group): 15	2nd Group (Telerehabilitation Group): The exercises given to Group 1 were given as prescribed for the patients to practice at home.	1st group (Controlled Exercise Group): Warming up, cooling down, stretching, strengthening, gait, balance and coordination exercises were given under the supervision of a physiotherapist.	12 weeks 3 times/ week	Functional independence, fatigue, quality of life	Significant improvements were found in all outcome measures in both groups after treatment. It was found that the quality of life of the patients in the 1st group increased more than the patients in the 2nd group, while their fatigue levels decreased more than the patients in the 2nd group. It was emphasized that a structured home-based exercise program could be an alternative to supervised exercises in patients with multiple sclerosis.
Kahraman et al. (2020) (50)	33 PwMS Experimental Group: 19 Control Group: 14	The participants in the experimental group were given motor imagery training by the physiotherapist via video conferencing. (20 min.)	The control group was a waiting list group that did not receive any additional specific treatment.	8 weeks 2 times/ week	Dynamic balance during walking, walking speed, endurance and perceived ability, balance performance assessed by a computerized posturography device, balance confidence, cognitive functions, fatigue, anxiety, depression, and quality of life.	Telerehabilitation-based motor imagery training is an effective method in improving walking, balance performance and cognitive functions in pwMS, reducing fatigue, anxiety, and depression levels, and increasing their quality of life compared to the control group who continue their routine treatment
Donkers et al. (2020) (51)	48 PwMS Telerehabilitation Group: 32 Control Group: 16	The website includes exercises (videos, text, and audio descriptions) that are individually prescribed by a physical therapist at the initial assessment. These exercises focused on core and upper-extremity strength. Participants in the web-based intervention arm were informed that every 2 weeks during the 6-month intervention period, the treating physical therapist would review their online exercise diaries and remotely change the difficulty level and/or a number of repetitions of the exercise programs.	Participants in the usual care exercise group were given a written, home-based exercise program consistent with the most common method for exercise prescription practice for outpatient physiotherapy services at the website.	26 weeks 2 times/ week	Number of exercise sessions over the study period of 26 weeks, dynamic grip strength and fatigability, functional mobility, fall history, anxiety, and depression	Nearly 50% of participants (23 of 48) exercised at least twice per week for at least 13 of the 26 weeks. There was no difference in exercise compliance between the web-based and control groups. There were no problems with the safety of web-based physiotherapy.

Novotna et al. (2019) (52)	39 PwMS Experimental group: 23 Control Group: 16	Patients in the treatment group performed home-based balance exercises using a portable tablet-based game platform. (at least 15 min.)	Control group continued their routine treatment.	7 weeks 7 times/ week	Balance, functional mobility, spatio-temporal gait parameter, falls efficacy	It was found that the patients in the treatment group had good compliance with game-based balance exercises. After the completion of the home-based balance exercise program, although the balance performance of the patients in the treatment group improved significantly compared to the patients in the control group, no significant differences were found between the gait parameters of the two groups.
Fjeldstad-Pardo et al. (2018) (53)	30 PwMS Group 1: (customized unsupervised home-based exercise program): 10 Group 2 (remote PT supervised via audio/ visual real-time telecommunication): 10 Group 3 (in-person PT at the medical facility): 10	2nd Group: Exercises consisting of visual and auditory feedback were given by videoconference method 2 days a week. 3rd Group: Exercise training was given 2 days a week in a clinical setting under the supervision of a physiotherapist.	1st Group: home exercises to be done 5 days a week are given.	8 weeks 1st Group: 5 times / week. 2nd Group: 2 times/ week 3rd Group: 2 times/ week	Gait and balance performed with a computerized system, functional gait assessment, quality of life, fatigue, disability	The functional gait assessment outcome measure improved significantly in all groups. No significant difference was found between the 2nd and 3rd groups in various outcome measures. Telerehabilitation training is a feasible treatment modality comparable to face-to-face treatment in improving gait and balance in people with MS.

fatigue and health profile compared to telerehabilitation. Kahraman et al. (50) found that telerehabilitation-based motor imagery training was an effective method to improve dynamic balance during walking, walking speed, perceived walking ability, balance confidence, most cognitive functions, fatigue, anxiety, depression, and quality of life compared to the control group who continued their routine treatment. Donkers et al. (51) investigated the effects of web-based exercise training given asynchronously and exercise programs given as home exercise prescriptions. As a result of the study, no significant difference was found between the groups regarding dynamic grip strength and fatigability, functional mobility, fall history, anxiety, and depression (51). Novotna et al. (52) compared asynchronous balance training with the control group that did not receive rehabilitation training. They found that asynchronous telerehabilitation-based balance training significantly increased balance in pwMS (52). Fjeldstad-Pardo et al. (53) formed two experimental groups in their study; one was given synchronous telerehabilitation-based exercise training, the other was given exercise training under the supervision of a physiotherapist in a clinical setting, and the control group was given an exercise prescription to apply at home (53). It was found that there were improvements in the functional gait, quality of life, fatigue, and disability in all three groups, and there was no significant difference between the synchronous telerehabilitation group and the face-to-face rehabilitation group (53). Based on the existing evidence, it is suggested that telerehabilitation-based interventions are as much effective as face-to-face methods in pwMS. In addition, pwMS are satisfied with their telerehabilitation-based interventions. However, it needs to be pointed out that thus far, the number of studies that have investigated the effects of telerehabilitation interventions on activities of daily living, fatigue, quality of life, pain, and self-efficacy in pwMS is limited.

Due to the progressive nature of the MS, long-term follow-up and rehabilitation are particularly important. This method is advantageous for providing long-term follow-up and

rehabilitation in patients with geographical distance, economic restrictions, and physical disabilities. Telerehabilitation-based interventions may be a viable alternative rehabilitation method for pwMS, but there is still insufficient evidence of the most effective type of telerehabilitation and its setting. Therefore, there is a need for further high-quality telerehabilitation research in pwMS.

Effects of Movement Analysis Systems in Technology-Based Rehabilitation for pwMS

Several approaches for assessing mobility and balance in pwMS include subjective assessment scales, self-reported measures, performance-based measures, and laboratory-based movement analysis measures. The significant disadvantages of subjective assessment methods, self-report scales, and performance-based measures are that they are insensitive to minor changes in mobility and balance impairments and they only provide information at a single time point. In addition, subjective measures have many systematic biases such as order, scale, and halo effects, which can be affected by psychological factors (54). Mobility and balance impairment in pwMS show fluctuations daily and even within one day (45). Therefore, easy-to-use, objective and inexpensive assessment tools are required to detect changes in balance and mobility and be used in pwMS.

Smart wearable devices have been developed rapidly in recent years with new technologies (55). These devices are mainly used in monitoring, management, diagnosis, medical treatment, and rehabilitation (55). They can be used on all human body parts, including the head, limbs, and torso. Sensors are mainly inserted into glasses, helmets, headbands, hearing aids, earrings, headphones for head wearable devices (55). Torso wearable devices are frequently inserted to underwear, belts, and suits (56). Upper extremity accessories (i.e., watch, bracelet) can be used in movement analysis and monitor physiological parameters such as body temperature and heart rate (57). Lower limb wearable devices are frequently inserted into shoes and socks (58). Wearable devices directly measure acceleration and angular velocity of body parts, respectively. Inertial measurement units (IMUs) are typically used for this purpose and include an accelerometer and a gyroscope. Accelerometers measure non-gravitational acceleration, and gyroscopes use the earth's gravity to help determine the orientation and angular velocity.

Some studies have investigated the concurrent validity and accuracy of sensor-based assessment systems in MS and found that they showed high accuracy and concurrent validity against the commonly used method (59-65). Sun et al. (66) have included a total of 33 studies involving 1292 pwMS in their systematic review evaluating the effects of technological approaches used for mobility and balance monitoring in pwMS. Results from this review and other studies have shown that wearable sensor systems were most frequently used to evaluate gait and balance in pwMS (59-66). Upper extremity dysfunction affects the quality of life, daily living activities, employment status of individuals, and the ability to use walking aids. On the other hand, evaluating upper extremity movements with sensors has received less attention in pwMS for many years. This may be due to the lack of understanding of the importance of upper extremity dysfunction compared to balance and gait disorders, which are prominent symptoms of MS (67). In order to reduce this deficiency, studies investigating upper extremity dysfunction in pwMS and the effects of these disorders on the functionality of patients should be increased. The importance of upper extremity dysfunction and objective assessment in MS rehabilitation should be emphasized. Elsworth-Edelsten et al. (68) have analyzed arm movements during walking in pwMS using a 12-camera movement analysis system (VICON Mx3+; ViconPeak® 101, Oxford, UK) and have found an increased mean elbow flexion and decreased overall arm movements during walking in pwMS compared to a healthy control group. Since the upper extremity function is also important for pwMS, more studies are needed to develop valid and accurate systems to evaluate it.

Close follow-up of patient is critical in chronic diseases (69). One of the most significant advantages of these systems is that they enable collecting and monitoring users' data during the day and provide a dynamic, intelligent, and comprehensive analysis of various indicators (55). Remote treatment planning and lifestyle management are other significant advantages of movement analysis systems. In addition, due to their lightweight and wearable properties, mobile movement analysis systems (e.g., IMUs) have a good potential for mobility assessment in real-world unsupervised environments. In contrast, cameras and other environment sensing technologies have limitations in their capture range and hardware portability and are better suited for controlled environments (e.g., laboratories, clinics, nursing homes). Some of the disadvantages of these systems are their limitations in evaluating movement analysis in social life, high costs, overly complex analysis requiring a trained team, and difficult calibration. Movement analysis systems to be used should be selected in line with the needs of the patient and the user's clinical and technological experience.

Conclusion and Recommendations

Technological systems provide various benefits to pwMS with features facilitating the realization of movement, providing task-specific training content, relying on motor learning principles, supporting treatment planning, minimizing obstacles (e.g., distance, time), and enabling objective evaluation of functional performance. These relatively new and promising systems are thought to complement conventional treatment and assessment methods. As the cost of technological systems decreases and their accessibility and usability increase, the

potential of the systems is suggested to be further explored in pwMS. However, it is recommended that professionals with appropriate clinical backgrounds apply these technologies and seek them for the sake of the patients and their caregivers. In addition, it appears helpful to involve and engage patients and their caregivers in the further development and evaluation of technology for rehabilitation in MS.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.K., B.S., T.K., Design: H.K., B.S., T.K., Data Collection or Processing: H.K., B.S., T.K., Analysis or Interpretation: H.K., B.S., T.K., Literature Search: H.K., B.S., T.K., Writing: H.K., B.S., T.K.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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DOI: 10.4274/jmsr.galenos.2022.2021-10-2
Journal of Multiple Sclerosis Research 2021;1(3):69-74

RESEARCH ARTICLE

Factors Associated with Depression and Anxiety Severity in Multiple Sclerosis Patients

Meral Seferoglu[1]*, Nizameddin Koca[2], Ali Ozhan Sivaci[1], Sukran Yurtogullari[3]

[1]University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Neurology, Bursa, Turkey
[2]University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Internal Medicine, Bursa, Turkey
[3]Private Bursa Hayat Hospital, Bursa, Turkey

Abstract

Objective: The most common psychiatric comorbidities with multiple sclerosis are depression and anxiety. The Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAM-A) are validated tests that are easy to administer and interpret, and are widely used to determine depression and anxiety, respectively. The aim of our study is to examine the association of depression and anxiety levels via the BDI and HAM-A with disease duration, disability, and treatments in patients with Multiple sclerosis (MS).

Materials and Methods: One hundred sixty-three MS patients who gave consent were included in the study. The BDI for depression and HAM-A scales for anxiety were applied. MS patients were analyzed in two subgroups: Relapsing-Remitting and progressive groups. Disability was evaluated with the Expanded Disability Status Scale (EDSS).

Results: A total of 163 patients, including 116 women and 47 men, had a mean age of 38.50±9.63 years, and the mean duration of MS diagnosis was 7.49±6.18 years. The rate of anxiety was 82.2% and depression was 33.7% according to HAM-A and BDI scale, respectively. In subgroup analysis, it was observed that anxiety and depression scores of RRMS patients were significantly lower than progressive subtypes. Anxiety and depression scores of patients with EDSS ≤3 were found to be significantly lower than those with EDSS >3. We found that disease modifying treatments did not have a significant effect on anxiety and depression scores.

Conclusion: In our study, it was observed that depression and anxiety were closely related to MS type and disability. The appropriate treatment of accompanying depression and anxiety is crucial for the management of the MS disease process.

Keywords: Multiple sclerosis, depression, anxiety, Beck Depression Inventory, Hamilton Anxiety Scale

Introduction

Multiple sclerosis (MS) is a neurodegenerative central nervous system (CNS) disease characterized by inflammation, demyelination, and axon damage. The incidence and prevalence of MS is increasing. It is the most common cause of disability in young adults after trauma (1,2). The etiology of MS is multifactorial and progresses with different clinical presentations. MS can progress with attacks and remissions, or with a progressive disease course. Clinical signs and symptoms may show individual differences. Visual, sensory, cerebellar, and psychiatric symptoms can be seen (3).

Psychiatric symptoms such as mania, hallucinations, and depression in MS patients were first described by Charcot et al. (4). Compared to the normal population, depression, anxiety, cognitive dysfunction, bipolar disorder, and psychosis are more common in MS patients (5). Studies have reported that 95% of the MS population are associated with psychiatric comorbidities throughout life. The most common psychiatric comorbidities are depression and anxiety disorder.

It has been reported that the lifetime prevalence of depression in MS patients varies between 19% and 54%, and in cross-sectional studies, the point prevalence of clinically important

Address for Correspondence: Meral Seferoglu, University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Neurology, Bursa, Turkey
E-mail: meralbozseferoglu@gmail.com **ORCID-ID:** orcid.org/0000-0003-3858-0306
Received: 21.10.2021 **Accepted:** 28.01.2022

depressive findings is observed to be up to 50% (6,7). Although the signs and symptoms of depression are common in MS patients, studies have shown that the rate of missed diagnoses is quite high and they are treated inadequately. In the study conducted by Mohr et al. (8), it was determined that 65.6% of MS patients with depression did not receive treatment, and only 26.6% were under appropriate treatment. Depression and anxiety disorders are treatable comorbid diseases. If they are treated, the quality of life will increase and the follow-up will be easier in MS treatment compliance and in the follow-up process. The important thing is to recognize and question the signs of depression and anxiety during the outpatient clinic applications.

In the MS diagnosis process, questioning the psychiatric history and screening are important for the management of immunomodulatory therapies. There are studies showing that interferons, which have been used in the treatment of MS for many years, may cause depression and should not be used in patients with a previous history of depression (9). On the other hand, there are study findings showing that the treatments did not have negative psychiatric effects and that some treatments reduced the incidence of depressive symptoms (10). There is no consensus on the effects of the treatments used in MS on depression and anxiety.

The pathogenesis of MS, localization of lesions, clinical presentation, progressive course, treatments used, and psychosocial factors have been shown as triggering factors for psychiatric disorders. Compared to other chronic diseases, psychiatric disorders accompanying MS were found to be associated with greater fatigue, poor quality of life, and decreased adherence to treatment (11). For these reasons, early diagnosis and treatment of psychiatric disorders that are present at the time of admission or that develop later are very important for the management of the disease course. In the intensive outpatient setting, the focus is on the neurological examination and anamnesis of MS, and psychiatric comorbidities may be overlooked.

The Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAM-A) are validated tests that are easy to administer and interpret, and are widely used to determine depression and anxiety. The aim of our study is to investigate the association between depression and anxiety levels via the BDI and HAM-A with disease duration, disability, and disease modifying treatments in patients with MS.

Materials and Methods

Patients who were followed up in Bursa Yuksek Ihtisas Training and Research Hospital MS outpatient clinic and diagnosed with MS according to the 2010 McDonald diagnostic criteria were evaluated cross-sectionally (12). After the ethics committee approval of the study was obtained from Yuksek Ihtisas Training and Research Hospital Ethics Committee, 163 MS patients who agreed to participate in the study and signed the informed consent form were included in the study. Age, gender, disease duration, EDSS scores, and disease modifying treatments used for MS were recorded at the time of admission. The BDI for depression and HAM-A scales for anxiety were applied.

Inclusion Criteria:

- Diagnosis with MS according to the 2010 McDonald criteria,
- Being between the ages of 18 and 65 years,
- Having no additional neurological disease,
- Not having a diagnosis of depression and/or anxiety by psychiatry prior to the time of the test,
- Not having received methylprednisolone treatment and/or attack treatment in the last 3 months,
- Being at least a primary school graduate,
- Not having a disease that would affect cognitive performance,
- Agreed to participate in the study.

Exclusion Criteria:

- Having a serious comorbid systemic disease,
- Stated that they would not be able to comply with the study and did not sign the consent form.

The patients constituted the Relapsing-Remitting (RR), Relapsing-Progressive (RP), and Primary Progressive (PP) groups. Analyses were done by forming two groups, RR and progressive forms (RP + PP). The disability of MS patients was evaluated with the Expanded Disability Status Scale (EDSS). The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time. The scale was developed by the neurologist John Kurtzke in 1983 and is widely used in clinical trials and in the assessment of people with MS (13). The patients were divided into two groups according to their EDSS scores. Those with EDSS ≤3 were grouped to represent patients with no or mild disability, and those with EDSS>3 were grouped to represent patients with moderate and severe disability (14).

Scales

Beck Depression Inventory (BDI): The purpose of this test is to measure the level of depressive symptoms; a high total score indicates the severity of the depression level. It can be self-applied. There are 21 questions, and the maximum possible score is 63. The cut-off point in this test, for which validity and reliability studies were conducted for the Turkish population, was determined as 17 (15-17).

Hamilton Anxiety Scale (HAM-A): This scale, developed by Hamilton, which questions the physical and mental effects of anxiety, consists of two parts. Yazıcı et al. (18) conducted the validity and reliability of the scale (19). In this test with a

maximum score of 56, a score between 6 and 14 points was considered as minor and a score of 15 and above was considered as major anxiety. Those who scored 6 or higher on the HAM-A scale were considered to have anxiety.

Statistical Analysis

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 26. For each continuous variable, data normality was confirmed using the Kolmogorov-Smirnov test (p>0.05). Pearson's correlation was used to examine the relationships among the measured variables. For independent groups categorized by the MS subtype and EDSS, an independent sample t-test was performed for the normally distributed data. A Bonferroni correction was used to determine the source of significance. In the comparison of categorical variables, the chi-square test was utilized. P values less than 0.05 were considered significant.

Results

A total of 163 patients, including 116 women and 47 men, were included in our study. The mean age of the patients was 38.50±9.63 years, and the mean duration of MS diagnosis was 7.49±6.18 years. The mean value of HAM-A and BDI are given along with sociodemographic characteristics in Table 1. It was determined that 82.2% of the patients had a score 6 or higher on the HAM-A scale. 33.7% of the patients had a score 17, determined as depression.

The relationships between the patients' age, MS duration, and HAM-A and BDI scales were evaluated. A positive correlation was found between the HAM-A and BDI scales. While a significant correlation was observed between the patient's age and MS duration, no correlation was found between these variables and anxiety and depression scales (Table 2).

There was a significant relationship between MS type and depression and anxiety scales. In subgroup analyses, the anxiety and depression scores of RR MS patients were significantly lower than progressive (PP and RP) subtypes (Table 3).

There was a significant relationship between EDSS scores and MS duration, anxiety and depression scores. Anxiety and depression scores of patients with EDSS ≤3 were found to be significantly lower than those of patients with EDSS >3 (Table 4).

Table 1. Sociodemographic data

	Mean ± SD (n=163)	Median, min-max
Age, years	38.50±9.63	39, 18-64
MS duration, years	7.49±6.18	6, 0-28
HAM-A (0-56)	25.46±10.96	13, 0-48
BDI (0-63)	13.58±9.28	11, 0-42

MS: Multiple sclerosis, HMA-A: Hamilton Anxiety Rating Scale, BDI: Beck Depression Inventory, SD: Standard deviation

Patients with different disease modifying treatments had similar anxiety and depression scores (Table 5).

Discussion

Depression and anxiety were found to be related to EDSS scores and clinical subtypes while no correlation was observed with MS duration. BDI and HAM-A scores were found to be significantly higher in RPMS and PPMS patients. No relationships were found with age, gender, and disease duration. According to our study, BDI and HAM-A scores were associated with disability and the progressive course of the disease. We did not find any correlations between treatments and scores of BDI and HAM-A scales.

The onset and symptoms of MS vary among individuals. The initial symptom may be a visual and sensory attack that can be easily diagnosed, or it may be a psychiatric complaint that can make the path to diagnosis long and difficult. Studies show that the frequency at which MS starts with psychiatric complaints varies from 1 to 2.3%, suggesting that the problem is only the tip of the iceberg (20,21). In another study conducted in psychiatry clinics, it was stated that 0.83% of the magnetic resonance images performed in patients diagnosed with psychiatry had hyperintense lesions and they met the diagnostic criteria for MS. It has been shown in the literature that the rate of psychiatric diagnosis before MS is diagnosed is 9%. In another study, the rate of being diagnosed with depression in MS patients was reported as 52% (22,23). It was reported that the diagnosis time of patients whose first MS attack started with psychiatric complaints was delayed by 7 years (24). This delayed period is a very important and lost time for the early treatment of the disease.

Psychiatric comorbidities with MS have long been recognized. In a comprehensive review of MS and accompanying comorbid diseases, it was shown that depression and anxiety affect more than 20% of the MS population (5,25). The psychiatric symptoms that appear at the beginning resolve later than the neurological symptoms, and complete well-being does not occur most of the time (21). It is thought that showing the presence of accompanying psychiatric symptoms from the beginning may also be a determinant of psychiatric morbidity that may

Table 2. Correlation analysis

		HAM-A	BDI	MS duration
HAM-A	**r**	1	**0.695**	0.026
	p		**0.000**	0.740
BDI	**r**	**0.695**	1	0.079
	p	**0.000**		0.320
MS duration	**r**	0.026	0.079	1
	p	0.740	0.320	

HMA-A: Hamilton Anxiety Rating Scale, BDI: Beck Depression Inventory, MS: Multiple sclerosis, r: Pearson's correlation coefficient, p: Probability

Table 3. Evaluation of the relationship between MS types and variables

		RR (n=137)	PP + RP (n=26)	Total (n=163)	p value
MS Duration	Mean ± SD	6.95 ± 6.10	10.40 ± 5.89	7.48 ± 6.18	**0.005**
	Median, min-max	5, 0-28	10.5, 1-22	6, 0-28	
HAM-A	Mean ± SD	14.17 ± 10.69	22.23 ± 10.01	15.46 ± 10.96	**<0.001**
	Median, min-max	12, 0-48	23, 7-43	13, 0-48	
BDI	Mean ± SD	12.27 ± 8.76	20.46 ± 9.06	13.58 ± 9.28	**<0.001**
	Median, min-max	10, 0-42	18, 7-37	11, 0-42	

HMA-A: Hamilton Anxiety Rating Scale, BDI: Beck Depression Inventory, RR: Relapsing remitting, PP: Primary progressive, RP: Relapsing progressive, MS: Multiple sclerosis

Table 4. Evaluation of the relationship between disability status score and variables

		EDSS ≤3 (n=122)	EDSS >3 (n=41)	Total (n=163)	p value
MS duration	Mean ± SD	6.53±5.78	10.40±6.51	7.48±6.18	**0.001**
	Median, min-max	5, 0-22	11, 0-28	6, 0-28	
HAM-A	Mean ± SD	13.97±10.85	19.88±10.20	15.46±10.96	**<0.001**
	Median, min-max	11, 0-48	17, 5-44	13, 0-48	
BDI	Mean ± SD	12.41 ± 9.14	17.05 ± 8.93	13.58±9.28	**0.002**
	Median, min-max	10, 0-42	17, 5-44	11, 0-42	

HMA-A: Hamilton Anxiety Rating Scale, BDI: Beck Depression Inventory, EDSS: Expanded disability status scale, MS: Multiple sclerosis

Table 5. Evaluation of the relationship between MS drugs and variables

	Interferon (n=50)	Glatiramer acetate (n=34)	Oral drugs (n=78)	Total (n=162)	P value	P1*	P2*	P3*
MS duration	6.27±4.93	5.56±5.93	9.18±6.69	7.49±6.18	0.006	>0.99	0.020	>0.99
HAM-A	14.22±11.41	16.82±12.10	15.69±10.268	15.46±10.966	0.744	0.869	>0.99	>0.99
BDI	13.70±10.73	11.74±7.46	14.26±9.05	13.58±9.28	0.458	>0.99	>0.99	0.569

HMA-A: Hamilton Anxiety rating scale, BDI: Beck Depression Inventory, MS: Multiple sclerosis

P1: Interferon vs. Glatiramer acetate, P2: Interferon vs. oral drugs, P3: Glatiramer acetate vs. oral drugs

*: Adjusted p-value with Bonferroni correction

accompany in the later period. Depression accompanying MS has been found to be associated with an increased risk of suicide, in addition to its adverse effects on the course of the disease, cognitive functions, treatment compliance, and quality of life (6). Studies have shown that accompanying depression during diagnosis of MS is overlooked at a rate of 23-30% and it is not treated at a rate of 20-36% (6,26,27). Depression and anxiety disorders are treatable illnesses once diagnosed. The combination of some symptoms such as insomnia, loss of appetite, introversion, and distraction may make the physician suspect the diagnosis of depression, but most of the time, the patients have difficulty in expressing themselves. These symptoms should be considered and questioned. There are scales that question these symptoms and offer a more detailed and objective evaluation. BDI, one of the commonly used assessment scales, was used in our study (17).

In our study, BDI and HAM-A scores showed a positive correlation with each other. There are a few studies in the literature examining the effects of anxiety and depression on each other in MS patients. In a study conducted with 189 MS patients in 2017, it was shown that the presence of anxiety was a risk factor for depression, both directly and indirectly (28). Regular screening and treatment of anxiety symptoms may be recommended to reduce the risk of depression.

Many studies have investigated the relationship between the severity of the illness and the symptoms of depression and/or anxiety. In the literature, it has been shown that there is an increase in the incidence and severity of depression and anxiety symptoms with worsening neurological symptoms and an increase in disability (29). In the same study, mild anxiety rates were found to be 38% for those with low disability and 66.7% for those with high disability. The rates of those experiencing mild depression symptoms were found to be 17.1% for those with low disability and 71.1% for those with high disability (29). In our study, a significant positive correlation was found between increased disability scores and anxiety and depression,

which is in line with the literature. BDI and HAM-A scores were found to be significantly higher in RPMS and PPMS patients. Relationships with age, gender, and disease duration have also been shown in the literature. In our study, no relationships were found with age, gender, and disease duration. According to our study, BDI and HAM-A scores were associated with disability and the progressive course of the disease.

Considering the relationship between disease modifying treatments and psychiatric comorbidities in MS, studies on interferon (IFN) therapy, which has been used in MS treatment for a long time, are encountered. In the literature, it has been shown that IFN therapy can cause depression in cancer, hepatitis C, MS, and skin diseases. Although it was reported that depressive symptoms started with IFN treatment and improved after IFN treatment was terminated, this relationship could not be fully demonstrated in subsequent studies (30,31). A systematic literature review study investigating the relationship between depression and IFN treatment, which was published in 2017, shows that the relationship has not been clearly demonstrated, but the presence of a history of depression in the past is a risk factor for developing depression in the first six months of IFN treatment (9). In the MS diagnosis process, questioning the psychiatric history and screening are important for early diagnosis of individuals at risk and for the management of immunomodulatory therapies. In a systematic literature review of psychiatric complaints associated with natalizumab, fingolimod, dimethyl fumarate, teriflunomide, and alemtuzumab in MS, changes in anxiety or depression scores following treatment were also examined as a secondary goal. As a result of the study, findings revealed that the treatments did not have negative psychiatric effects, and that some treatments reduced the incidence of depressive symptoms. It has been argued that this may be related to the direct immunomodulatory effects of treatments and indirectly to their positive effects on disease activity (10). Inflammation, serotonin, norepinephrine, glutamate, brain derived neurotrophic factor and regulatory disorders in the hypothalamic-pituitary axes have been listed as common pathways for depression and MS. The effective treatment of depression and the regulatory effect of the antidepressant treatment on these pathways may provide a secondary benefit such as neuroprotection (32). In our study, we did not find any correlation between treatments and scores of the BDI and HAM-A scales. However, the use of scales in terms of monitoring depression and anxiety symptoms during the treatment process provides convenience for the early diagnosis of psychiatric comorbidities, as suggested in the literature. Treating depression in MS alters the course of the disease positively by affecting treatment compliance, cognitive impairment, pathological fatigue, quality of life, and reducing cytokine production (6).

MS is a lifelong chronic disease that may cause severe disability in young adults. Accompanying psychiatric signs and symptoms, especially depression and anxiety, can cause loss of function, increase in disability, and mislead in the treatment process of MS. It is important to diagnose and treat psychiatric comorbidities early for accurate follow-up of MS.

Study Limitations

Small sample size and unequal distribution of subgroups can be considered as the limitations of our study.

Conclusion

Our results show a positive association of BDI and HAM-A scores with disability and progression of MS. The appropriate treatment of accompanying depression and anxiety is crucial for the management of the MS disease process. Screening scales, which can be performed at certain intervals during clinical visits, may be useful for the diagnosis of comorbid psychiatric diseases in patients.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Bursa Yuksek Ihtisas Training and Research Hospital (decision no: 2011-KAEK-25 2016/13-21, date: 13.07.2016).

Informed Consent: It was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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

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DOI: 10.4274/jmsr.galenos.2022.2021-12-1
Journal of Multiple Sclerosis Research 2021;1(3):75-78

RESEARCH ARTICLE

The Efficacy of Fampridine on Upper Extremity Functions in Individuals with Multiple Sclerosis: Is There a Difference between Cerebellar and Pyramidal Dysfunction?

Asiye Tuba Ozdogar[1]*, Sinem Ozcelik[2], Seda Dastan[3]

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

Abstract

Objective: Similar to its positive effect on the lower extremities, fampridine can also affect upper extremity dysfunction. This study evaluated the potential effect of fampridine therapy on upper extremity functions in patients with multiple sclerosis (pwMS) by comparing these on the basis of cerebellar and pyramidal dysfunctions.

Materials and Methods: Patients aged between 18 and 60 years with a diagnosis of multiple sclerosis and eligible for fampridine therapy due to walking difficulties were followed-up. Of these, patients with problems such as lack of coordination in hand functions or deficiencies in fine motor skills, dressing, writing, and/or buttoning were invited to take part in the study. Upper extremity functions were evaluated using the 9-Hole Peg Test (9-HPT), and general disability was evaluated with the Expanded Disability Status Scale.

Results: One hundred fifty-nine patients were followed-up for 12 months, and 151of them were included in the analysis. Seventy-seven (50 women) healthy controls (HCs) were also included. There was no statistically significant difference between the demographic characteristics of the two groups. A 19.8% improvement was observed in 9-HPT scores after one month of treatment (p=0.004). This improvement was observed to persist at the 24th month. Patients with a cerebellar FS score of 0 to 2 (n=76) improved significantly more (p<0.001) than those (23.5%) with a cerebellar FS score of 3 or higher (9.2%).

Conclusion: The results of this study show that fampridine improves upper extremity functions in pwMS. This improvement was more pronounced in the group with cerebellar dysfunction.

Keywords: Multiple sclerosis, fampridine, upper extremity, disability level

Introduction

Upper extremity impairment is a common and disabling symptom reported in 66% of persons with multiple sclerosis (pwMS). The most extensive clinical signs and symptoms are loss of sensation, muscle weakness, tremor, loss of vibration sense, and reduced range of motion in the upper extremities. Bilateral upper limb disability occurs in more than half of pwMS (1). Manual dexterity is one of the most affected daily life activities in MS. Seventy-five percent of pwMS are reported to experience decreased manual dexterity, while 50% experience limitations in daily life activities (2).

There is no cure for MS. Although the use of disease-modifying therapies reduces the rates of relapse and disability associated with the disease activity, symptomatic therapy is still a crucial component of treatment (3). The aim of several symptomatic treatments is therefore to reduce disease-related symptoms. However, there is still no proven symptomatic therapy capable of effectively treating upper limb impairment (4).

Fampridine is a voltage-dependent, specific blocker of neuronal fast potassium channels that promotes the transmission of neural flow through the demyelinated axons, thereby strengthening neuromuscular transmission (5). A previous

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: 16.12.2021 **Accepted:** 27.01.2022

review study has shown that fampridine exhibits substantial effects on the ability to walk short distances and on perceived walking capacity. However, other effects, such as improving visual function, spasticity, fatigue, quality of life, and upper limb and cognitive functions, remain unclear (6). Additionally, a recent meta-analysis has reported that fampridine can improve disability related to ambulation in MS (7).

Although fampridine appears to be effective in terms of gait and mobility, most studies did not investigate its effects against upper limb impairment, which commonly affects pwMS. Jensen et al. speculated that fampridine might be as effective in upper limb impairment as in the lower limbs (8). However, a recent systematic review investigating the effects of fampridine has reported no significant changes in terms of the Nine-Hole Peg Test (9-HPT) in either the short or long terms (6). Pickering et al. (9) has reported that fampridine does not affect ABILHAND scores. Marion et al. (4) has detected no significant improvement in 9-HPT grip strength, sensory function, or discrimination capacity. Upper extremity functions have been identified as a secondary outcome measure in the majority of studies. More case-control research is therefore needed for a better understanding of the effectiveness of fampridine on upper limb impairment in pwMS. The purpose of this study was to assess the effect of fampridine therapy on upper limb functions in pwMS.

Materials and Methods

Participants

This study was carried out in our multiple sclerosis (MS) clinic. The study protocol was approved by the Non-invasive Research Ethics Committee. Patients aged between 18 and 60 years with the diagnosis of MS (2017 McDonald criteria) and eligible for fampridine therapy due to walking difficulties were followed-up. Those patients with problems such as lack of coordination in hand functions, or deficiencies in fine motor skills, dressing, writing and/or buttoning were invited to take part in the study. Patients who had experienced an attack in the last 30 days, who refused to provide written/verbal consent, or who were unable to complete the 12-month follow-up period for any reason were excluded from the study.

Outcome Measures

The participants' demographic and clinical data were collected. The Expanded Disability Status Scale (EDSS) is the most frequently used measure of disability in pwMS. Scoring is based on the neurological examination of seven functional systems, involving the patient's pyramidal, cerebellar, brainstem, sensory, bladder and bowel, visual, cerebral, and ambulatory status (10). The same senior neurologist examined the patients and calculated their global EDSS scores and cerebellar and pyramidal functional system scores. The 9-HPT is the most commonly used scale for evaluating upper extremity functions in pwMS (11). The 9-HPT is valid and reliable in pwMS and is considered the gold standard for evaluating upper extremity functions (12). 9-HPT data were evaluated for the affected dominant hand.

Procedure

All participants were evaluated before fampridine therapy and after the first month of treatment. If the treatment was effective, they were also evaluated at the 3rd, 6th, 12th, and 24th months in order to investigate the persistence of the effect. Age and sex-matched healthy controls were evaluated in the same periods in order to avoid the learning effect. Healthy relatives of patients admitted to the hospital and who agreed to participate in the study were included as the healthy control group.

Statistical Analysis

Data were analyzed on IBM SPSS 2019 Statistics for Windows software. The Shapiro-Wilk test and histogram graphs were employed to evaluate whether the data were normally distributed. Descriptive analyses were presented using mean plus standard deviation for continuous variables and numbers and percentages for categorical variables. Parametric tests were applied since all data were normally distributed.

Results

One hundred fifty-nine patients were followed-up for 12 months, 151 of them were followed-up for 24 months after the initiation of treatment and were included in this study. Seventy-seven (50 female) healthy controls were also enrolled. No significant statistical differences were observed in terms of demographic characteristics between these two groups (Table 1). The pre-treatment mean EDSS score of the study group was 5.3, which decreased to 5.1 in the first month (p=0.002). The mean EDSS scores also remained stable for two years (Figure 1). The mean pyramidal functional scores were 3.22±1.7 in the group with cerebellar functional scores of 0-2 and 3.52±2.1

Table 1. The study group characteristics

	Patients with MS (n=159)	Healthy control (n=77)	p value
Female, n (%)	111 (69.8%)	50 (64.9%)	NS
Age (years)	45.5±8.1	46.4±7.9	NS
Education (years)	11.3±3.8	11.7±4.1	NS
EDSS (mean) Baseline 24th month	5.3 5.1 ***0.002***	 -	
9-HPT score (mean) Baseline 24th month	19.8 17.6 ***0.004***	14.2 14.08 >0.05	

EDSS: Expanded Disease Status Scale, 9-HPT: Nine-Hole Peg test, MS: Multiple sclerosis, NS: Not significant

Significant values are shown in bold and italic.

in the group with a cerebellar functional scores of 3 or above (p=0.08) (p>0.05). However, the patient group with cerebellar functional system scores of 0-2 exhibited significantly greater improvement than the patients (23.5%) with cerebellar functional system scores of 3 or more (9.2%) (p<0.001).

9-HPT scores, which are frequently used to evaluate the effects of both pyramidal and cerebellar functions on the upper extremity, were evaluated regularly before treatment and during follow-up. 9-HPT scores improved from 19.8 to 17.3 after one month of treatment (p=0.004). This improvement was also sustained in months 3, 6, 12, and 24 (Figure 2). The healthy controls' 9-HPT results also improved (3.6%), although this was not statistically significant (p>0.05).

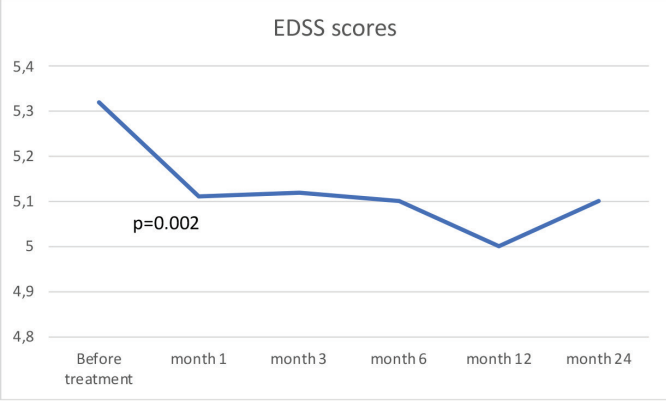

Figure 1. EDSS scores at follow-up in fampridine group
EDSS: Expanded Disease Status Scale

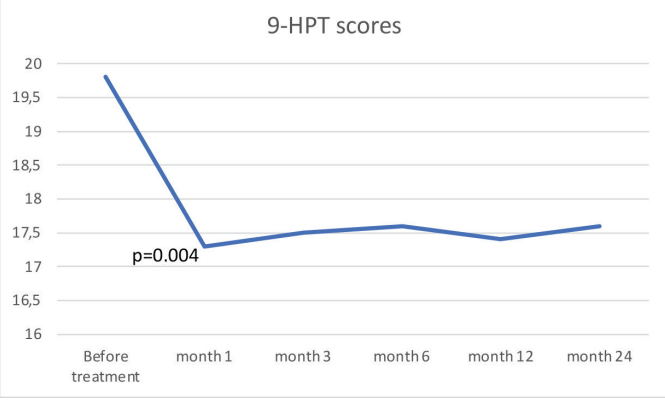

Figure 2. 9-HPT scores at follow-up in fampridine group
9-HPT: Nine-Hole Peg Test

Discussion

Walking disorders due to causes such as weakness in the lower extremities, spasticity, cerebellar disorder, or profound sensory impairment are prominent symptoms in the great majority of individuals with MS. However, impairments in upper extremity functions secondary to tremor, lack of coordination, and paresis can also be observed in the course of the disease in most pwMS. Similar to lower extremity functions, upper extremity functions also restrict patients' activities of daily living. Although this occurs more in the progressive phase, hand functions may still be affected at a high rate in the early period. The therapeutic options for coping with the deterioration of fine motor skills, which is often not noticed by patients and their relatives, are limited.

Two of the well-defined disadvantages of the EDSS are its inability to assess upper extremity functions and its low reproducibility. The EDSS does not include upper extremity dysfunction after certain levels of disability have been reached but is used as an ambulation index. Differences also occur among practitioners. Although a number scales are used to evaluate upper extremity functions, the most commonly used tool in MS is 9-HPT. Studies have mainly concentrated on the effects of fampridine on the walking abilities of pwMS, and only limited studies have focused on its effects on upper extremity functions as a primary endpoint. The data concerning the effects of fampridine on upper extremity functions in these studies are also inconsistent (6).

The main finding of this study is that fampridine provides effective symptomatic treatment in the context of upper extremity functions in pwMS compared to healthy controls. Moreover, the effect of the treatment persists for up to 24 months. Fampridine does not exhibit selective actions on nerve fibers, and it may be expected to work on all fibers and to increase nerve transmission. A recent systematic review investigating the effects of fampridine in pwMS has included four studies that assessed upper extremity functions. All four used the 9-HPT to evaluate upper extremity functions, and all reported no significant changes (8,9,13,14). In contrast, similarly to our own results, Savin et al. (15) reported improvement in 9-HPT after three months of fampridine therapy. Such inconsistent results may be attributed to the differences in patient selection and disability levels.

MS relapse can occur in any part of the central nervous system, with no preference being exhibited. Long tracts may therefore be expected to have a greater lesion load than comparatively shorter fibers, due to their greater surface area and higher probability of demyelination. The lower extremities of pwMS may therefore be affected more than the upper extremities. For the most part, problems with upper extremity functions become noticeable in the advanced stages of the disease when the patient is already restricted to a wheelchair. This may explain the lack of significant improvement in upper extremity functions after fampridine trials in patients with lower disability levels. It would therefore be logical to select patients with decreased upper extremity functions, which can be determined by performing baseline measurements. In other words, we would expect the patient to improve with fampridine therapy if a loss of function is already present. The healthy controls in

the present study exhibited no significant improvement in their 9-HPT results. A healthy control group was also established to assist with controlling the learning factor. Patients with lower disability levels on the cerebellar EDSS subscore improved more than those with higher disability levels. Cerebellar dysfunction can alter motor functions through loss of coordination. We hypothesize that improved motor functions may overcome lower disability levels on cerebellar functional scores. Furthermore, improved motor performance was unable to compensate for higher cerebellar disability.

Study Limitations

The strength of this study is that it presents patients' long-term results between the period before the start of drug therapy and up to the 24th month of use. The study findings showed that although the maximum improvement was seen in the first month, the effect of treatment also persisted in the 24th month. No improvement was observed in 9-HPT, such as indicating a learning effect in the healthy control group. The main limitation of this study was the absence of a control group of pwMS who had never used fampridine for the purpose of comparing upper extremity functions. The lack of analysis by classifying cases as progressive or non-progressive may also be a limiting factor. A final limitation is that data for disease modifying drugs (DMDs) used by patients were not included in the analysis.

Conclusion

Fampridine caused an improvement in the upper extremity functions of PwMS, and its positive effect lasted for up to 24 months. Patients with more severe cerebellar dysfunction exhibited less improvement in upper extremity functions than the group with mild cerebellar dysfunction.

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

Ethics

Ethics Committee Appproval: Ethics committee approval for this study was obtained from the Local Ethics Committee of Dokuz Eylul University. The study protocol was approved by the Non-invasive Research Ethics Board (protocol number: 3696-GOA, approval Number: 2017/29-10).

Informed Consent: Written consent received from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions:

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

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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DOI: 10.4274/jmsr.galenos.2022.2022-1-1
Journal of Multiple Sclerosis Research 2021;1(3):79-83

RESEARCH ARTICLE

Investigating the Relationship Between Balance and Upper Extremity Function in People with Multiple Sclerosis

Seda Dastan[1]*, Nurbanu Aygunduz Yapici[2], Asiye Tuba Ozdogar[1]

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

Abstract

Objective: Upper extremity dysfunction and balance problem are two important symptoms that are common in individuals with multiple sclerosis and reduce their quality of life. However, there is limited evidence of a direct relationship between these two symptoms. Therefore, this study aims to reveal the relationship between balance and upper extremity function, which is essential for pwMS.

Materials and Methods: Nine hundred and sixty-six patients were included [681 (70.5%) female, 285 (29.5%) male]. The Nine-Hole Peg Test (9HPT) was applied to evaluate upper extremity function. With the Activity-Specific Balance Confidence (ABC) Scale patients evaluated their confidence in their balance during activities and balance was tested with the The Timed Up and Go (TUG) test.

Results: There was a significant moderate positive correlation between the 9HPT and TUG (rho=0.566) and a moderate negative correlation with ABC score (rho=-0.464) in total participants. However, while there was a significant moderate negative correlation between 9HPT and ABC score in relapsing form, there was no relationship between 9HPT and TUG in pwMS with progressive form.

Conclusion: There is a significant relationship between upper extremity function and balance. In addition, the trunk, upper and lower extremities should be considered as a whole, since distal stabilization cannot be achieved without poximal stabilization. Consideration should be given to the upper extremity within the scope of balance assessments.

Keywords: Balance, multiple sclerosis, upper extremity

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) resulting in chronic, progressive disability resulting from genetic and environmental factors (1,2). Although the incidence and prevalence of the disease are increasing, it is more common in females and at the age from 20 to 40 years (3,4). Although the symptoms differ according to the area of neurological involvement, the most common symptoms are motor and sensory impairments, cerebellar symptoms, vision loss, pain, bladder dysfunction, and cognitive impairment in people with MS (pwMS) (5,6).

Lower extremity dysfunction is the most common motor disorder reported in 75% of pwMS (7). Lower extremity dysfunction causes a decrease in walking capacity from the early stages of the disease, and it is evident even in patients with low Expanded Disability Status Scale (EDSS) scores (8,9). Therefore, studies have focused on lower extremity function, and upper extremity dysfunction has not been adequately defined (9). Recent studies have shown that upper extremity dysfunction is a widespread motor symptom at a rate of 66% regardless of the disease stage and it affects bimanual activities of daily life such as changing clothes, washing hands, and eating (9-11). The general activity level and participation in daily life decrease due to upper extremity dysfunction, and this circle causes a worse quality of life (12).

Another common symptom that reduces the quality of life, mobility, and independence in pwMS is a balance disorder which reported by pwMS around 75% (13,14). There are three abnormalities associated with balance control in pwMS: lack of postural stability, reduced limits of stability, and slowness to

Address for Correspondence: Seda Dastan, Dokuz Eylul University, Graduate School of Health Sciences, Izmir, Turkey
E-mail: sedaadastann@gmail.com **ORCID-ID:** orcid.org/0000-0001-8323-3114
Received: 05.01.2022 **Accepted:** 27.01.2022

return to the starting position when bending over or performing reaching movements (15). During the activities of daily living, the person interacts with the environment (16). Many stimuli from the environment are perceived by the proprioceptive input of the lower and upper extremities (16). Proper trunk control is necessary for obtaining correct proprioceptive input for a proper upper extremity function and subsequent balance (17). Trunk and balance control should be considered for standing activity and for independent upper extremity activities and task performance that requires dexterity (18). As a result, the trunk has a proximal stabilizer role in providing distal mobility, and the reverse of this relationship can be examined in terms of the effect of the extremities on the trunk (19).

At the same time, the use of functional upper extremities is important in providing postural stability and balance compensation movements (20). Considering all these components that provide interaction with the environment, maintaining the balance and using the upper extremity function correctly are essential for daily life, activity, and participation (21).

There are question marks about the relationship between these two common symptoms (21). Chua et al. (22) stated that applying an internal perturbation originating from the upper extremity with functional movement integrated into the balance program would be helpful in determining balance strategies. As a result, when pwMS's participating in daily living activities, both balance strategies and upper extremity functions are of great importance. Furthermore, the inclusion of exercise programs is emphasized. Apart from all these mentioned points, another point that causes a slight difference in the symptoms of pwMS in their daily lives is the type of disease (relapsing form/progressive form) (23). The transition to the progressive form causes an effect in daily life as a result of the increase in symptoms over time, although pwMS do not realize this at the beginning (23). However, little is known about the interrelationship of these two crucial issues. Therefore, this study aims to reveal the relationship between balance and upper extremity function, which is essential for pwMS. The secondary aim of our study is to reveal how MS type affects the relationship between balance and upper extremity.

Materials and Methods

Study Design

This cross-sectional study was implemented in the MS Center of Dokuz Eylul University. The baseline data used in the analyses were obtained from the ongoing data on "Follow-up of physical, psychosocial and cognitive influences in people with multiple sclerosis: a prospective cohort study" (ClinicalTrials.gov identifier: NCT03878836). The research protocol was approved by the Dokuz Eylul University University Ethics Committee (protocol number: 2959-GOA and approval number: 2016/27-08). Written consent was obtained from all individuals participating in the study.

Participants

The inclusion criteria were having MS based on the 2017 version of McDonald's criteria (24) and a relapse-free period of at least 30 days. The exclusion criteria were relapse during the study period, having another neurological disorder or any orthopedic surgery history comprising the hip, knee, ankle-foot, or spine, affecting balance and gait. The data of eligible people with MS were obtained from the registry database [iMed (version 6.9.0; MSBase Foundation)] collected between October 2016 and October 2020 for the current study.

Outcome Measures

Demographic and clinical characteristics of the pwMS, such as gender, age, disease duration, MS type, and MS diagnosis year, were recorded from the medical reports.

The EDSS is the most widely used scale to assess disability in people with MS (25). EDSS scoring is based on the neurological examination of eight functional systems and the patient's ambulation status. Functional systems are pyramidal, cerebellar, brainstem, sensory, bladder and intestinal, visual, cerebral, and others (25). The same neurologist calculated EDSS scores of all people with MS by examination.

The Nine-Hole Peg Test (9HPT) is a valid, reliable, and widely used tool to measure finger dexterity in pwMS (26). Test materials consist of nine holes on a flat, a small test battery, and nine matching rods. The subjects are asked to take the sticks one by one from the chamber in the test battery and place them into the holes on the battery, then take the sticks out of the holes and put them back into the chamber. Two repetitions are performed for both extremities, and the score is recorded in mean time (26).

The Activity-Specific Balance Confidence (ABC) Scale, consisting of 16 items, is a reliable and valid measurement tool for pwMS. Participants were asked to rate their confidence in their balance between 0% (no confidence) and 100% (full confidence) while performing 16 different daily activities (27).

The Timed Up and Go (TUG) Test is a reliable, simple, and objective measurement method for assessing balance and functional mobility (28). The person is asked to get up from a chair, walk 3 meters, turn around, walk back to the chair, and sit, and the score is calculated by measuring how many seconds he or she completes the test (28).

Statistical Analysis

Normal distribution of data was checked using the Kolmogorov-Smirnov test and histograms. Since the data showed non-normal distribution, non-parametric statistics were used. Descriptive analyses were presented by giving median and interquartile ranges for continuous variables and numbers and

percentages for categorical variables. The Spearman's correlation coefficients were used to investigate the relationship between the balance and upper extremity function. A correlation ≤0.30 was considered small, between 0.31 and 0.59 as moderate, and ≥0.60 as strong (29). Statistical significance was set at p<.05. Data were analyzed using the IBM® SPSS® Statistics software (Version 25.0. Armonk, NY: IBM Corp.).

Results

A total of 966 pwMS were included in this study. The mean EDSS of the study participants was 1.56±1.66 (range: between 0 and 6.5). There was a significant difference between pwMS with relapsing form and pwMS with progressive form in all variables (p<0.05). Demographic and clinical characteristics of the pwMS are shown in Table 1.

There was a significant moderate positive correlation between the N-HPT and TUG (rho= 0.566) and a moderate negative correlation with ABC score (rho= -0.464) in all participants. The relationship between N-HPT and TUG and ABC score was consistent in pwMS with relapsing form. However, while there was a significant moderate negative correlation between N-HPT and ABC score, there was no relationship between N-HPT and TUG in pwMS with progressive form (Table 2).

Discussion

This study reveals a moderate correlation between upper extremity function and balance, which are two essential parameters that should be followed from an early period of MS. Symptoms in pwMS often appear as a cluster of symptoms rather than a single problem. The resulting cluster of symptoms reduces the quality of life by affecting the activities of daily living and participation (30,31).

Johansson et al. (7) reported that 76% of pwMS, whose EDSS scores ranged from 0 to 9.5, had manual dexterity problems. Bertoni et al. (11) reported that 75% of pwMS had bilateral upper extremity dysfunction, even at an early stage of the disease. When bilateral upper extremity involvement is examined according to ICF, upper extremity dysfunction, impaired tactile sensitivity, and decreased muscle strength are found to be mostly reported impairment at the body structure and functions level (11). At the activity level, limitations in object manipulation were observed even in individuals with an EDSS score below four and in gross motor movements and muscle strength in individuals with EDSS >6.5 (11). Subsequently, these problems affect the performance of many participation activities, thus reducing functional independence and quality of life (26,27,31)

Balance impairment, another element of the symptom cluster, is a common symptom that increases the risk of falling and limits life activities in pwMS (32). Among the causes of balance impairment that increase the risk of falling are motor dysfunction, sensory disturbances, lack of integration of sensory inputs, and inadequate motor response (14). It has been stated that somatosensory disorders in individuals with MS are the predictors of balance limitation (16). Although the sense of proprioception, touch, and vibration are more affected in the lower extremities than in the upper extremities, the involvement of both extremities is associated with balance limitation (16).

Table 1. Demographic and clinical characteristics of the participants

	All participants (n=966)	pwMS with relapsing course (n=911)	pwMS with progressive course (n=55)	p value
Age (years)	36.0 (15.0)*	35.0 (16.0)*	48.0 (14.0)*	<0.001
Gender, n				
Female	681 (70.5%)	651 (71.5%)	30 (54.5%)	0.008
Male	285 (29.5%)	26 (28.5%)	25 (45.5%)	
EDSS score, possible range: 0-10	1.5 (2.0)*	1.0 (2.0)*	6.0 (0.50)*	<0.001
Disease duration (years)	5.0 (10.0)*	5.0 (9.0)*	16.0 (8.0)*	<0.001
Classification				
CIS	4 (0.4%)	4 (0.4%)	NA	-
RRMS	907 (93.9%)	907 (93.9%)	NA	
SPMS	43 (4.5%)	NA	43 (4.5%)	
PPMS	12 (1.2%)	NA	12 (1.2%)	
N-HPT	20.62 (5.21)*	20.43 (4.60)*	28.05 (8.91)*	<0.001
TUG, sec.	7.31 (2.69)*	7.19 (2.26)*	20.96 (18.69)*	<0.001
ABC, possible range: 0-100	84.38 (36.88)*	86.25 (32.5)*	38.13 (29.38)*	<0.001

*Values are presented as median (interquartile range) unless specified.

EDSS, Expanded Disability Status Scale, CIS: Clinically isolated syndrome, RRMS: Relapsing-remitting multiple sclerosis, SPMS: Seconder progressive multiple sclerosis, PPMS: Primer progressive multiple sclerosis, N-HPT: Nine-Hole Peg test, TUG: The Timed Up and Go test, NA: Not applicable

Table 2. Correlation between upper extremity function and balance in pwMS

	Total participants			pwMS with relapsing course			pwMS with progressive course		
Test variables	N-HPT	TUG	ABC	N-HPT	TUG	ABC	N-HPT	TUG	ABC
N-HPT	1.000			1.000			1.000		
TUG	0.566**	1.000		0.518**	1.000		0.179	1.000	
ABC	-0.464**	-0.572**	1.000	-0.407**	-0.517**	1.000	-0.433**	-0.063	1.000

pwMS: People with MS, N-HPT: Nine-Hole Peg Test, TUG: The Timed Up and Go test

**Correlation is significant at the 0.01 level (2 tailed)

Aruin et al. (33) investigated the effect of Anticipatory Postural Adjustments (APAs) control-focused training, including ball throwing, on improving balance control in pwMS. They showed that perturbation occurred with arm activation and APA formation, which is seen as early muscle activation, increased (33). This result has provided preliminary evidence that balance and postural control are involved in maintaining movement during upper extremity function (33). In another study examining the relationship between upper extremity movement and postural stability, it was stated that participation of the postural system was required to maintain balance depending on the strength of upper extremity movement (34). Chua et al. (22) revealed an increase in balance corrections due to perturbation provided by arm movements during the balance provided in fixed stance. Similarly, as in above- mentioned studies, our findings support the relationship between balance and upper extremity functions.

Study Limitations

We should note that our study has some limitations. First, we did not assess the trunk stabilization, which is necessary to perform upper extremity function. Second, using more objective measurement methods would have given us better results. Using the measurement of postural stability limits as an objective method to evaluate the relationship between balance and upper extremity could strengthen our study. We recommend using these measurement methods for future studies. Finally, using the cut-off value in our measurement methods could have been sharper to classify in terms of disability.

Conclusion

As a result, it is necessary to maintain balance during the upper extremity activities such as dressing, cleaning, and transfer activities in daily life. At the same time, since distal stabilization cannot be achieved without proximal stabilization, the trunk, upper and lower extremities should be considered as a whole. Within the scope of balance assessments, the upper extremity should be given as much importance as the lower extremity.

Ethics

Ethics Committee Approval: The research protocol was approved by the Dokuz Eylul University Ethics Committee (protocol number: 2959-GOA and approval number: 2016/27-08).

Informed Consent: Written consent was obtained from all individuals participating in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: Authors have nothing to disclose, neither financial interests nor non-financial interests.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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DOI: 10.4274/jmsr.galenos.2022.2022-1-2
Journal of Multiple Sclerosis Research 2021;1(3):84-93

RESEARCH ARTICLE

Attitudes of Patients with Multiple Sclerosis Towards Disease and Physical Activity Behaviors During the COVID-19 Pandemic

Pinar Yigit[1]*, Ergi Kaya[2], Zuhal Abasiyanik[1,3], Ozge Sagici[1]

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

Abstract

Objective: This study aimed to investigate the considerations of patients with multiple sclerosis (pwMS) related to their disease and treatment, the frequency of going out, treatment and routine examination interruptions, and physical exercise habits during the pandemic.

Materials and Methods: Seven hundred forty-four pwMS (mean age: 41.44 years, 29.2% male, 70.8% female), who were followed in MS Outpatient Clinic in Dokuz Eylul University Hospital, Izmir, Turkey, were recruited. A structured survey was created and administered via phone to assess attitudes towards disease, the frequency of going out, treatment and routine examination interruptions, and physical exercise behavior. Additionally, demographic and clinical characteristics, their health status, and coronavirus disease 2019 (COVID-19) symptoms were also asked.

Results: 66.5% (n=495) of responders stated that their thoughts about the disease did not change during the pandemic. 94% (n=699) of the pwMS reported that they did not experience any disruption in their treatment. 59.9% (n=446) of the pwMS indicated no disruption in their routine controls. 25% of responders reported less physical activity, 17.1% reported more physical activity, 16.5% continued physical activity as usual. 41.4% reported that they did not perform any physical activity in the past and did not do so during the pandemic.

Conclusion: This large cross-sectional study has shown that the attitudes of the majority of pwMS towards their disease have not changed. The continuation of the follow-up of the patients during the COVID-19 period with telehealth applications may ensure the maintenance of treatment adherence and patients' attitudes about the disease.

Keywords: Multiple sclerosis, COVID-19 pandemic, clinical practice, physical activity, exercise, treatment adherence

Introduction

The global outbreak of the coronavirus disease 2019 (COVID-19) has dramatically spread from person to person worldwide, and its dissemination is still intensifying in many areas. The COVID-19 represents various clinical manifestations, including fever, dry cough, myalgia, upper respiratory tract, gastrointestinal symptoms, and fatigue (1).

Multiple sclerosis (MS) is the immune-mediated chronic, inflammatory disease of the central nervous system, and pwMS receive disease-modifying therapies. Those with preexisting medical conditions, additional comorbidities, and advanced age have the infection-related potential risks factors for COVID-19 (2,3). In managing MS disease, there are many care services such as routine clinical examinations, relapse management, and rehabilitation services that will require patients to access the hospital. As mentioned above, home confinement has caused pwMS to postpone to schedule their follow-up examinations, the laboratory blood tests, their magnetic resonance, initiation therapies, or taking pulse methyl-prednisolone treatment (4).

Evidence is accumulating that MS or MS immunotherapies do not increase the incidence of infection or the severity of infection (5). However, in the first months of the pandemic outbreak, there was no experience in this regard. This study aimed to collect data on the considerations of patients with MS (pwMS) related to their disease and treatment and daily routine outside and physical exercise habits during the pandemic. In addition, we both followed their ongoing therapies in

Address for Correspondence: Pinar Yigit, Dokuz Eylul University, Graduate School of Health Science, Izmir, Turkey
E-mail: psypinaryigit@gmail.com **ORCID-ID:** orcid.org/0000-0002-1461-069X
Received: 07.01.2022 **Accepted:** 25.01.2022

the current situation and interrogated the impact of home confinement in pwMS.

Materials and Methods

Participants and Procedure

This study protocol was confirmed by the Turkey Ministry of Health and Dokuz Eylul University Ethics Committee (protocol number: 5507-GOA and approval number: 2020/15-32). Informed consent was obtained verbally from all participants before the assessment during the pandemic.

The inclusion criteria were the diagnosis of definite MS according to revised criteria by an MS neurologist confirmation (6), and being aged 18 years and older. The exclusion criteria were having a current neurological disease other than MS, having any verbal skill deficiency or impairment that might influence response to the survey.

During the recruitment period, the routine assessments were performed via teleassessment by neurologist. Patients could reach the MS nurses, psychologists, and physiotherapists for their questions.

Assessments

We asked about the demographic characteristics (age, education level, marital status, residence, employment status, number of households, and children). Besides, we also inquired about their health status by using the survey mentioned above, involving COVID-19 symptoms for them or their close relatives, the last time of hospital admission for various reasons, the last time they went out, and the level of physical activity. We obtained clinical features from our database (disease duration, course of MS, disability level, and using disease-modifying therapies (DMTs), Expanded Disability Status Scale (EDSS).

A structured survey was created by the three members of our research group, including a psychologist, physiotherapist, and senior neurologist. The survey was performed by the Multiple Sclerosis Research Group, which included an MS neurologist specialized in managing pwMS, physiotherapists, psychologists, and MS nurses. Seven hundred forty-four (female 70.8%, 29.2% male) respondents were reached by mobile phones from May 5 to June 5, 2020, in the MS Outpatient Clinic of a tertiary hospital affiliated with the Medical Sciences of Dokuz Eylul University, Izmir, Turkey. We enrolled with patient self-reporting and questionnaire, including information about MS and COVID-19, via phone calls. Firstly, we interviewed and got feedback from 10% of participants in this study and ensured survey questions to be consistent. We phoned again to pwMS, who did not respond to the first call, about 5 or 7 days later. The content is provided in the tables presented in the results section.

Statistical Analysis

Statistical analyses were performed with IBM® SPSS® Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp.). Descriptive analysis was shown as means and standard deviation (SD) for numerical variables and percentages for categorical variables. The t-tests analysis and chi-square test were performed to obtain two group comparisons between the individual groups. The Pearson correlation coefficient r was used to examine the relationship between the numerical variables. The One-way ANOVA was used to compare EDSS among the groups (positive, negative, neutral/not changed, the decreased frequency, never get out). The Levene test was employed to assess the homogeneity of the variances. A p value ≤ 0.05 was considered statistically significant.

Results

Seven hundred forty-four pwMS were interviewed by phone during the first six-month-period of COVID-19 pandemic. 527 (70.8%) and 217 (29.2%) were female and male, respectively. The mean age, EDSS, and disease duration were 41.44±11.58 years (range: between 18 and 77 years), 2.12±2.24 (range: between 0 and 8.5), and 11.54±8.5 years (range: between 0 and 41), respectively (Table 1). Also, thirty-one cases who were the relatives of pwMS (4.1%) had reported as COVID-19 positive. None of the pwMS experienced new relapse/attacks from the initial of pandemic to the date when we administered the survey.

There were 608 (81.7%), 94 (12.6%), 23 (3.1%), and 19 (2.6%) patients with relapsing-remitting course (RRMS), secondary-progressive (SPMS), primary-progressive (PPMS), and clinically isolated syndrome (CIS), respectively. Thirty-one (4.1%) patients were not administered any DMTs. Nine patients (1.2%) had systemic corticosteroids, 130 (17.5%) interferon-beta, 88 (11.8%) glatiramer acetate, 218 (39.2%) fingolimod, 14 (1.9%) dimethyl fumarate, 43 (5.8%) teriflunomide, 28 (3.8%) natalizumab, 176 (23.7%) ocrelizumab, 4 (0.5%) azathioprine, and 1 (0.1%) rituximab. One patient (0.1%) was in the phase 3 trial of ofatumumab (Table 2).

Responders were asked, "Have your attitude changed about MS during the pandemic?". Four hundred and ninety-five pwMS (66.5%) answered as "not changed" regarding their thoughts about the disease during the pandemic, while 249 pwMS (33.5%) responded as "changed". Age, duration of the formal education, marital status, disease duration, EDSS, and last time they went out were not significantly different between those with changing and fixed thoughts about MS ($p>0.05$). Those who did not change their attitudes on their diseases generally stated that their diseases were also under control during the pandemic. Of the participants whose attitudes had changed, 158 (21.2%) rated it as "If I get infected with the virus, MS symptoms will get worse" (Table 3).

One hundred fourteen (15.3%) responders stated that the frequency of going out did "not changed" during the pandemic, 501 (67.3) rated as "decreased", and 129 (17.3) rated as "never

Table 1. Demographic and clinical characteristics of the participants

	Mean (SD)
Age (years)	41.44±11.58
Gender, n (%)	
Female	527 (70.8%)
Male	217 (29.2%)
Marital status, n (%)*	
Married	508 (68.2)
Single	236 (32.0)
Number of households	2.13±2.00
Number of children	1.11±0.97
Educational status, n (%)**	
Primary school	130 (17.5)
Secondary school	60 (8.1)
High school	199 (26.7)
University	342 (46.0)
Marital status**	
Married	506 (68.0)
Single	234 (31.5)
Disease course, n (%)	
Relapsing-remitting MS	608 (81.7%)
Secondary progressive MS	94 (12.6%)
Primary progressive MS	23 (3.1%)
Clinically isolated MS	19 (2.6%)
EDSS***	2.17±2.28
Disease duration (years)	11.55±8.50

EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis, SD: Standard deviation

*Missing: 2, **Missing: 13, ***Missing: 30

get out". The mean EDSS of those rated "never get out" was significantly higher than other groups. Two hundred forty-nine pwMS (33.5%) reported that staying at home negatively affected their disease, while 114 participants (15.3%) reported that it had a positive effect and 381 (51.2%) had no effect (Table 4).

Six hundred ninety-nine pwMS (94.0%) reported that they had not experienced an interruption in the treatment due to the pandemic. Twenty-five pwMS (3.4%) stated that they could not get planned monthly methylprednisolone because they could not go to the hospital during the pandemic. 0.4% of patients quit the treatment because of the fear of getting COVID-19 (Table 5).

Four hundred forty-six pwMS (59.9%) reported no interruption in their routine controls. Two hundred forty-two respondents (32.5%) stated that their routine examination had been performed via a telephone call by a neurologist. The examinations of 56 respondents (7.4%) had not been completed for several

Table 2. Data regarding the medications used for MS

	n (%)
Fingolimod	218 (39.2)
Ocrelizumab	176 (23.7)
Interferon-beta	130 (17.5)
Glatiramer acetate	88 (11.8)
Natalizumab	28 (3.8)
Dimethyl fumarate	14 (1.9)
Azathioprine	4 (0.5)
Rituximab	1 (0.1)
Ofatumumab phase 3 study	1 (0.1)
Monthly pulse methylprednisolone	9 (1.2)
No treatment	31 (4.2)

MS: Multiple sclerosis

Table 3. Has your attitude changed about MS during the pandemic?

	Given answers	n (%)	EDSS
Not changed (66.5%)	It has not changed	495 (66.5)	2.11±2.16
Changed (33.5%)	It has changed.	249 (33.5)	2.30±2.34
If changed, please state the best describes your opinion about the effect of pandemic on your disease?	I care more about not getting infected with the virus.	81 (10.9)	
	If I get infected with the virus, MS symptoms will get worse.	158 (21.2)	
	The stress caused by the pandemic causes an increase in MS complaints.	10 (1.3)	
*p<0.05			

EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis

reasons, including patients' fear of going out, inability to reach the clinic, and travel restrictions (Table 6).

One hundred eighty-six respondents (25%) reported less physical activity, 127 (17.1%) more physical activity, 122 (16.5%) continued physical activity as usual. Three hundred eight (41.4%) reported that they did not perform any physical activity in the past and did not do so during the pandemic (Table 7).

Discussion

This study investigated the changes in the attitudes towards MS due to the pandemic, the frequency of going out, the rate of treatment and routine examination interruption, and physical activity behaviors. We also revealed the characteristics of a large sample during the COVID-19 pandemic. Our results showed

Table 4. The frequency of going out during the pandemic

	Given answers	n (%)	EDSS
Please state the best option to describe your opinion about the frequency of going out during the pandemic.	Not changed	114 (15.3)	1.16±1.57[a]
	Decreased	501 (67.3)	1.85±1.99[b]
	Never get out	129 (17.3)	4.26±2.58[c]
Please state the best option to describe your opinion about the effect of staying at home during the pandemic on your disease.	Positive	114 (15.3)	1.80±1.96[d]
	Negative	249 (33.5)	1.98±2.03[e]
	Neutral	381 (51.2)	2.40±2.49[f]

EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis

[a]Not changed vs. never get out p<0.001,[b]The decreased frequency vs. not changed p<0.001, [c]Never get out vs. the decreased frequency p<0.001, [d]Positive vs. Neutral p=0.028, [e]Negative vs. positive p=0.812, [f]Negative vs. neutral p=0.072

Table 5. The rate of treatment interruption

	Given answers	n (%)
Is there any interruption in your treatment due to the pandemic?	Not changed	699 (94.0)
	I cannot get my drugs from pharmacies.	2 (0.3)
	I could not get drugs because I was afraid to go out.	3 (0.4)
	I could not get monthly methylprednisolone because I could not go to the hospital.	25 (3.4)
	I quit treatment because I am afraid of getting COVID-19.	6 (0.8)
	Pregnancy	9 (1.2)

COVID-19: Coronavirus disease-2019

Table 6. The rate of interruption in routine examination

	Given answers	n (%)
Is there any interruption in your routine examination due to the pandemic?	There is no interruption in my planned appointment.	446 (59.9)
	My planned appointment has been canceled, but my examination has been performed via phone by neurologist.	242 (32.5)
	I could not my control appointment because I'm afraid to go out.	30 (4.0)
	My planned appointment has been canceled / I cannot reach the clinic.	13 (1.7)
	I could not my control appointment due to travel restrictions.	13 (1.7)

Table 7. Physical activity behavior during the pandemic

	Given answers	n (%)
Please state the option that best describes your physical activity behavior during the pandemic.	I have not performed any physical activity in the past and did not do so during the pandemic.	308 (41.4)
	I performed less physical activity during the pandemic.	186 (25.0)
	I continued performing my physical activity as usual during the pandemic.	122 (16.5)
	I performed more physical activity than usual during the pandemic.	127 (17.1)

that most pwMS did not change their attitudes towards the disease. Although the rate of going out and physical activity level decreased, there was no interruption in their medical treatments, and routine examinations were continued by phone.

Most of the pwMS have made an effort to adopt stringent preventive measures during the pandemic. A great deal of states, such as home confinement, losing social support, feelings of hopelessness, deprivation, and dispiritedness, seem cause to precipitate the depression and anxiety symptoms (7). The personal opinions on chronic disease and the illness perception and treatment adherence can be altered in stressful pandemic situations. PwMS may make different sense of their disease and experiences during the pandemic. In a recent study, 69.9%

of patients have reported that they are concerned that MS diagnosis alone puts them at higher risk for COVID-19 infection (8). In our study, the majority of pwMS (66.5%) reported that their attitudes towards the disease did not change. Although there is a lot of concern about infection in the first months of the pandemic, these results show that an early attempt by health professionals and informing the patients could help manage the distress. The fact that the rates of treatment and routine examination interruptions are very low compared to the literature also supports this result (8).

In the early months of the pandemic, there was uncertainty about whether DMTs increase the risk of infection with COVID-19 or the severity of disease in MS (9). Lately, it has been understood that the risk of acquiring the infectious disease in pwMS is similar to that in the general or disease population as long as they care social distancing, follow the recommended hygiene rules and the national health authority guidance's protocol on quarantine, and adopt the curfew isolation (10). 67.3% of responders have chosen to decrease the frequency of going out during the pandemic. Those not going out because of MS already had a higher disease duration and disability level than other pwMS (Table 3).

Previous studies asserted that social distancing and quarantine could cause limitations in receiving treatments and health service support, therefore cause feeling apprehension regarding their DMTs and exacerbating disease activity (11). This study reported no alteration in 94.0% of patients' treatment programs during the pandemic, and 59.9% of pwMS continued their routine controls. Hence, their treatment adherence seems to be relatively high despite the unprecedented conditions of the pandemic. The rate of changing the therapy programs and delaying in infusions, disruption to rehabilitative services was lower than in a similar survey study (12). These results may be due to the fact that 72.7% responders had high and upper education level in our study, and also the routine assessments were performed by health professionals with a timely teleassessment during the recruitment period. These findings can be interpreted as a significant concordance between physician-patient to enhance treatment adherence (13). Considering the role of the immune mechanisms against infection in MS, the pandemic virus may exacerbate MS disease activity irrespective of the fact that immunosuppressive/immunomodulatory therapies may theoretically increase the susceptibility to COVID-19 (14). Only three pwMS (0.4%) discontinued immunotherapy without consultation because DMTs deteriorated the immune system. Specialists have conveyed these patients to be pay attention to potential risks (prognostic factors, rebound, recurrence, etc.) with postponement DMTs in MS and appropriately informed.

PwMS had to bear psychological impacts, stress, loneliness, cabin fever, depression, healthy anxiety, and isolation caused by the outbreak, and this period may yield them a changed lifestyle and reduced physical activity (15). Our findings showed that 25% of pwMS did less exercise than before. These results were consistent with those reporting physical activity levels in the Israeli cohort (16). However, while the rate of patients who did not exercise both before and during the pandemic was 41.4% in our sample, this rate was 10.8% in Israel. This result shows that our sample was also physically inactive before the pandemic. Surprisingly, it was observed that 33.6% of patients increased or maintained the physical activity level during the pandemic. We realized during the interviews that participants generally considered that the number of steps was adequate in their daily life (walking in the workplace, going shopping, meeting friends etc.). However, they acquired regular physical activities to report considering they adopted the curfew, quarantine, or self-isolation at home. This result can also be explained by the increased awareness of patients about physical activity, social media support, and promising use of technology (17).

Study Limitations

Several limitations were present in this study. Although our sample is quite large compared to the studies in the literature, obtaining data from a single center may affect the generalizability of the results. There may be positive cases among the patients we could not be reached. The timing of the study might also have altered the results, as participants may have reacted differently earlier or later in the ongoing pandemic. Additionally, we have not asked the type of exercises that patients performed. Longitudinal follow-up studies are needed to examine whether these effects are sustained.

Conclusion

This study showed the importance of closer monitoring and advice on risk diminishment strategies meticulously during the pandemic. Additionally, the importance of decision-making between the provider and the patient has been underlined on continuing therapy. In our study, the attitudes of the majority of pwMS towards their disease have not changed. Informing the patient (advanced age, comorbidity, use of immunosuppressive drugs, etc.) and performing examinations via teleassessment may have reduced the health anxiety of the patients and ensured that their attitudes towards the disease did not change. Furthermore, it may have contributed to keeping the adherence rate to treatment at a high level. Our study has suggested that priority should be given to increasing or maintaining physical activity and preventing sedentary behavior during the ongoing pandemic and before the pandemic.

Ethics

Ethics Committee Approval: The Noninvasive Research Ethics Board of Dokuz Eylul University approved the study protocol (decision no: 2020/15-32, date: 06.07.2020).

Informed Consent: Informed consent was obtained verbally from all participants before the assessment during the pandemic.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: Authors have nothing to disclose, neither financial interests nor non-financial interests.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Ozlem Ethemoglu
Rabia Gokcen Gozubatik Celik
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