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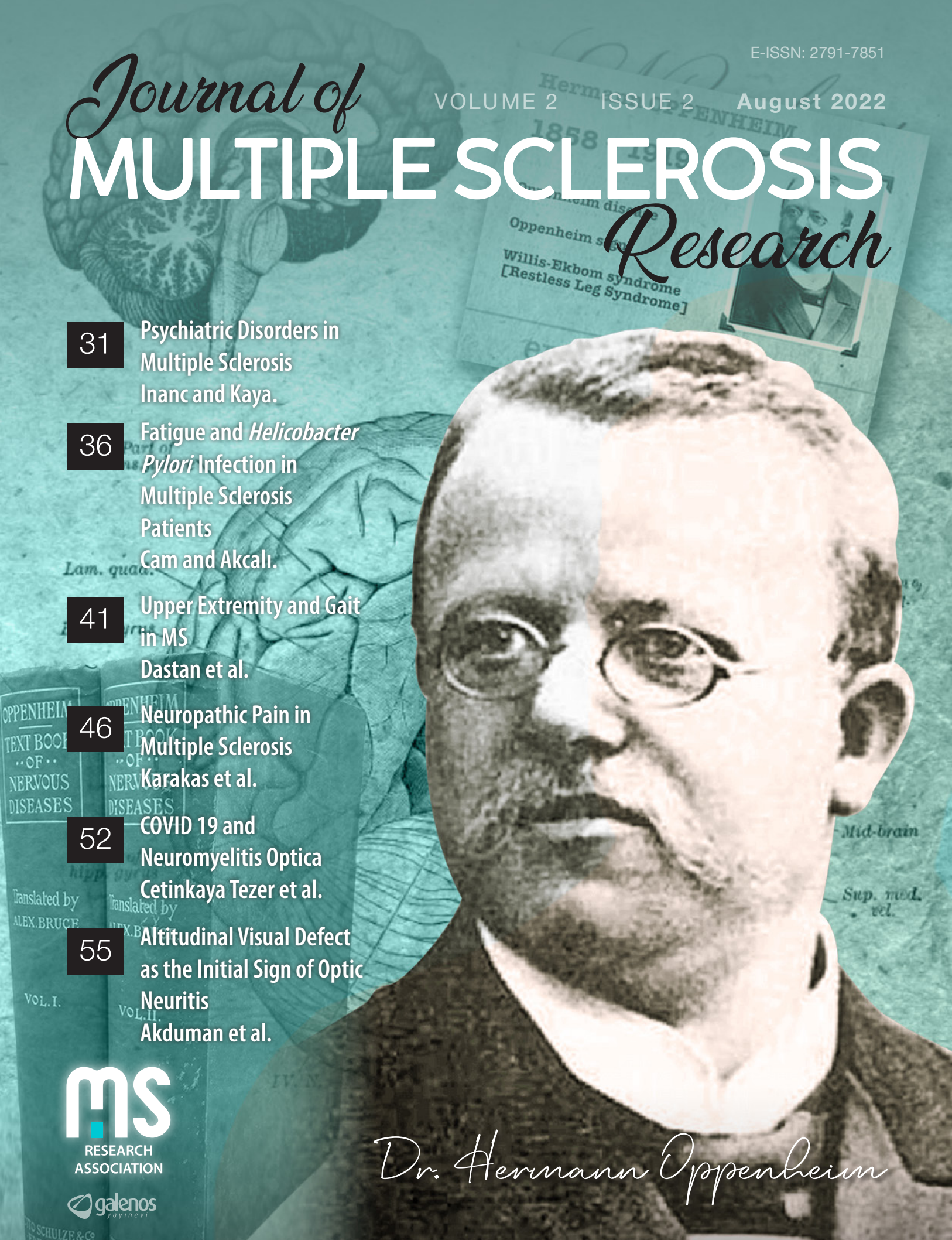
# Journal of MULTIPLE SCLEROSIS Research



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Journal of MULTIPLE SCLEROSIS Research

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# ABOUT US

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

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

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

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

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

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

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

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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.

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

**Editorial Process**

The manuscript submission and editorial review process are as follows:

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

**The Review Process**

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

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

**Preparation of Manuscript**

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

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

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

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

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

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

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

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

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

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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.

**Title Page**

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

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

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

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

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

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

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

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

**Abstract**

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

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

**Materials and Methods:** Important methods should be written respectively.

**Results:** Important findings and results should be provided here.

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

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

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

**1. Original Articles:**

An article is considered original research if;

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

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

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# INSTRUCTIONS TO AUTHORS

Original articles should have the following sections:

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

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

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

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

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

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

**Conclusion:** The conclusion of the study should be highlighted.

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

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

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

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

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

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

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

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

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

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

**Examples of References**

**1. List All Authors**

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

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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.

**Tables, Graphics, Figures, and Images**

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

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

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

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

**Authorship**

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

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

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

**Acknowledgement**

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

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

**Ethics**

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

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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.

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

**Plagiarism Detection**

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

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

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

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

All authors are responsible for the manuscript's content.

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

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

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

**Abbreviations and Symbols**

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

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# PEER REVIEW

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

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

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

**Ethics**

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

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

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

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

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# CONTENTS

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REVIEW

# Psychiatric Disorders in Multiple Sclerosis

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## Abstract

Multiple sclerosis (MS) is an autoimmune, inflammatory, neurodegenerative disease of the central nervous system, characterised by demyelinisation and axonal damage. The probability of MS patients experiencing psychiatric disorders is much greater than that of the population not diagnosed with MS. The symptoms of MS, the side-effects of pharmacological treatments, family history, and psychosocial factors can cause the possibility of psychiatric disorders developing, such as depression, anxiety, adjustment disorder, psychosis, bipolar mood disorder, chronic stress, and suicidal thoughts. Literature search for original articles and review in the databases, including PubMed, Google scholar and Scopus from 1996 to 2021. Studies suitable for the purpose of this review were selected and reported. The frequency of psychiatric disorders in MS and the radiological findings in these cases were evaluated. Depression has been reported to be the psychiatric disorder with the highest prevalence as a comorbidity in individuals diagnosed with MS. Depression affects an average of 30% of MS patients, which is a rate 2-5-fold higher than in the general population. The presence of additional psychiatric diagnoses has a high prevalence in MS disease, but the majority are overlooked in the diagnosis and treatment process.

**Keywords:** Anxiety, comorbiditiy, depression, multiple sclerosis, psychiatric disorders

## Introduction

Multiple sclerosis (MS) is an autoimmune, inflammatory, neurodegenerative disease of the central nervous system, characterized by demyelination and axonal damage. Approximately 2.8 million people worldwide have been diagnosed with MS, and the highest frequency has been determined in North America, Western Europe, and Australia. MS generally emerges in early adulthood, progresses chronically causing physical, psychological, and cognitive problems, and is the most widely seen neurological disease (1-4).

A very wide range of symptoms may be seen in MS. Findings in MS cases include gait impairment, loss of strength, spasticity, urinary tract disorders, sexual dysfunction, fatigue, psychiatric disorders, and cognitive changes (5,6).

The multidimensional symptomatology of MS is closely linked to disability status, fatigue level, and emotional status. As a result, the quality of life of patients with MS is adversely affected. A previous study stated that the presence of psychiatric findings caused an increase in Expanded Disability Status Scale scores, and there was a two-way effect of psychiatric findings and disability status on each other. The inflammatory process is the key factor in the pathology of MS, and this has been associated with depressive and bipolar mood disorders. An increase in the inflammatory process and neurodegenerative process can trigger depression (7-10).

The probability of patients with MS experiencing psychiatric disorders is much greater than that of the population without MS. The symptoms of MS, side effects of pharmacological treatment, family history, and psychosocial factors can increase the risk of psychiatric disorders development, such as depression, anxiety, adjustment disorder, psychosis, bipolar mood disorder, chronic stress, and suicidal thoughts. In a meta-analysis, which included 44,452 patients with MS and 220,849 healthy controls, the annual incidence was 979/100,000 for depression, 638/100,000 for anxiety, 328/100,000 for bipolar disorder, and 60/100,000 for schizophrenia in patients with MS, which were higher than those in healthy controls (11-14).

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Many studies have supported the view that there could be a connection between psychiatric disorders and lesions detected in certain brain regions based on magnetic resonance imaging (MRI) findings of patients with MS. In a previous study, follow-up MRI of patients with psychiatric problems revealed white matter hyperintensities on T2-weighted images, which are consistent with MS in 0.83% of 2,783 patients. Frontal lobe lesions are accompanied by mania, psychosis, and catatonic episodes in patients with MS, and this finding is supported by previous studies. More frontal lobe pathologies have been determined in patients with MS and depression than in patients with MS without depression (15-18).

## Materials and Methods

The literature search for original and review articles in databases, including PubMed, Google Scholar, and Scopus from 1996 to 2021, was conducted. PubMed and Scopus searched for relevanct articles using the following medical topics terms and keywords: "multiple sclerosis", "psychiatric disorders", "depression", "anxiety", "bipolar disorders", "schizophrenia", "obsessive-compulsive disorders". Studies that met the purpose of this review were selected and reported. The frequency of psychiatric disorders in MS and the radiological findings in these cases were evaluated.

### Combination of MS and Depression

Depression was reported to have the highest prevalence as a comorbidity in individuals diagnosed with MS. Depression affects an average of 30% of patients with MS, which is two- to fivefold higher than that in the general population. Just as depression may be seen during the clinical course of MS, it may also occur as a side effect of pharmacological treatments.

The chronic structure of MS causing disability and negatively affecting functionality and quality of life may be reasons why depression is seen more widely in patients with MS than in those with other neurological diseases. The World Health Research of the World Health Organization stated that depression seen as a comorbidity with a chronic disease causes a greater disease burden and a higher rate of workforce loss than a chronic disease alone or depression alone. In patients with MS, depression affects their quality of life, fatigue level, cognitive levels, physical disability, and sleep quality. Therefore, to improve these symptoms, psychiatric treatments should be administered to patients with MS and depression (19-22).

Many cross-sectional and longitudinal studies revealed that depression in patients with MS negatively affects quality of life. In a study of 193 patients with MS, a high level of depression was determined to significantly decrease the health-related quality of life in these patients (23-25). It is thought that depression triggers fatigue in patients with MS, and fatigue, which is seen significantly in patients with MS, negatively affects cognitive functions, and this could trigger depressive symptoms. In short, depressive symptoms and fatigue have a reciprocal effect on each other, causing a vicious circle (26).

In a study of 126 patients with MS and 59 healthy controls, a broad-diameter bilateral cortical atrophy was found to affect all brain lobes in patients with MS, and this atrophy could have caused depression (27). Feinstein et al. (28) examined patients with both MS and depression and reported that T1 and T2 lesion volume was greater in the left medial inferior prefrontal cortex, the gray matter volume was lower, and the cerebrospinal fluid volume in the left anterior temporal region was greater (29).

Lower white matter volume, a decrease in uncinate fascicle fractional anisotropy, and lower resting-state functional connectivity between the amygdala and frontal regions have been determined in patients with both MS and depression than in patients with MS not diagnosed with depression.

### Combination of MS and Anxiety

Anxiety disorder affects an average of 22% of patients with MS, which is threefold higher than that in the general population. In patients with relapsing-remitting MS, attack, and remission could be a significant cause of anxiety. As anxiety is together with depression and increased physical disability in most cases, it is associated with impaired functionality and accepted as a trigger for an attack (30-32).

In quantitative volumetric MRI studies by Sobanski et al. (33), with voxel-based morphometry, a significant decrease in gray matter volume was found in the right midtemporal gyrus (Brodmann area) (21) in patients with panic disorder compared with healthy controls. Di Legge et al. (34) reported that in patients with a clinically isolated syndrome, no correlation was found between the initial anxiety points and number of Gd+ lesions and the total lesion burden (volume of T2 and T1 lesions) in the first 6 months of clinical follow-up.

In patients with a chronic disorder that significantly disrupts functionality, they may be more predisposed to anxiety and thoughts of death than the healthy population. According to the data of a 60-year longitudinal study, 291 of 1,388 patients with MS died because of MS, and compared with the general population, the life expectancy of patients with MS was 7 years shorter, with an approximately threefold higher mortality rate. In accordance with these data, a poor general health condition is a factor increasing the level of concern about death (35).

### Combination of MS and Bipolar Mood Disorder

Bipolar mood disorder is seen in approximately 13% of patients with MS. The etiology of MS and bipolar disorder comorbidity has not yet been fully clarified. A family history of bipolar disorder is a major risk factor for the development of MS and bipolar coexistence. Some studies have supported the genetic transfer of both diseases. Previous studies have also

shown genetic relationships between bipolar mood disorder and MS in the human leukocyte antigen (HLA) *DR2* gene and mitochondrial transcriptomes (36-38).

Some of the pharmacological treatments used in MS treatment may trigger episodes of bipolar mood disorder. Steroid treatment was reported to cause manic attacks, and pharmacological agents such as tizanidine, baclofen, and dantrolene can cause hypomania.

Literature findings related to brain changes associated with bipolar disorder are heterogeneous. While some studies aim to determine the underlying objective biomarkers of this disease such as functional and structural brain abnormalities, the pathophysiology remains uncertain. Lorefice et al. (39) reported no difference in the whole brain, white matter, and cortical gray matter volumes between MS patients with and without comorbid bipolar disorder, but in patients with MS and bipolar disorder, the volumes of the putamen, nucleus accumbens, and pallidus were lower.

### Combination of MS and Psychotic Disorder

Psychosis affects approximately 4% of patients with MS, which is two- to threefold higher than that in the general population. Genetic and immunological causes have been the subject of many studies of the relationship between schizophrenia and MS, and studies have reported that immune system disorders seen in the fetal period and early childhood increase the risk of a psychiatric disorder (40,41). Clinically, there are common directions for both diseases. Both diseases are seen more often in young adults, there are periods of remission and exacerbation in the clinical course, and immunologically, the proinflammatory immune status is predominant.

Genome studies have determined serious intersections in certain genes between schizophrenia and MS. Previous studies have reported 21 independent loci with a connection to both schizophrenia and MS, and there has been a focus on the common points of similar HLA alleles in schizophrenia and MS (42,43).

Feinstein et al. (44) reported that the psychotic group of patients with MS tended to have higher total lesion points, especially around periventricular areas, and lesions in areas specifically around the temporal horn were more significant.

### Combination of MS and Obsessive-compulsive Disorder

Obsessive-compulsive disorder (OCD) is seen in approximately 31% of MS patients, and the average prevalence in the general population is 2%. Although no definitive information is related to the etiology of OCD, serotonin and brain dysfunction could influence the development of OCD (45-47). The MRI results of patients with OCD without other neurological disease have shown structural and/or functional abnormalities in the frontostriatothalamic circuit, and this could be a marker that a psychiatric disorder could be associated with an organic-based cause. The functional interactions between cortical-cortical and/or cortical-subcortical regions and brain white matter abnormalities in MS may contribute to the pathogenesis of OCD (48,49).

A study reported a decrease in gray matter volume in the frontotemporal cortex, especially in the volume affecting the right inferior frontal gyrus and the inferior and midtemporal gyruses in patients with MS and OCD compared with patients with MS without other psychiatric disorder (50). In a case study, Douzenis et al. (51) reported that OCD symptoms seen after a diagnosis of MS could be linked to MS plaque found in the right parietal white matter (52).

Moreover, many studies have shown that autoimmunity also influence the development of OCD, and this could support the view that autoimmunity affects the occurrence of OCD in patients with MS.

## Conclusion

MS is an autoimmune disease that usually emerges in early adulthood, has a course of attacks and remissions but in some cases has a clinically progressive course, can cause disability, and has a serious effect on functionality and quality of life. Comorbid diseases are frequently seen together with MS as a result of progression in the clinical course, that is, it is a cause of disability and a side effect of pharmocological treatments, and as a result of the increased disease burden.

Other psychiatric diagnoses have a high prevalence in MS, but the majority are overlooked in the diagnosis and treatment process. This results in negative outcomes in the clinical course, functionality, and quality of life. During neurological examinations, the decision for diagnosis and treatment methods must be made based on the scores of neuropsychological tests and MRI findings. In a multidisciplinary diagnosis and treatment process, comorbid psychiatric disorders can be diagnosed early. The early determination of psychiatric problems will significantly contribute to the quality of life and prevention of disease progression.

### Ethics

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

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## References


1. Gustavsen S, Olsson A, Søndergaard HB, Andresen SR, Sørensen PS, Sellebjerg F, Oturai A. The association of selected multiple sclerosis symptoms with disability and quality of life: a large Danish self-report survey. BMC Neurol 2021;21:317.
2. Wiendl H, Gold R, Berger T, Derfuss T, Linker R, Mäurer M, Aktas O, Baum K, Berghoff M, Bittner S, Chan A, Czaplinski A, Deisenhammer F, Di Pauli F, Du Pasquier R, Enzinger C, Fertl E, Gass A, Gehring K, Gobbi C, Goebels N, Guger M, Haghikia A, Hartung HP, Heidenreich F, Hoffmann O, Kallmann B, Kleinschnitz C, Klotz L, Leussink VI, Leutmezer F, Limmroth V, Lünemann JD, Lutterotti A, Meuth SG, Meyding-Lamadé U, Platten M, Rieckmann P, Schmidt S, Tumani H, Weber F, Weber MS, Zettl UK, Ziemssen T, Zipp F; 'Multiple Sclerosis Therapy Consensus Group' (MSTCG). Multiple Sclerosis Therapy Consensus Group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper). Ther Adv Neurol Disord 2021;14:17562864211039648.
3. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459-480.
4. Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. Autoimmunity reviews 2010;9:A387-A394.
5. Parker LS, Topcu G, De Boos D, das Nair R. The notion of "invisibility" in people's experiences of the symptoms of multiple sclerosis: a systematic meta-synthesis. Disability and rehabilitation 2021;43:3276-3290.
6. Lakin L, Davis BE, Binns CC, Currie KM, Rensel MR. Comprehensive Approach to Management of Multiple Sclerosis: Addressing Invisible Symptoms-A Narrative Review. Neurol Ther 2021;10:75-98.
7. Altamura AC, Buoli M, Pozzoli S. Role of immunological factors in the pathophysiology and diagnosis of bipolar disorder: comparison with schizophrenia. Psychiatry Clin Neurosci 2014;68:21-36.
8. Schmidt S, Jöstingmeyer P. Depression, fatigue and disability are independently associated with quality of life in patients with multiple Sclerosis: Results of a cross-sectional study. Mult Scler Relat Disord 2019;35:262-269.
9. McKay KA, Tremlett H, Fisk JD, Zhang T, Patten SB, Kastrukoff L, Campbell T, Marrie RA; CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. Neurology 2018;90:e1316-e1323.
10. Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, Laursen H, Sorensen PS, Lassmann H. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 2009;132:1175-1189.
11. Davis BE, Lakin L, Binns CC, Currie KM, Rensel MR. Patient and Provider Insights into the Impact of Multiple Sclerosis on Mental Health: A Narrative Review. Neurol Ther 2021;10:99-119.
12. Silveira C, Guedes R, Maia D, Curral R, Coelho R. Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art. Psychiatry Investig 2019;16:877-888.
13. Murphy R, O'Donoghue S, Counihan T, McDonald C, Calabresi PA, Ahmed MA, Kaplin A, Hallahan B. Neuropsychiatric syndromes of multiple sclerosis. J Neurol Neurosurg Psychiatry 2017;88:697-708.
14. Jun-O'Connell AH, Butala A, Morales IB, Henninger N, Deligiannidis KM, Byatt N, Ionete C. The Prevalence of Bipolar Disorders and Association With Quality of Life in a Cohort of Patients With Multiple Sclerosis. J Neuropsychiatry Clin Neurosci 2017;29:45-51.
15. Lyoo IK, Seol HY, Byun HS, Renshaw PF. Unsuspected multiple sclerosis in patients with psychiatric disorders: a magnetic resonance imaging study. J Neuropsychiatry Clin Neurosci 1996;8:54-59.
16. Blanc F, Berna F, Fleury M, Lita L, Ruppert E, Ferriby D, Vermersch P, Vidailhet P, de Seze J. Inaugural psychotic events in multiple sclerosis? Rev Neurol (Paris) 2010;166:39-48.
17. Sidhom Y, Ben Djebara M, Hizem Y, Abdelkefi I, Kacem I, Gargouri A, Gouider R. Bipolar disorder and multiple sclerosis: a case series. Behav Neurol 2014;2014:536503.
18. Hotier S, Maltete D, Bourre B, Jegouzo X, Bourgeois V, Guillin O. A manic episode with psychotic features improved by methylprednisolone in a patient with multiple sclerosis. Gen Hosp Psychiatry 2015;37:621.e1-2.
19. Boeschoten RE, Braamse AMJ, Beekman ATF, Cuijpers P, van Oppen P, Dekker J, Uitdehaag BMJ. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. J Neurol Sci 2017;372:331-341.
20. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851-858.
21. Julian L, Merluzzi NM, Mohr DC. The relationship among depression, subjective cognitive impairment, and neuropsychological performance in multiple sclerosis. Mult Scler 2007;13:81-86.
22. Marrie RA, Patten SB, Berrigan LI, Tremlett H, Wolfson C, Warren S, Leung S, Fiest KM, McKay KA, Fisk JD; CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis (ECoMS). Diagnoses of depression and anxiety versus current symptoms and quality of life in multiple sclerosis. Int J MS Care 2018;20:76-84.
23. Storm Van's Gravesande K, Blaschek A, Calabrese P, Rostásy K, Huppke P, Kessler J J, Kalbe E, Mall V; MUSICADO Study group. Fatigue and depression predict health-related quality of life in patients with pediatric-onset multiple sclerosis. Mult Scler Relat Disord 2019;36:101368.
24. Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. Eur J Neurol 2016;23:1482-1486.
25. Rodgers S, Manjaly ZM, Calabrese P, Steinemann N, Kaufmann M, Salmen A, Chan A, Kesselring J, Kamm CP, Kuhle J, Zecca C, Gobbi C, von Wyl V, Ajdacic-Gross V. The Effect of Depression on Health-Related Quality of Life Is Mediated by Fatigue in Persons with Multiple Sclerosis. Brain Sci 2021;11:751.
26. Fernández-Muñoz JJ, Cigarán-Méndez M, Navarro-Pardo E, Pérez-de-Heredia-Torres M, Parás-Bravo P, Fernández-de-Las-Peñas C. Is the association between health-related quality of life and fatigue mediated by depression in patients with multiple sclerosis? A Spanish cross-sectional study. BMJ Open 2018;8:e016297.
27. Pravatà E, Rocca MA, Valsasina P, Riccitelli GC, Gobbi C, Comi G, Falini A, Filippi M. Gray matter trophism, cognitive impairment, and depression in patients with multiple sclerosis. Mult Scler 2017;23:1864-1874.
28. Feinstein A, Roy P, Lobaugh N, Feinstein K, O'Connor P, Black S. Structural brain abnormalities in multiple sclerosis patients with major depression. Neurology 2004;62:586-590.
29. van Geest Q, Boeschoten RE, Keijzer MJ, Steenwijk MD, Pouwels PJ, Twisk JW, Smit JH, Uitdehaag BM, Geurts JJ, van Oppen P, Hulst HE. Fronto-limbic disconnection in patients with multiple sclerosis and depression. Mult Scler 2019;25(5):715-726.
30. Podda J, Ponzio M, Messmer Uccelli M, Pedullà L, Bozzoli F, Molinari F, Monti Bragadin M, Battaglia MA, Zaratin P, Brichetto G, Tacchino A. Predictors of clinically significant anxiety in people with multiple sclerosis: A one-year follow-up study. Mult Scler Relat Disord 2020;45:102417.
31. Paparrigopoulos T, Ferentinos P, Kouzoupis A, Koutsis G, Papadimitriou GN. The neuropsychiatry of multiple sclerosis: focus on disorders of mood, affect and behaviour. Int Rev Psychiatry 2010;22:14-21.
32. Silveira C, Guedes R, Maia D, Curral R, Coelho R. Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art. Psychiatry Investig 2019;16:877-888.
33. Sobanski T, Wagner G, Peikert G, Gruhn U, Schluttig K, Sauer H, Schlösser R. Temporal and right frontal lobe alterations in panic disorder: a quantitative volumetric and voxel-based morphometric MRI study. Psychol Med 2010;40:1879-1886.
34. Di Legge S, Piattella MC, Pozzilli C, Pantano P, Caramia F, Pestalozza IF, Paolillo A, Lenzi GL. Longitudinal evaluation of depression and anxiety in patients with clinically isolated syndrome at high risk of developing early multiple sclerosis. Mult Scler 2003;9:302-306.

35. Lunde HMB, Assmus J, Myhr KM, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psychiatry 2017;88:621-625.
36. Minden SL, Feinstein A, Kalb RC, Miller D, Mohr DC, Patten SB, Bever C Jr, Schiffer RB, Gronseth GS, Narayanaswami P; Guideline Development Subcommittee of the American Academy of Neurology. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82:174-181.
37. Bozikas VP, Anagnostouli MC, Petrikis P, Sitzoglou C, Phokas C, Tsakanikas C, Karavatos A. Familial bipolar disorder and multiple sclerosis: a three-generation HLA family study. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:835-839.
38. Konradi C, Sillivan SE, Clay HB. Mitochondria, oligodendrocytes and inflammation in bipolar disorder: evidence from transcriptome studies points to intriguing parallels with multiple sclerosis. Neurobiol Dis 2012;45:37-47.
39. Lorefice L, Fenu G, Carta E, Frau J, Coghe G, Contu F, Barracciu MA, Carta MG, Cocco E. Bipolar disorders and deep grey matter in multiple sclerosis: A preliminary quantitative MRI study. Mult Scler Relat Disord 2020;46:102564.
40. Marrie RA, Fisk JD, Tremlett H, Wolfson C, Warren S, Tennakoon A, Leung S, Patten SB; CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis. Differences in the burden of psychiatric comorbidity in MS vs the general population. Neurology 2015;85:1972-1979.
41. Bundey S. Genetics and neurology. Elsevier. 2014.
42. Arneth BM. Multiple Sclerosis and Schizophrenia. Int J Mol Sci 2017;18:1760.
43. Carrieri PB, Montella S, Petracca M. Psychiatric onset of multiple sclerosis: description of two cases. J Neuropsychiatry Clin Neurosci. 2011;23:E6.
44. Feinstein A, du Boulay G, Ron MA. Psychotic illness in multiple sclerosis: a clinical and magnetic resonance imaging study. Br J Psychiatry 1992;161:680-685.
45. Martin P. The epidemiology of anxiety disorders: a review. Dialogues Clin Neurosci 2003;5:281-298.
46. Schirmbeck F, Esslinger C, Rausch F, Englisch S, Meyer-Lindenberg A, Zink M. Antiserotonergic antipsychotics are associated with obsessive-compulsive symptoms in schizophrenia. Psychol Med 2011;41:2361-2373.
47. Shimizu E. Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica. 2011;113:54-59.
48. Radua J, van den Heuvel OA, Surguladze S, Mataix-Cols D. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Arch Gen Psychiatry 2010;67:701-711.
49. Fontenelle LF, Harrison BJ, Yücel M, Pujol J, Fujiwara H, Pantelis C. Is there evidence of brain white-matter abnormalities in obsessive-compulsive disorder?: a narrative review. Top Magn Reson Imaging 2009;20:291-298.
50. Tinelli E, Francia A, Quartuccio EM, Morreale M, Contessa GM, Pascucci S, Sbardella E, Pozzilli C, Pantano P. Structural brain MR imaging changes associated with obsessive-compulsive disorder in patients with multiple sclerosis. AJNR Am J Neuroradiol 2013;34:305-309.
51. Douzenis A, Michalopoulou PG, Voumvourakis C, Typaldou M, Michopoulos I, Lykouras L. Obsessive-compulsive disorder associated with parietal white matter multiple sclerosis plaques. World J Biol Psychiatry 2009;10:956-960.
52. Foroughipour M, Behdani F, Hebrani P, Marvast MN, Esmatinia F, Akhavanrezayat A. Frequency of obsessive-compulsive disorder in patients with multiple sclerosis: A cross-sectional study. J Res Med Sci 2012;17:248-253.

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RESEARCH ARTICLE

# Relationship Between Fatigue and *Helicobacter pylori* Infection in Patients with Multiple Sclerosis

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## Abstract

**Objective:** One of the common complaints in patients with multiple sclerosis (MS) is fatigue. Studies have reported that 75-87% of patients complain of fatigue. In our study, the possible relationship between fatigue severity and *Helicobacter pylori* (*H. pylori*) infection in patients with MS was investigated.

**Materials and Methods:** The fatigue severity scale was applied to patients who presented to the neurology clinic during the study to assess fatigue. The Beck Depression Inventory was used to evaluate depression, and the Epworth sleepiness scale was used to assess sleepiness. Serum quantitative Immunoglobulin G (IgG) levels for *H. pylori* were measured using the enzyme-linked immunoassay. IBM SPSS Statistics version 26.0 was used for analysis.

**Results:** The MS and control groups consisted of 105 and 79 people, respectively. *H. pylori* seropositivity was not significant in the intergroup analysis. In the MS group, *H. pylori* IgG level was significantly higher in patients with fatigue than in patients without fatigue. The Beck Depression Scale and Expanded Disability Status Scale scores were significantly higher in the MS group.

**Conclusion:** Individual, environmental, and developmental factors were thought to play a role in fatigue, which is common in patients with MS. Another factor could be depression. In our study, *H. pylori* IgG levels were significantly higher in patients with fatigue in the MS group. This result suggests that *H. pylori* may be a factor in the pathophysiology of fatigue.

**Keywords:** Fatigue, multiple sclerosis, *Helicobacter pylori*

## Introduction

Multiple sclerosis (MS) is a degenerative, autoimmune disease of the central nervous system characterized by inflammation and demyelination (1). Genetic and environmental factors that cause immune defects are thought to lead to MS development (2). Lesions known as MS plaques are associated with inflammation and loss of axons, leading to signs involving the entire central nervous system (3). MS is a heterogeneous disease and causes clinical symptoms and signs depending on the involved regions, which can be related to motor, coordination, sensory, and visual pathways (4). Fatigue was reported to be an irritating symptom that affected 50-80% of patients with MS (5).

Fatigue is defined as a subjective emotional state that is thought to develop with different pathophysiological mechanisms in MS and causes difficulty in initiating or maintaining an effort that one wishes to voluntarily realize (6). Fatigue may be due to the disease itself, or it may be caused by secondary causes. Although its etiology is not exactly known, individual, environmental, and developmental factors were thought to play a role (7).

*Helicobacter pylori* (*H. pylori)* is a Gram-negative bacterium that exhibits broad-spectrum pathogenicity that is not limited to the gastrointestinal tract, although it is mainly found in the human stomach (8,9). Studies have shown that it is associated with some diseases outside the gastrointestinal system, such as migraine, coronary heart disease, cirrhosis, pancreatic cancer, and stroke (10). Thus, this study aimed to contribute to the etiology of fatigue by investigating the possible relationship between fatigue, which is a very common complaint in patients with MS, and *H. pylori* infection.

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## Materials and Methods

This case-control study was conducted on patients who applied to our clinic between January 2019 and September 2020. The study included a patient group diagnosed with MS and clinically isolated syndrome according to the 2017 revised McDonald criteria (11). The control group included patients who stated that they were tired when presenting to the neurology outpatient clinic, but did not have MS or any other known chronic/acute disease diagnosis.

The Turkish version of the Fatigue Severity Scale (FSS) was used to determine the fatigue levels of the patients (12). Each question was scored between 1 (totally disagree) and 7 (totally agree), and patients with an FSS score of ≥4 were considered to have fatigue (13). The Beck Depression Inventory, whose Turkish validity and reliability were confirmed, was used to assess depression (14). Clinical disability status was evaluated using the Expanded Disability Status Scale (EDSS) (15). Epworth sleepiness scale (ESS) was used to assess sleepiness, with the following scoring guide: 0-5, normal; 6-10, increased daytime sleepiness; 11-12, moderate daytime sleepiness; 13-15, moderate sleepiness; and 16-24, severe sleepiness. The Turkish version of the ESS was used for evaluation (16). Patients' blood samples (5-10 mL) were obtained, and sera were separated with 3,350 g for 15 min by centrifugation. All samples were stored at -80 °C until enzyme immunoassays (EIAs) were performed. *H. pylori* Immunoglobulin G (IgG) levels were measured using Dia. Pro HP IgG ELISA kit (Diagnostic Bioprobes Srl, Milano, Italy). EIAs were performed according to the manufacturer's instructions. Assay washings were made using BioTek ELx50 microplate washer, and microplate readings were performed using BioTek EL800 (Biotek, Winooski, USA) devices. Samples with an IgG level ≥5 arbU/mL were accepted as seropositive for *H. pylori*.

The exclusion criteria were as follows: pregnancy; demyelinating diseases other than MS; recent use of amantadine, modafinil, and corticosteroids; and psychotic disorder.

The study was conducted following the approval of the Canakkale Onsekiz Mart University Clinical Research Ethics Committee (decision number: 2018-20, date: 11.14.2018). All patients were informed about the study and a written consent form was signed by all participants.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Normal distribution was assessed using Kolmogorov-Smirnov test and Shapiro-Wilk-Francia test. The Mann-Whitney U test and Monte Carlo test were used to compare two independent groups. After controlling for sex, the partial correlation test was used to examine it with the EDSS score. Monte Carlo simulation technique, Pearson chi-square, and Fisher-Freeman-Holton tests were used to compare categorical variables. The ratios were compared with each other and expressed according to Benjamini-Hochberg corrected p-value results. In the tables, quantitative variables are presented as mean ± standard deviation. Categorical variables are indicated as n (%). Confidence analysis of the variables was at the level of 95%, and p-value of <0.05 was considered significant. All patients with MS who applied during the study period were enrolled in the study, so the sample size was not calculated.

## Results

A total of 105 and 79 individuals were included in the patient and control groups, respectively. The female-to-male ratio was 77:28 (73.3%) in the MS group and 50:29 (63.3%) in the control group. The mean age values were 42.47±9.75 and 44.82±13.61 years for the MS and control groups, respectively. The groups did not differ significantly in terms of age and sex. *H. pylori* seropositivity was detected in 73 (69.5%) patients in the MS group and 61 (77.2%) patients in the control group (Table 1).

No significant difference was found between the groups in terms of *H. pylori* seropositivity. The Beck Depression and EDSS scores were higher in the MS group than in the control group. The ESS scores were not significant in the intergroup analysis (Table 1). When MS and control groups were divided into two groups according to the severity of fatigue, the mean age and EDSS scores in patients with MS and fatigue were significantly higher than in those in the group without fatigue (Table 2).

While a significant positive correlation was found between EDSS scores and mean age, a significant negative correlation was found with ESS score. No significant relationship was noted between EDSS scores and *H. pylori* IgG levels and Beck Depression Scale score (p=0.240, p=0.463) (Table 3).

## Discussion

Fatigue significantly impairs the quality of life of patients with MS. It is believed to be distinctly different from fatigue seen in other chronic conditions described by healthy individuals, with its frequency, severity, and long-term persistence. Moreover, two-thirds of these patients stated fatigue as one of the three worst symptoms of their illness (17).

In our study, 69% of the patients in the MS group had fatigue. FSS scores were not significantly different in the analysis between the control and MS groups. The EDSS scores in patients with MS and fatigue were significantly higher than in those without fatigue. These findings suggest that the fatigue that develops in patients with MS is related to its unique characteristics and impairs the quality of life.

Another factor that causes fatigue can be depression. Depression can manifest itself in fatigue, and symptoms can be confused with fatigue. This makes it difficult to distinguish depressive symptoms from MS-related fatigue (18). Depression

**Table 1. Clinical characteristics of the study group**

| | Total (n=184) | Control group (n=79) | Patient group (n=105) | p-value |
|---|---|---|---|---|
| **Age median (Q1/Q3)** | 44.5 (36/51) | 46 (40/51) | 43 (33/51) | 0.134[u] |
| **Sex, n (%)** | | | | 0.151[p] |
| Female | 127 (69.0) | 50 (63.3) | 77 (73.3) | |
| Male | 57 (31.0) | 29 (36.7) | 28 (26.7) | |
| ***Helicobacter pylori*,** median (Q1/Q3) | 41.65 (13.6/72.2) | 53.5 (11.8/84.9) | 37.4 (17.1/62) | 0.427[u] |
| ***Helicobacter pylori* presence**, n (%) | | | | 0.315[p] |
| Positive | 50 (27.2) | 18 (22.8) | 32 (30.5) | |
| Negative | 134 (72.8) | 61 (77.2) | 73 (69.5) | |
| **Fatigue**, n (%) | | | | 0.095[p] |
| Non-fatigue | 73 (39.7) | 37 (46.8) | 36 (34.3) | |
| Fatigue | 111 (60.3) | 42 (53.2) | 69 (65.7) | |
| **Beck**, n (%) | | | | **0.036[ff]** |
| Minimal depression | 61 (33.2) | 21 (26.6) | 40 (38.1) | ns |
| Mild depression | 86 (46.7) | 46 (58.2) | 40 (38.1) | **0,007** |
| Moderate depression | 36 (19.6) | 12 (15.2) | 24 (22.9) | ns |
| Severe depression | 1 (0.5) | 0 (0.0) | 1 (1.0) | ns |
| **Epworth**, n (%) | | | | 0.318[p] |
| Rare | 135 (73.4) | 61 (77.2) | 74 (70.5) | |
| Often | 49 (26.6) | 18 (22.8) | 31 (29.5) | |
| **EDSS,** median (Q1/Q3) | 0 (0/2) | 0 (0/0) | 1 (0.5/4.5) | **<0.001[u]** |

[u]Mann-Whitney U test (Monte Carlo), [p]Pearson chi-square test (Monte Carlo), [ff]Fisher-Freeman-Halton test (Monte Carlo); post hoc test: Benjamini-Hochberg correction, Q1: 25th percentile; Q3, 75th percentile, ns: Not significant, EDSS: Expanded Disability Status Scale

is seen in up to 50% of patients with MS (19). In this study, Beck Depression and EDSS scores were significantly higher in the MS group than in the control group.

*H. pylori* is found in >50% of humans in the gastric mucosa (20). Studies have shown that it is associated with neurodegenerative diseases (21). Some studies have investigated the serology of MS and *H. Pylori;* however, conflicting and limited data have been published regarding the correlation between *H. Pylori* seropositivity and MS (22-24). *H. pylori* is quite high in the population and can become chronic. In addition to chronic diseases, *H. pylori* is also known to affect the development of anemia, peptic ulcer, and cancer (25). Various hypotheses such as bacterial translocation and gut microbiota dysbiosis have been put forward to explain the possible mechanism of fatigue (26,27). The relationship between fatigue and immuno-inflammatory pathways has begun to attract more attention from clinicians. Fatigue is a common complaint in other chronic diseases and gastrointestinal diseases besides MS. Thus, *H. pylori* may need to be investigated as a cause of fatigue, especially in patients with chronic diseases, who were selected in our study (28).

To our knowledge, no other study has shown the relationship between *H. pylori* seropositivity and fatigue symptoms in patients with MS. In our study, we found *H. pylori* seropositivity in 73 (69.5%) patients in the MS group and 61 (77.2%) patients in the control group. No significant relationship was found between the two groups.

To our best knowledge, no study has included the relationship between *H. pylori* seropositivity and fatigue symptoms in patients with MS. According to our results, *H. pylori* was seropositive in 73 (69.5%) patients in the MS group and 61 (77.2%) patients in the control group, and no significant relationship was found between the two groups. In our study, we investigated the relationship between the presence of fatigue and *H. pylori* levels in patients with MS.

The *H. pylori* IgG levels in patients with fatigue were significantly higher than in those without fatigue. Thus, patients with MS and fatigue should be screened for *H. pylori* and treated if necessary. However, considering the limitations of our study, we believe that multicenter studies with more patient groups will be needed.

Despite these results, this study has some limitations. First, it was conducted in a single center. Second, since *Helicobacter* culture was not performed, it may be difficult to establish a relationship with active infection. Third, the sample size was not

**Table 2. Comparison of the MS group and control group according to fatigue severity**

| | Total | | p-value | Control group | | p-value | Patient group | | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Non-fatigue | Fatigue | | Non-fatigue | Fatigue | | Non-fatigue | Fatigue | |
| Age, median (Q1/Q3) | 43 (32/48) | 46 (38/53) | 0.004[u] | 48 (39/50) | 45 (40/51) | 0.870[u] | 36.5 (26/44) | 48 (37/54) | <0.001[u] |
| EDSS, median (Q1/Q3) | 0 (0/0.5) | 1 (0/4) | <0.001[u] | 0 (0/0) | 0 (0/0) | 1 | 0.5 (0/1) | 2.5 (1/5) | <0.001[u] |
| *Helicobacter pylori*, median (Q1/Q3) | 27.6 (11.9/63.9) | 53.1(16.74/72.9) | 0.239[u] | 57.4 (12.8/88.7) | 53.1 (9.2/79) | - | 18.8(9.2/26.3) | 53.25 (18.75/71.2) | <0.001[u] |
| *Helicobacter pylori* serology, n (%) | | | 0.092[p] | | | 0.283[p] | | | <0.001[p] |
| Negative | 25 (34.2) | 25 (22.5) | | 6 (16.2) | 12 (28.6) | | 19 (52.8) | 13 (18.8) | |
| Positive | 48 (65.8) | 86 (77.5) | | 31 (83.8) | 30 (71.4) | | 17 (47.2) | 56 (81.2) | |
| Beck, n (%) | | | <0.001[ff] | | | 0.004[p] | | | <0.001[ff] |
| Minimal depression | 40 (54.8) | 21 (18.9) | <0.001 | 16 (43.2) | 5 (11.9) | 0.002 | 24 (66.7) | 16 (23.2) | <0.001 |
| Mild depression | 25 (34.2) | 61 (55.0) | 0,006 | 18 (48.6) | 28 (66.7) | ns | 7 (19.4) | 33 (47.8) | 0,004 |
| Moderate depression | 8 (11.0) | 28 (25.2) | 0,017 | 3 (8.1) | 9 (21.4) | ns | 5 (13.9) | 19 (27.5) | ns |
| Severe depression | 0 (0.0) | 1 (0.9) | - | 0 (0.0) | 0 (0.0) | - | 0 (0.0) | 1 (1.4) | ns |
| Epworth, n (%) | | | 0.088[p] | | | 0.106[p] | | | 0.507[p] |
| Rare | 59 (80.8) | 76 (68.5) | | 32 (86.5) | 29 (69.0) | | 27 (75.0) | 47 (68.1) | |
| Often | 14 (19.2) | 35 (31.5) | | 5 (13.5) | 13 (31.0) | | 9 (25.0) | 22 (31.9) | |

[u]Mann-Whitney U test (Monte Carlo), [p]Pearson chi-square test (Monte Carlo), [ff]Fisher-Freeman-Halton test (Monte Carlo); post hoc test: Benjamini-Hochberg correction; Q1, 25th percentile; Q3, 75th percentile, ns: Not significant, MS: Multiple sclerosis

**Table 3. EDSS corelations in the patient group**

| Patient group | EDSS | |
|---|---|---|
| | R | p-value |
| Age | 0.571 | <0.001 |
| *Helicobacter pylori* presence | 0.140 | 0.240 |
| Beck Depression Scale | 0.088 | 0.463 |
| Epworth sleepiness scale | -0.273 | 0.020 |

Partial correlation test; sex effect was controlled; r: Corelation coefficient, EDSS: Expanded Disability Status Scale

calculated because all patients in the study were those who presented within the dates specified in the ethics committee approval. Fourth, in a study conducted against myelin antigens, especially against heat shock proteins (Hsp), in patients with MS, a positive significant correlation was found between high levels of Hsp60 antibodies and patients' age, disease duration, and EDSS (29). However, in our study, no significant difference was found between the MS group and the control group in terms of *H. pylori*, and cerebrospinal fluid (CSF) examination was not considered. Further studies involving Hsp60 level measurement in CSF would be more beneficial for investigations between fatigue and *H. pylori*.

## Conclusion

In our study, no significant difference was found between patients and controls in terms of *H. pylori* seropositivity. In the patient group, the *H. pylori* IgG levels in patients with MS and fatigue were significantly higher than in those without fatigue. This result suggests that *H. pylori* may be a factor in patients with MS and fatigue. Therefore, the investigation and treatment of patients with MS and fatigue for *H. pylori* may be considered. We think that our study may lead to other studies that can be evaluated in terms of fatigue complaints after *H. pylori* treatment.

### Ethics

**Ethics Committee Approval:** The study was conducted following the approval of the Canakkale Onsekiz Mart University

Clinical Research Ethics Committee (decision number: 2018-20, date: 11.14.2018).

**Informed Consent:** All patients were informed about the study and a written consent form was signed by all participants.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

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

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## References

1. Seferoglu M, Koca N, Sivaci AO, Yurtogullari S. Factors Associated with Depression and Anxiety Severity in Multiple Sclerosis Patients. Journal of Multiple Sclerosis Research 2021;1:69-74.
2. Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, Langer-Gould A. Environmental and genetic risk factors for MS: an integrated review. Ann Clin Transl Neurol 2019;6:1905-1922.
3. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, Rocca MA. Multiple sclerosis. Nat Rev Dis Primers 2018;4:43.
4. Freiha J, Riachi N, Chalah MA, Zoghaib R, Ayache SS, Ahdab R. Paroxysmal Symptoms in Multiple Sclerosis-A Review of the Literature. J Clin Med 2020;9:3100.
5. Razazian N, Kazeminia M, Moayedi H, Daneshkhah A, Shohaimi S, Mohammadi M, Jalali R, Salari N. The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: a systematic review and meta-analysis. BMC Neurol 2020;20:93.
6. Rooney S, Wood L, Moffat F, Paul L. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. Mult Scler Relat Disord 2019;28:276-282.
7. Krupp LB, Serafin DJ, Christodoulou C. Multiple sclerosis associated fatigue. Expert Rev Neurother 2010;10:1437-1447.
8. Muñoz AB, Stepanian J, Trespalacios AA, Vale FF. Bacteriophages of Helicobacter pylori. Front Microbiol 2020;11:549084.
9. de Brito BB, da Silva FAF, Soares AS, Pereira VA, Santos MLC, Sampaio MM, Neves PHM, de Melo FF. Pathogenesis and clinical management of Helicobacter pylori gastric infection. World J Gastroenterol 2019;25:5578-5589.
10. Baj J, Forma A, Flieger W, Morawska I, Michalski A, Buszewicz G, Sitarz E, Portincasa P, Garruti G, Flieger M, Teresiński G. Helicobacter pylori Infection and Extragastric Diseases-A Focus on the Central Nervous System. Cells 2021;10:2191.
11. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-173.
12. Armutlu K, Keser I, Korkmaz N, Akbiyik DI, Sümbüloğlu V, Güney Z, Karabudak R. Psychometric study of Turkish version of Fatigue Impact Scale in multiple sclerosis patients. J Neurol Sci 2007;255:64-68.
13. Induruwa I, Constantinescu CS, Gran B. Fatigue in multiple sclerosis – a brief review. J Neurol Sci 2012;323:9-15.
14. Hisli N. Beck depresyon envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji Dergisi 1989;7:3-13.
15. Tombak KB, Armutlu K, Karabudak R. The Effect of Walking Distance on EDSS Score in Patients with Multiple Sclerosis. Turk Norol Derg 2010;16:72-77.
16. Ağargün MY, Çilli AS, Kara H, Bilici M, Telcioğlu M, Semiz ÜB, Başoğlu C. Epworth Uykululuk Ölçeğinin geçerliği ve güvenirliği. Türk Psikiyatri Dergisi 1999;10:261-267.
17. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol 1988;45:435-437.
18. Figved N, Klevan G, Myhr KM, Glad S, Nyland H, Larsen JP, Harboe E, Omdal R, Aarsland D. Neuropsychiatric symptoms in patients with multiple sclerosis. Acta Psychiatr Scand 2005;112:463-468.
19. Patrick E, Christodoulou C, Krupp LB; New York State MS Consortium. Longitudinal correlates of fatigue in multiple sclerosis. Mult Scler 2009;15:258-261.
20. Haddad JJ, Saadé NE, Safieh-Garabedian B. Cytokines and neuro-immune endocrine interactions: a role for the hypothalamic-pituitary-adrenal revolving axis. J Neuroimmunol 2002;133:1-19.
21. Kountouras J, Papaefthymiou A, Gavalas E, Polyzos SA, Boziki M, Kyriakou P, Katsinelos P, Zavos C, Liatsos C, Tzivras D, Tzitiridou-Chatzopoulou M, Dardiotis E, Deretzi G, Vardaka E, Doulberis M. Helicobacter pylori infection as a potential risk factor for multiple sclerosis. Med Hypotheses 2020;143:110135.
22. Gavalas E, Kountouras J, Boziki M, Zavos C, Polyzos SA, Vlachaki E, Venizelos I, Tsiptsios D, Deretzi G. Relationship between Helicobacter pylori infection and multiple sclerosis. Ann Gastroenterol 2015;28:353-356.
23. Li W, Minohara M, Su JJ, Matsuoka T, Osoegawa M, Ishizu T, Kira J. Helicobacter pylori infection is a potential protective factor against conventional multiple sclerosis in the Japanese population. J Neuroimmunol 2007;184:227-231.
24. Long Y, Gao C, Qiu W, Hu X, Shu Y, Peng F, Lu Z. Helicobacter pylori infection in Neuromyelitis Optica and Multiple Sclerosis. Neuroimmunomodulation 2013;20:107-112.
25. Chimonas MA, Baggett HC, Parkinson AJ, Muth PT, Dunaway E, Gessner BD. Asymptomatic Helicobacter pylori infection and iron deficiency are not associated with decreased growth among Alaska Native children aged 7-11 years. Helicobacter 2006;11:159-167.
26. Tsai SY, Chen HJ, Lio CF, Kuo CF, Kao AC, Wang WS, Yao WC, Chen C, Yang TY. Increased risk of chronic fatigue syndrome in patients with inflammatory bowel disease: a population-based retrospective cohort study. J Transl Med 2019;17:55.
27. Giloteaux L, Goodrich JK, Walters WA, Levine SM, Ley RE, Hanson MR. Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome 2016;4:30.
28. Kuo CF, Shi L, Lin CL, Yao WC, Chen HT, Lio CF, Wang YT, Su CH, Hsu NW, Tsai SY. How peptic ulcer disease could potentially lead to the lifelong, debilitating effects of chronic fatigue syndrome: an insight. Sci Rep 2021;11:7520.
29. Efthymiou G, Dardiotis E, Liaskos C, Marou E, Tsimourtou V, Scheper T, Meyer W, Daponte A, Sakkas LI, Hadjigeorgiou G, Bogdanos DP. Anti-hsp60 antibody responses based on Helicobacter pylori in patients with multiple sclerosis: (ir)Relevance to disease pathogenesis. J Neuroimmunol 2016;298:19-23.

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RESEARCH ARTICLE

# Relationship Between Upper Extremity Functions and Gait in People with Multiple Sclerosis

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## Abstract

**Objective:** Approximately 66% of people with multiple sclerosis (pwMS) have upper extremity dysfunction that is underestimated in the evaluation and treatment process. Gait interference is another important motor problem identified. In pwMS, changes seen in gait parameters include decreased stride length, decreased cadence, and decreased joint range of motion. Although the relationship between gait and arm swing has been investigated in the general population, the existing relationship has not been clearly demonstrated for pwMS. This study aimed to examine the relationship between upper extremity function and gait in pwMS.

**Materials and Methods:** The study included 29 pwMS followed at the outpatient Multiple Sclerosis Clinic of Dokuz Eylul University Hospital. The arm function in MS questionnaire (AMSQ), nine-hole peg test (N-HPT), and Jamar hand dynamometer were used for upper extremity assessment. Gait was assessed with weekly step count according to the SenseWear armband (SWA) and preference-based MS index (PMSI) walking subparameter. The Expanded Disability Status Scale (EDSS), age, sex, and disease duration were recorded. The partial correlation controlling for the EDSS, age, sex, and disease duration was used.

**Results:** The clinical and demographic profiles of the participants were as follows: mean age, 44.41±11.30; mean EDSS score, 3.34±1.68; mean disease duration, 12.44±9.63; mean N-HPT, 25.72±7.13; mean Jamar score, 20.94±9.12; mean PMSI, 0.65±0.24; mean step count, 29037.9±18638.62; mean AMSQ score, 68.86±32.40. A moderately negative correlation was found between SWA and AMSQ (r=-0.483, p=0.017). Moreover, a moderately positive correlation was found between AMSQ and PMSI walking sub parameter (r=0.430, p=0.036).

**Conclusion:** The results of this study revealed no significant relationship between upper extremity performance-based measurement and gait, whereas a significant relationship was noted between upper extremity function and gait in the self-reported assessment.

**Keywords:** Multiple sclerosis, upper extremity, gait

## Introduction

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system (CNS) characterized by chronic autoimmune processes, axonal loss, demyelination, and gliosis (1). MS symptoms are differentiated according to the involved area of the nervous system. The spectrum of symptoms ranges from motor to cognitive problems (2). The most common symptoms were as follows: weakness, spasticity, tremors, visual symptoms, sensory symptoms, executive dysfunction, and memory problems (2). Motor impairment is the most common reported symptom that affects the daily living activities and psychosocial status of people with MS (pwMS) (3).

Walking problem, which is the most common motor symptom of pwMS with a high rate of approximately 75%, is reflected as ambulatory dysfunction and occurs because of factors such as weakness and spasticity in the lower extremities (4,5). Motor and sensory problems (paresis, spasticity, cerebellar ataxia, etc.) resulting from CNS damage are the primary causes of gait disturbance (6). Depending on the labeling, walking speed and step length decrease, double support time increases, and as a result, people restrict walking (6). Although measurements such as the timed 25-foot walk (T25FW) objectively reflect ambulation in a climatic setting, they may not reflect walking activity beyond the clinical setting (7). Block et al. (8) showed

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that fewer steps beyond the clinic were associated with disability and lower ambulation. They also emphasized that performance-based disability scores and the number of steps reflect similar results (8).

While lower extremity motor problems appear more critical because they affect daily activities such as walking performance, balance, climbing stairs, and sitting, >60% of pwMS are highly affected by the motor control of upper extremity function, i.e., ability to build and relax muscle strength quickly (9-11). In addition, disease progression results in the accumulation of disability over time, and individuals need unilateral or bilateral support within 15-20 years (12). As a result, pwMS must rapidly build up upper extremity muscle strength during daily living activities by using walking aids and prevent falls or object manipulation (10). In addition, an arm swing during human movement increases stability during walking, reduces energy expenditure during walking, and facilitates leg movements (13,14). Eke-Okoro et al. (15) reported that people who walk with restricted arm movements have lower step frequency, slower walking speed, and shorter stride length than those who walk without restraint.

Since pwMS can walk with a shorter stride length, lower walking speed, and more prolonged double support phase than healthy controls, increasing the arm swing will contribute to the gait pattern. In light of this information, it is necessary to examine the relationship between upper extremity and lower extremity more closely in pwMS (16). For this reason, we aimed to reveal the relationship between the upper and lower extremities in pwMS with the number of steps reflecting daily living.

## Materials and Methods

### Participants and Procedures

The study was approved by the Dokuz Eylul University Ethics Committee (approval number: 2021/23-20, date: 18.08.2021). The study was conducted in the MS Center of Dokuz Eylul University Hospital. All participants included in the study signed an informed consent form before the assessments.

The eligibility criteria were as follows: provided consent to participate in the study, aged >18 years, and diagnosed with definite MS according to 2017 McDonald criteria (17). The exclusion criteria were having a disabling neurological disease other than MS, a relapse up to 30 days before the study, and an orthopedic or cognitive problem that may affect the evaluations.

### Outcome Measures

Information such as the date of diagnosis, disease duration, and MS type was obtained from the iMed 7.02 software used to create the database.

### Expanded Status Disability Scale

Expanded Status Disability Scale (EDSS) is the most widely used scale for assessing disability in MS, consisting of neurological examination of eight functional systems, designated as pyramidal, cerebellar, brainstem, sensory, bladder and intestinal, visual, cerebral, and others (18). The neurologist calculates in 0.5-point increments from 0 (no physical disability) to 10 (death due to MS) (18).

### Upper Extremity Assessments

The nine-hole peg test (N-HPT) is an upper extremity skill test consisting of nine sticks and nine holes in which these sticks are placed. Participants place the sticks one by one and collect them in the same way (19). Two trials are taken for both hands, first the dominant and then the non-dominant hand. The test completion time was recorded, and the average was calculated separately (19).

Upper extremity grip strength was evaluated with Jamar hand dynamometer (20). In the sitting position, with the knees and elbows flexed to 90° and the wrist in a neutral position, the pwMS was asked to squeeze the device as hard as possible. Three attempts were made for each hand (20). The average of the enemas was recorded in kilograms (kg). The average of the trials was taken. The highest of the three attempts was recorded as Jamar Max (20).

The arm function in MS questionnaire (AMSQ) evaluates the limitation during activities of daily living related to arm function in pwMS in the last 2 weeks (21). Each activity is scored at six levels and consists of 31 activities. The total score is obtained by summing up all the scores. An increase in limitation in function characterizes an increase in the score (21).

### Gait Assessments

The preferential MS index (PMSI) is a patient-based assessment scale consisting of five items: fatigue, walking, concentration, mood, roles, and responsibilities (22). Items are intended to assess health-related quality of life. In this study, we included the analysis of walking subparameters of PMSI. Scoring was provided by a special algorithm, and a higher score was associated with worse walking (22).

The SenseWear armband is a 3-axis accelerometer (23). It provides information about the person's physical activity level by making metabolic equivalent and energy expenditure with special algorithms (24). It also provides information such as the sleep duration and number of steps. It has been recommended for use in pwMS. In the study, 1-week step count of individuals was taken (25).

### Statistical Analysis

The normality distributions of the variable were checked using the Shapiro-Wilk test, plot investigation, and histogram. Partial correlation coefficients were performed to determine the

relationship between upper extremity and gait measurements while controlling for the EDSS, disease duration, age, and sex. The correlation coefficients between 0.1 and 0.29, 0.3 and 0.49, and 0.5 and1.0 were considered weak, moderate, and strong correlations, respectively (26). All data analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The significance level was set at $p<0.05$.

## Results

Consistent with the sex discrimination in MS, the majority of the 29 study participants were women. At the same time, most of our study group had the relapsing-remitting MS phenotype. Although the age range was wide, the EDSS score also reflected that there may be upper extremity problems even at different disability levels. The mean and minimum-maximum values of outcome measures varied widely (Table 1).

It would be more correct to express this sentence as follows: no significant correlation was found between participants' grip strength and N-HPT scores ($p>0.05$). The same insignificant relationship was found between N-HPT and Jamar Max scores. No significant relationship was found between the number of steps and the N-HPT score and Jamar score ($p>0.05$). The PMSI walking subscore was not significantly associated with objective upper extremity measurements, but a significant moderate positive correlation was found between the patient-reported scale and the AMSQ (0.430; $p<0.05$). Similarly, although no difference was found between the number of steps and objective upper extremity measurements, a significant moderately negative correlation was found between the number of steps and the AMSQ (-0,483; $p<0.05$). Detailed information is presented in Table 2.

## Discussion

This study revealed the relationship between the upper and lower extremities in pwMS, with the number of steps reflecting daily living. Our results showed a significant relationship between the patient-based upper extremity assessment and the number of steps and walking sub parameter of the PMSI. However, no significant difference was found between the upper extremity objective measurements and gait assessments.

Normal walking has patterns of coordination between the lower and upper body according to the walking speed (27). Although not a primary condition for walking, an arm swing is an important point in balancing the contralateral pelvis and lower extremity movement (28). In daily living, people manipulate objects around them while walking, which limits their typical arm swing. Restricted arm swing causes persons to change their lower and upper body movements (27).

Ortega et al. (29) suggest that the increased metabolic expenditure maintains stability when they limit arm swings during walking. Moreover, Meyns et al. (13) emphasized the importance of participation of the upper extremities in gait coordination for proper gait patterns. Delabastita et al. showed that children achieved stability by increasing stride width because of restricted arm movement in children with cerebral palsy (30). As a result, the gait pattern of this disease group was affected by upper extremity movement (30). A similar situation is seen in patients with Parkinson's disease whose gait is characterized by decreased symmetry, stride length, and walking speed. In addition to altered gait, upper extremity function is affected due to asymmetric arm swing. This situation affects the coordination between the upper and lower extremities (31). Our study showed a relationship between patient-determined

**Table 1. Demographic and clinical data of the participants**

| | Minimum-Maximum | Mean (SD) |
|---|---|---|
| Age (year) | 23-67 | 44.41±11.30 |
| EDSS | 1.0-6.5 | 3.34±1.68 |
| Disease duration (months) | 0.50-34.75 | 12.44±9.63 |
| N-HPT (seconds) | 17.98-47.10 | 25.72±7.13 |
| Jamar (kilograms) | 2.42-45.37 | 20.94±9.12 |
| SenseWear number of steps (week) | 2855-70871 | 29037.9±18638.62 |
| PMSI gait score | 0-1 | 0.65±0.24 |
| AMSQ | 31-144 | 68.86±32.40 |
| **Regular exercise, n (%)** | | |
| Yes | 12 (40%) | |
| No | 17 (56.7%) | |
| **Sex, n (%)** | | |
| Female | 24 (80%) | |
| Male | 5 (16.7%) | |
| **Employment, n (%)** | | |
| Unemployed | 8 [26.7 11 (36.7%)] | |
| Employed | 11 (36.7%) | |
| Retired | 9 [30 11 (36.7%)] | |
| Student | 1 [3.3 11 (36.7%)] | |
| **Education, n (%)** | | |
| Primary school | 1 (3.3%) | |
| Secondary school | 2 (6.7%) | |
| High school | 14 (46.7%) | |
| Graduate | 12 (40%) | |
| **Disease course, n (%)** | | |
| Relapsing-remitting MS | 24 (80%) | |
| Secondary-progressive MS | 3 (10%) | |
| Primary-progressive MS | 2 (6.7%) | |

SD: Standard deviation, N-HPT: Nine-hole peg test, PMSI: Preference-based MS index, AMSQ: Arm function in MS, EDSS: Questionnaire, Expanded disability status scale, MS: Multiple sclerosis

**Table 2. Relationship between upper extremity and gait measurements**

| | N-HPT-average | Jamar-average | Dominant-Jamar Max | Nondominant-Jamar Max | Number of steps per week | PMSI gait | AMSQ |
|---|---|---|---|---|---|---|---|
| N-HPT-average | 1.000 | -0.297 | -0.294 | -0.273 | -0.213 | 0.168 | 0.353 |
| Jamar-average | -0.297 | 1.000 | 0.834** | 0.717** | 0.126 | -0.147 | -0.243 |
| Dominant-Jamar Max | -0.294 | 0.834** | 1.000 | 0.624** | 0.284 | -0.382 | -0.520* |
| Nondominant-Jamar Max | -0.273 | 0.717** | 0.624** | 1.000 | -0.080 | -0.089 | -0.287 |
| Number of steps per week | -0.213 | 0.126 | 0.284 | -0.080 | 1.000 | -0.658** | -0.483* |
| PMSI gait | 0.168 | -0.147 | -0.382 | -0.089 | -0.658** | 1.000 | 0.430* |
| AMSQ | 0.353 | -0.243 | -0.520* | -0.287 | -0.483* | 0.430* | 1.000 |

Adjusted for EDSS, disease duration, age, and sex. *Significant at p<0.05, **Significant at p<0.001. N-HPT: Nine-hole peg test, PMSI: Preference-based MS index, AMSQ: Arm function in MS questionnaire, EDSS: Expanded disability status scale, MS: Multiple sclerosis

upper extremity involvement in pwMS and the number of steps that are important for walking in daily living.

Despite deteriorations in the temporal and spatial parameters of walking in pwMS, the contribution of the upper extremity to this deterioration has not been clearly stated (32). Elsworth-Edelsten et al. (33) found that affected arm movements in MS would affect walking. However, it is unclear whether the impairment in arm movements is caused by the nature of MS or impaired walking. Benedict et al. (34) examined the relationship between upper extremity, lower extremity, and cognition based on MSFC (clinical assessment of disability progression) and determined a relationship between executive functions and motor activity. However, they did not state a conclusion about the relationship between upper and lower extremity motor performance. Likewise, we could not reveal a significant relationship between upper extremity objective measurements and the number of steps or the walking sub parameter of the PMSI. We think that this is due to the small number of people included in the study (35).

Although assessment measures such as N-HPT are widely used in clinical studies, detecting disease progression and mild change may be insufficient in examining the effects of deterioration (36). Patient-reported outcomes take the information directly from the patient and assess the effect of even mild symptoms on a person's quality of life (36). Thus, although no relationship was found between objective measurements and the upper and lower extremities, our study revealed that this relationship exists and is reflected in daily living.

### Study Limitations

This study has some strengths and limitations. Owing to limited information regarding gait and upper extremity function, our study has brought a new perspective on this topic. First, our sample size was small. Second, although we included the N-HPT measurement result under the MSFC, we did not include the T25FW evaluation as an outcome measure. Finally, since the results of the SenseWear device are affected by the correct use of the patient, the study was conducted with the results related to its use by the patients. For future studies, we suggest conducting gait assessments using gait analysis or sensors for objective assessment.

## Conclusion

The results of this study revealed no significant relationship between upper extremity performance-based measurement and gait, whereas a significant relationship was found between upper extremity function and gait in the self-reported assessment. Therefore, although handgrip strength and manual dexterity could not be related to gait, upper extremity functions that reflect daily living activities could affect the step count and perceived gait performance.

### Ethics

**Ethics Committee Approval:** The study was approved by the Dokuz Eylul University Ethics Committee (approval number: 2021/23-20, date: 18.08.2021).

**Informed Consent:** All participants included in the study signed an informed consent form before the assessments.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

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## References

1. Milo R, Miller A. Revised diagnostic criteria of multiple sclerosis. Autoimmun Rev 2014;13:518-524.

2. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy Citation: Ghasemi N, Razavi Sh, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. Cell J 2017;19:1-10.
3. Maggio MG, Russo M, Cuzzola MF, Destro M, La Rosa G, Molonia F, Bramanti P, Lombardo G, De Luca R, Calabrò RS. Virtual reality in multiple sclerosis rehabilitation: A review on cognitive and motor outcomes. J Clin Neurosci 2019;65:106-111.
4. Ramari C, Hvid LG, David AC de, Dalgas U. The importance of lower-extremity muscle strength for lower-limb functional capacity in multiple sclerosis: Systematic review. Ann Phys Rehabil Med 2020;63:123-137.
5. Stolt M, Laitinen AM, Ruutiainen J, Leino-Kilpi H. Research on lower extremity health in patients with multiple sclerosis: A systematic scoping review. J Foot Ankle Res 2020;13:54.
6. Bethoux F. Gait disorders in multiple sclerosis. Continuum (Minneap Minn) 2013;19:1007-1022.
7. Andersen LK, Knak KL, Witting N, Vissing J. Two- and 6-minute walk tests assess walking capability equally in neuromuscular diseases. Neurology 2016;86:442-445.
8. Block VJ, Lizée A, Crabtree-Hartman E, Bevan CJ, Graves JS, Bove R, Green AJ, Nourbakhsh B, Tremblay M, Gourraud PA, Ng MY, Pletcher MJ, Olgin JE, Marcus GM, Allen DD, Cree BA, Gelfand JM. Continuous daily assessment of multiple sclerosis disability using remote step count monitoring. J Neurol 2017;264:316-326.
9. Lamers I, Maris A, Severijns D, Dielkens W, Geurts S, Van Wijmeersch B, Feys P. Upper Limb Rehabilitation in People With Multiple Sclerosis: A Systematic Review. Neurorehabil Neural Repair 2016;30:773-793.
10. Uygur M, de Freitas PB, Barone DA. Rate of force development and relaxation scaling factors are highly sensitive to detect upper extremity motor impairments in multiple sclerosis. J Neurol Sci 2020;408:116500.
11. Piri Cinar B, Kalaycı G, Acikgoz M, Ozakbas S. Relationship between Physical Disability and Black Holes in Multiple Sclerosis: Upper Extremity Functions - an Important Parameter. J Mult Scler Res 2021;1:17-21.
12. Kremenchutzky M, Rice GPA, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: A geographically based study 9: Observations on the progressive phase of the disease. Brain 2006;129:584-594.
13. Meyns P, Bruijn SM, Duysens J. The how and why of arm swing during human walking. Gait Posture 2013;38:555-562.
14. Collins SH, Adamczyk PG, Kuo AD. Dynamic arm swinging in human walking. Proc Biol Sci 2009;276:3679-3688.
15. Eke-Okoro ST, Gregoric M, Larsson LE. Alterations in gait resulting from deliberate changes of arm-swing amplitude and phase. Clin Biomech (Bristol, Avon) 1997;12:516-521.
16. Kempen JC, Doorenbosch CA, Knol DL, de Groot V, Beckerman H. Newly Identified Gait Patterns in Patients With Multiple Sclerosis May Be Related to Push-off Quality. Phys Ther 2016;96:1744-1752.
17. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-173.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-1452.
19. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Mult Scler 1999;5:244-250.
20. Severijns D, Lamers I, Kerkhofs L, Feys P. Hand grip fatigability in persons with multiple sclerosis according to hand dominance and disease progression. J Rehabil Med 2015;47:154-160.
21. Mokkink LB, Knol DL, Van Der Linden FH, Sonder JM, D'hooghe M, Uitdehaag BMJ. The Arm Function in Multiple Sclerosis Questionnaire (AMSQ): Development and validation of a new tool using IRT methods. Disabil Rehabil 2015;37:2445-2451.
22. Kuspinar A, Bouchard V, Moriello C, Mayo NE. Development of a bilingual MS-specific health classification system: The preference-based multiple sclerosis index. Int J MS Care 2016;18:63-70.
23. Casey B, Coote S, Galvin R, Donnelly A. Objective physical activity levels in people with multiple sclerosis: Meta-analysis. Scand J Med Sci Sports 2018;28:1960-1969.
24. Laeremans M, Dons E, Avila-Palencia I, Carrasco-Turigas G, Orjuela JP, Anaya E, Brand C, Cole-Hunter T, de Nazelle A, Götschi T, Kahlmeier S, Nieuwenhuijsen M, Standaert A, De Boever P, Int Panis L. Physical activity and sedentary behaviour in daily life: A comparative analysis of the Global Physical Activity Questionnaire (GPAQ) and the SenseWear armband. PLoS One 2017;12:e0177765.
25. Coote S, O'Dwyer C. Comparative validity of accelerometer-based measures of physical activity for people with multiple sclerosis. Arch Phys Med Rehabil 2012;93:2022-2028.
26. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Routledge; 2013.
27. Ford MP, Wagenaar RC, Newell KM. Arm constraint and walking in healthy adults. Gait Posture 2007;26:135-141.
28. Zehr EP, Duysens J. Regulation of arm and leg movement during human locomotion. Neuroscientist 2004;10:347-361.
29. Ortega JD, Fehlman LA, Farley CT. Effects of aging and arm swing on the metabolic cost of stability in human walking. J Biomech 2008;41:3303-3308.
30. Delabastita T, Desloovere K, Meyns P. Restricted arm swing affects gait stability and increased walking speed alters trunk movements in children with cerebral palsy. Front Hum Neurosci 2016;10:354.
31. Weersink JB, de Jong BM, Maurits NM. Neural coupling between upper and lower limb muscles in Parkinsonian gait. Clin Neurophysiol 2022;134:65-72.
32. Dujmovic I, Radovanovic S, Martinovic V, Dackovic J, Maric G, Mesaros S, Pekmezovic T, Kostic V, Drulovic J. Gait pattern in patients with different multiple sclerosis phenotypes. Mult Scler Relat Disord 2017;13:13-20.
33. Elsworth-Edelsten C, Bonnefoy-Mazure A, Laidet M, Armand S, Assal F, Lalive P, Allali G. Upper limb movement analysis during gait in multiple sclerosis patients. Hum Mov Sci 2017;54:248-252.
34. Benedict RH, Holtzer R, Motl RW, Foley FW, Kaur S, Hojnacki D, Weinstock-Guttman B. Upper and lower extremity motor function and cognitive impairment in multiple sclerosis. J Int Neuropsychol Soc 2011;17:643-653.
35. Uygur M, de Freitas PB, Barone DA. Rate of force development and relaxation scaling factors are highly sensitive to detect upper extremity motor impairments in multiple sclerosis. J Neurol Sci 2020;408:116500.
36. D'Amico E, Haase R, Ziemssen T. Review: Patient-reported outcomes in multiple sclerosis care. Mult Scler Relat Disord 2019;33:61-66.

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RESEARCH ARTICLE

# Investigation of Neuropathic Pain Distribution and Related Factors in People with Multiple Sclerosis

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## Abstract

**Objective:** The primary aim of the study was to examine the distribution of neuropathic pain according to body areas in people with multiple sclerosis (pwMS) with neuropathic pain. The secondary aim was to examine the relationship between neuropathic pain and psychosocial (fatigue, sleepiness, anxiety, and depression levels) parameters in pwMS.

**Materials and Methods:** This study analyzed 70 pwMS. The PainDETECT questionnaire was used to assess neuropathic pain. Psychosocial parameters such as fatigue, sleepiness, anxiety, and depression were assessed.

**Results:** The most frequently reported neuropathic pain areas were the neck (58.6%), foot/ankle (50%), and knee (48.6%). In addition, in every 1-point increase in the depression survey, the likelihood of having neuropathic pain increases 0.66 times, and in every 1-point increase in the psychosocial parameter of the fatigue survey, the likelihood of having neuropathic pain increases 2.12 times ($p<0.05$).

**Conclusion:** The results of this study reveal that neuropathic pain is frequently seen in the neck, foot/ankle, and knee areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS.

**Keywords:** Multiple sclerosis, neuropathic pain, depression, fatigue

## Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, progressive neurological disease of the central nervous system that is usually seen in young adults aged 20-40 years (1). Common symptoms in people with MS (pwMS) include decreased muscle strength, balance and coordination disorders, deterioration in gait patterns, pain, paresthesia, monocular vision loss, dizziness, and vertigo (2). Other accompanying symptoms and signs may include fatigue, spasticity, ataxia, sensation loss, urinary incontinence, depression, cognitive dysfunction, and many others (3). These symptoms and findings affect the health of pwMS holistically and cause physical, cognitive, and psychosocial deficiencies (4). Gait disturbances, fatigue, and pain are among the most common symptoms in MS (5).

PwMS show a wide range of pain symptoms, from chronic pain symptoms that may occur in conditions such as postural disorders and spasticity to acute pain (6). Pain is an important symptom of MS and is often associated with disability (7). In a systematic review study (17 studies, 5,319 pwMS), the prevalence of pain was 63% (8). In another study, pain was reported as the first symptom in pwMS with a prevalence of 11-23% (7).

Pain in MS is classified according to its duration, severity, and underlying mechanisms. The mechanisms underlying pain in MS are still unclear. However, two separate pain classifications have been proposed according to pathophysiology (7,9). Despite differences between the two classification systems, the classification of pain as neuropathic, nociceptive, and mixed type remains.

In a descriptive study, pain characteristics were investigated in 842 pwMS with chronic pain, and 42% of the patients had nociceptive pain, 27% had mixed type pain, and 32% had neuropathic pain (10). Neuropathic pain is defined by the

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International Association for the Study of Pain as pain resulting from a lesion or dysfunction in the central nervous system (11). Neuropathic pain in MS is directly related to the demyelination process of the disease (12). In a study examining the relationship between pain complaints and plaque formation in MS, lesions in the pons, periventricular gray matter, cerebellum, corpus callosum, thalamus, and medulla oblongata were found to be associated with pain (13).

Two key mechanisms are thought to cause neuropathic pain in MS (12):

1- The occurrence of ectopic stimuli in demyelinating lesions in response to neural damage.

2- Interruption of inhibitory impulses from the brain and absence of inhibitory impulses from the brain, which eliminates the modulation of the afferent A-delta and C pain pathways and leads to central sensitization. As a result, decreased pain thresholds occur after discharges, which increase spontaneous activity.

Neuropathic pain is one of the most common symptoms in pwMS. However, the distribution of neuropathic pain by body areas is unclear. Examining the distribution of neuropathic pain according to body areas may help diversify area-specific rehabilitation approaches. The primary aim of the study was to examine the distribution of neuropathic pain according to body areas in pwMS with neuropathic pain. The secondary aim was to examine the relationship between neuropathic pain and psychosocial (fatigue, sleepiness, anxiety, and depression levels) parameters in pwMS.

## Materials and Methods

### Participants and Procedures

The study protocol was approved by the Ethics Board of Dokuz Eylul University (decision number: 2022/29-02, date: 14.09.2022). This study included data from 70 definitively diagnosed pwMS with neuropathic pain from the outpatient MS clinic of Dokuz Eylül University Hospital, Izmir, Turkey (14). People with a definite diagnosis of MS according to the 2017 McDonald criteria were included (14). Participants with a PainDETECT Questionnaire (PD-Q) score of ≥13 were considered to have neuropathic pain and were included in the study (15). Participants with musculoskeletal, cardiovascular, pulmonary, metabolic, or other diseases severe enough to preclude participation in the study; participants with conditions other than MS that can cause pain, such as cancer, diabetes, overt osteoarthritis, or rheumatoid arthritis based on laboratory or imaging findings; participants with severe cognitive impairment; and pregnancy as determined by the neurologist were excluded from the study.

### Outcome Measures

Neurological examinations of all participants were performed by the neurologist, and the Expanded Disability Status Scale (EDSS) scores were calculated.

The PD-Q has an accuracy rate of 80% compared with expert judgment in identifying neuropathic pain (16). The Turkish version of the PD-Q was also found to be valid and reliable (17). A PD-Q score of ≥13 was considered neuropathic pain. In our study, PD-Q was determined as the primary outcome measure. Participants with a PD-Q score of ≥13 were considered to have neuropathic pain and were included in the study. Participants were asked to mark the areas with neuropathic pain on the body diagram in PD-Q and indicate with an arrow if their pain radiates to other body parts.

The Hospital Anxiety and Depression Scale (HADS) was used to assess the anxiety and depression levels of the participants. HADS is a two-way self-assessment scale used to assess depression (HADS-D) and anxiety (HADS-A) (18). The Turkish version of the questionnaire was found to be also valid and reliable (19).

The Modified Fatigue Impact Scale (MFIS) is frequently used in clinical and experimental studies to determine the level of fatigue (20). The MFIS consists of a total of 21 questions that evaluate the physical (MFIS-physical), cognitive (MFIS-cognitive), and psychosocial (MFIS-psychosocial) effects of fatigue. Each item is given a score of 0-4, and a low score indicates a low level of fatigue. The Turkish version of the MFIS was found to be valid and reliable (21).

Epworth sleepiness scale (ESS) evaluates the daytime sleepiness of the participants (22). It consists of eight items. The score of each item varies between 0 and 3, and the total score varies between 0 and 24. The higher the total score, the higher the participant's degree of daytime sleepiness. The Turkish version of the ESS was found to be valid and reliable (23).

### Sample Size and Statistical Analysis

For the primary aim of the study, the required sample size was calculated using the OpenEpi program (Version 3.01), assuming that 2,000 pwMS were followed in our unit, and the default pain percentage frequency in the population was calculated as 80%+/−5, with a 95% confidence level, as 220 pwMS (24). In a study evaluating the relationship between pain and fatigue level in pwMS with pain, the variance (R2) was 0.57 (25). In this context, the smallest sample size to be included in the study was calculated using G*Power (version 3.1), which required at least 22 pwMS, with variance (R2) =0.57, power =95%, error probability =0.05, and predictor number =9.

The normal distribution of data was checked using the Kolmogorov-Smirnov test and histograms. Descriptive analyses were presented by giving the mean and standard deviation for continuous variables and numbers and percentages for categorical variables. Hierarchical multivariate linear regression

for continuous variables and numbers and percentages for categorical variables. Hierarchical multivariate linear regression models were structured to explain the relationship between neuropathic pain and EDSS, disease duration, age, daytime sleepiness, anxiety and depression, and fatigue. Significance was set at $p<0.05$. Data were analyzed using the IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA)

## Results

The most frequently reported neuropathic pain areas were the neck (58.6%), foot/ankle (50%), and knee (48.6%) (Figure 1). Table 1 presents the demographic and clinical characteristics of the participants. Table 2 provides two hierarchical multivariate linear regression models to assess the influence of EDSS, disease duration, age, ESS, HAD-A, HAD-D, and MFIS on the severity of neuropathic pain. Although there was no risk factor in step 1, HAD-D and MFIS-Psychosocial subparameter were risk factors of neuropathic pain in step 2. The results revealed that in every 1-point increase in the depression survey, the likelihood of having neuropathic pain increases 0.66 times, and every 1-point increase in the psychosocial parameter of the fatigue survey, the likelihood of having neuropathic pain increases 2.12 times ($p<0.05$).

## Discussion

As the main findings of this study, neuropathic pain was the most common in the neck (58.6%), foot/ankle (50%), and knee (48.6%) areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS. In this study, we collected data by the online survey method. In a study investigating chronic pain phenotypes in pwMS across the country, data were collected using an online questionnaire, similar to our research method (10).

Considering the results of previous studies, no association was found between pain and clinical and demographic characteristics of pwMS such as EDSS, disease duration, age, and sex (13,15,26,27). According to our results, no significant relationship exists between pain and sex, disease duration, age, and EDSS. We hypothesized that these mixed results could indicate the nature of pain. Since it is a subjective symptom, it varies among patients, and the definition of pain may be different (28).

Neuropathic pain in pwMS is persistent, and one of the most common bothersome symptoms that occur even in the early stages of the disease (7,29). PwMS complain of various neuropathic pain symptoms. The most common neuropathic

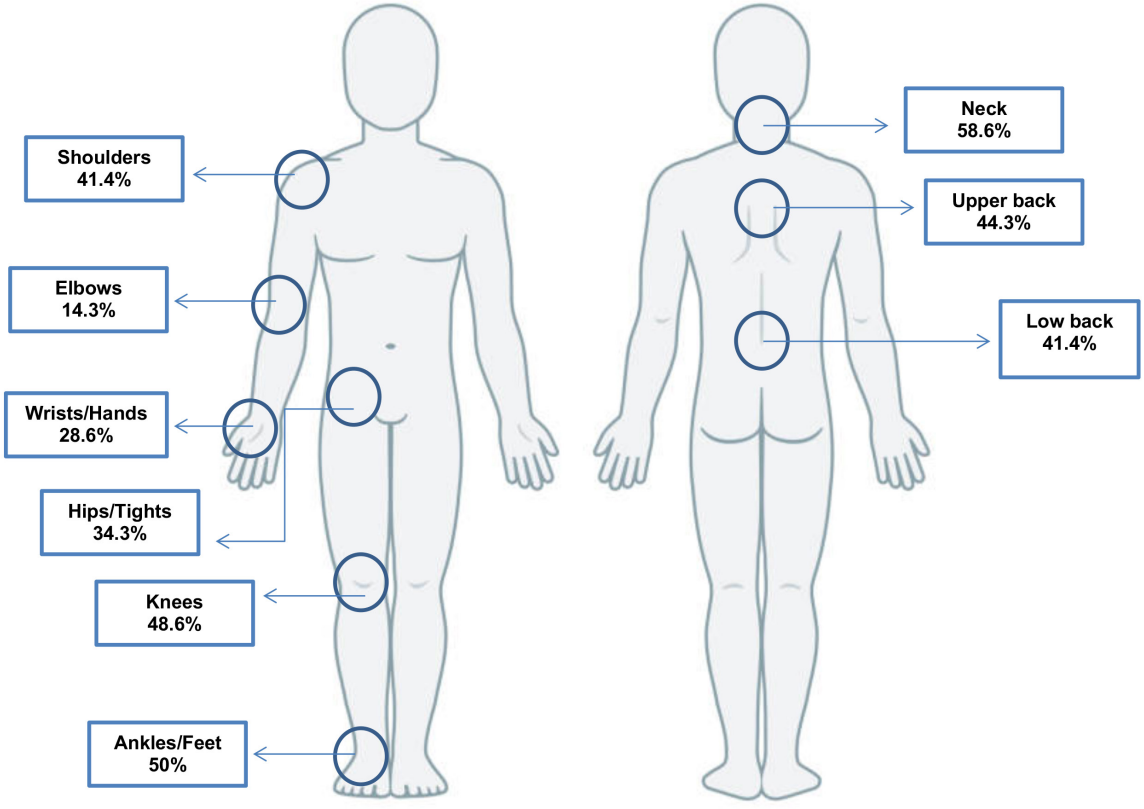


**Figure 1.** Neuropathic pain among body areas in patients with multiple sclerosis

pain conditions associated with MS include dysesthetic pain and paroxysmal pain (L'hermitte phenomenon and trigeminal neuralgia) (7,30,31). Neuropathic pain types appear to be more common in pwMS than in the general population (32). The most common type of neuropathic pain seen in pwMS is dysesthetic limb pain, with a prevalence of 12-28% (33,34). Common examples of dysesthetic pain in MS include tingling, burning, and pain, mostly in the feet and legs, which is usually aggravated at night and with physical activity (7,31,35). Chronic dysesthesias are typically less intense, but their permanent nature can be challenging for the patient (36). When the distribution of neuropathic pain according to body areas was examined, 50% of neuropathic pain was reported in the foot and ankle area and 48.6% in the knee area. The foot/ankle and knee areas ranked second and third as the most common neuropathic pain areas reported by the participants. Frequent reporting of neuropathic pain in the lower extremities by the participants is thought to be associated with dysesthetic pain.

**Table 1. Demographic and clinical characteristics of the participants (n=70)**

| | |
|---|---|
| Age (years) | 36.9 (30.55-46.0) |
| **Sex** | |
| Female | 53 (75.7%) |
| Male | 17 (24.3%) |
| **Level of education** | |
| Secondary school | 7 (10%) |
| High school | 20 (28.6%) |
| University | 36 (51.4%) |
| **Marital status** | |
| Married | 53 (75.7%) |
| Single | 15 (21.4%) |
| Divorced/widowed | 2 (2.9%) |
| **Employment status** | |
| Unemployed | 19 (27.1%) |
| Employed | 43 (61.4%) |
| Retired | 5 (7.1%) |
| Student | 3 (4.3%) |
| EDSS | 1.5 (1.0-2.5) |
| Disease duration (years) | 9.0 (3.0-14.25) |
| ESS | 7.0 (4.0-10.0) |
| HADS-A | 12.5 (10.0-14.0) |
| HADS-D | 9.0 (7.25-10.0) |
| MFIS-Cognitive | 4.0 (3.0-5.0) |
| MFIS-Physical | 5.0 (3.0-6.0) |
| MFIS-Psychosocial | 2.0 (1.0-3.0) |
| MFIS-Total | 11.0 (7.75-14.0) |

Values are presented as number and percent, except age, disease duration, EDSS, ESS, HADS-A, HADS-D, MFIS-Cognitive, MFIS-Psychosocial, MFIS-Total, which are presented as median and interquartile range.

EDSS: Expanded Disability Status Scale, ESS: Epworth sleepiness scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, MFIS: Modified Fatigue Impact Scale

The L'hermitte phenomenon is one of the most common pain symptoms examined in neuropathic pain types in pwMS. The prevalence of the phenomenon ranges from 9% to 41% in pwMS (37). The L'hermitte phenomenon is defined as a temporary, short-term paroxysmal electrical sensation that starts from the neck and spreads to the lower extremities and is usually related to neck movement. In the present study, 58.6% of neuropathic pain cases occured in the neck area. Research results suggest that neuropathic pain, which is frequently reported in the neck area, may be compatible with the L'hermitte phenomenon.

Pain affects pwMS more than other neurological conditions. Studies have shown that pain in MS is highly correlated with fatigue, depression, and anxiety (38-40). In addition, studies have stated that pain in MS negatively affects the quality of life, sleep quality, daily life activities, social functionality, and work-life of pwMS (7,41).

Depression is a common psychiatric diagnosis in people with chronic neuropathic pain and affects approximately 57% of individuals with chronic neuropathic pain (42). The prevalence of depression in the general population ranges from 4% to 8% (42). However, the risk of depression in patients with chronic pain is 2-5 times greater than that in the general population (43). Studies have found that neuropathic pain is associated with disability and depression in pwMS (44). According to our research results, in every 1-point increase in the depression survey, the likelihood of having neuropathic pain increases 0.66 times.

Limited studies have reported a significant relationship between pain and fatigue in pwMS (4,15). In addition, in the present study, similar to previous studies, every 1-point increase in the psychosocial parameter of fatigue survey increases the likelihood of having neuropathic pain 2.12 times. A previous study found that pain is associated with a higher level of sleepiness in pwMS (15). In our study, sleepiness did not significantly affect the presence of neuropathic pain. Studies with a large sample size are needed to investigate the effect of neuropathic pain on the level of sleepiness.

In this study, neuropathic pain frequently occurs in the neck, foot/ankle, and knee areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS.

### Study Limitations

This study has several limitations. First, given the retrospective nature of this study, the results obtained are not conclusive. Second, the presence of neuropathic pain was diagnosed by

**Table 2. Risk factors on the severity of neuropathic pain**

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| **Risk Factors** | **SCB** | **95% CI** | **p-value** | **SCB** | **95% CI** | **p-value** |
| EDSS score | 0.473 | -0.777 to 1.522 | 0.518 | -0.023 | -1.190 to 1.027 | 0.883 |
| Disease duration | -0.049 | -0.228 to 0.212 | 0.941 | -0.006 | -0.214 to 0.205 | 0.968 |
| Age | -0.018 | -0.130 to 0.171 | 0.781 | -0.059 | -0.166 to 0.115 | 0.713 |
| ESS | | | | -0.100 | -0.357 to 0.174 | 0.491 |
| HADS-A | | | | -0.144 | -0.549 to 0.188 | 0.329 |
| HADS-D | | | | 0.665 | 0.130 to 1.199 | **0.016** |
| MFIS-Cognitive | | | | -0.019 | -1.681 to 1.588 | 0.955 |
| MFIS-Psychosocial | | | | 2.124 | 0.007 to 4.240 | **0.025** |
| MFIS-Total | | | | -0.255 | -1.125 to 0.614 | 0.557 |

Significant p-values are presented in bold. EDSS: Expanded Disability Status Scale, ESS: Epworth Sleepiness Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, MFIS: Modified Fatigue Impact Scale, CI: Confidence interval, SCB: Standardized coefficients beta

areas were not evaluated.

## Conclusion

The results of this study reveal that neuropathic pain is frequently seen in the neck (58.6%), foot/ankle (50%), and knee (48.6%) areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Ethics Board of Dokuz Eylul University (decision number: 2022/29-02, date: 14.09.2022).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

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

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

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## References

1. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. JAMA 2021;325:765-779.
2. Di Cara M, Lo Buono V, Corallo F, Cannistraci C, Rifici C, Sessa E, D'Aleo G, Bramanti P, Marino S. Body image in multiple sclerosis patients: a descriptive review. Neurol Sci 2019;40:923-928.
3. Macías Islas MÁ, Ciampi E. Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. Biomedicines 2019;7:22.
4. Motl RW, McAuley E, Snook EM, Gliottoni RC. Physical activity and quality of life in multiple sclerosis: intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. Psychol Health Med 2009;14:111-124.
5. Zwibel HL. Contribution of impaired mobility and general symptoms to the burden of multiple sclerosis. Adv Ther 2009;26:1043-1057.
6. Kerns RD, Kassirer M, Otis J. Pain in multiple sclerosis: a biopsychosocial perspective. J Rehabil Res Dev 2002;39:225-232.
7. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. Pain 2008;137:96-111.
8. Foley PL, Vesterinen HM, Laird BJ, Sena ES, Colvin LA, Chandran S, MacLeod MR, Fallon MT. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. Pain 2013;154:632-642.
9. Truini A, Galeotti F, La Cesa S, Di Rezze S, Biasiotta A, Di Stefano G, Tinelli E, Millefiorini E, Gatti A, Cruccu G. Mechanisms of pain in multiple sclerosis: a combined clinical and neurophysiological study. Pain 2012;153:2048-2054.
10. Kratz AL, Whibley D, Alschuler KN, Ehde DM, Williams DA, Clauw DJ, Braley TJ. Characterizing chronic pain phenotypes in multiple sclerosis: a nationwide survey study. Pain 2021;162:1426-1433.
11. Merskey H. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Pain 1986;Suppl 3:226.
12. Solaro C, Trabucco E, Messmer Uccelli M. Pain and multiple sclerosis: pathophysiology and treatment. Curr Neurol Neurosci Rep 2013;13:320.
13. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis--prevalence and clinical characteristics. Eur J Pain 2005;9:531-542.
14. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-173.
15. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911-1920.
16. Alkan H, Ardic F, Erdogan C, Sahin F, Sarsan A, Findikoglu G. Turkish version of the painDETECT questionnaire in the assessment of neuropathic pain: a validity and reliability study. Pain Med 2013;14:1933-1943.
17. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes 2003;1:29.

16. Alkan H, Ardic F, Erdogan C, Sahin F, Sarsan A, Findikoglu G. Turkish version of the painDETECT questionnaire in the assessment of neuropathic pain: a validity and reliability study. Pain Med 2013;14:1933-1943.
17. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes 2003;1:29.
18. Aydemir Ö, Guvenir T, Kuey L, Kultur S. Validity and reliability of Turkish version of hospital anxiety and depression scale. Turk Psikiyatri Dergisi 1997;8:280-287.
19. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994;18 Suppl 1:S79-83.
20. Armutlu K, Keser I, Korkmaz N, Akbiyik DI, Sümbüloğlu V, Güney Z, Karabudak R. Psychometric study of Turkish version of Fatigue Impact Scale in multiple sclerosis patients. J Neurol Sci 2007;255:64-68.
21. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
22. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath 2008;12:161-168.
23. ShayestehAzar M, Kariminasab MH, Saravi MS, Abedini M, Fazli M, Hashemi SA, Abdizadeh P. A Survey of Severity and Distribution of Musculoskeletal Pain in Multiple Sclerosis Patients; a Cross-Sectional Study. Arch Bone Jt Surg 2015;3:114-118.
24. Amtmann D, Askew RL, Kim J, Chung H, Ehde DM, Bombardier CH, Kraft GH, Jones SM, Johnson KL. Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. Rehabil Psychol 2015;60:81-90.
25. Beiske AG, Pedersen ED, Czujko B, Myhr KM. Pain and sensory complaints in multiple sclerosis. Eur J Neurol 2004;11:479-482.
26. Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler 2005;11:322-327.
27. Kahraman T, Özdoğar AT, Ertekin Ö, Özakbaş S. Frequency, type, distribution of pain and related factors in persons with multiple sclerosis. Mult Scler Relat Disord 2019;28:221-225.
28. Williams ACC, Craig KD. Updating the definition of pain. Pain 2016;157:2420-2423.
29. Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. Lancet Neurol 2010;9:1182-1199.
30. Truini A, Barbanti P, Pozzilli C, Cruccu G. A mechanism-based classification of pain in multiple sclerosis. J Neurol 2013;260:351-367.
31. Khan N, Smith MT. Multiple sclerosis-induced neuropathic pain: pharmacological management and pathophysiological insights from rodent EAE models. Inflammopharmacology 2014;22:1-22.
32. Vacca G, Marano E, Brescia Morra V, Lanzillo R, De Vito M, Parente E, Orefice G. Multiple sclerosis and headache co-morbidity. A case-control study. Neurol Sci 2007;28:133-135.
33. Nurmikko TJ, Gupta S, Maclver K. Multiple sclerosis-related central pain disorders. Curr Pain Headache Rep 2010;14:189-195.
34. Truini A, Galeotti F, Cruccu G. Treating pain in multiple sclerosis. Expert Opin Pharmacother 2011;12:2355-2368.
35. Osterberg A, Boivie J. Central pain in multiple sclerosis - sensory abnormalities. Eur J Pain 2010;14:104-110.
36. Solaro C, Lunardi GL, Mancardi GL. Pain and MS. Int MS J 2003;10:14-19.
37. Nurmikko TJ, Gupta S, Maclver K. Multiple sclerosis-related central pain disorders. Curr Pain Headache Rep 2010;14:189-195.
38. Marck CH, De Livera AM, Weiland TJ, Jelinek PL, Neate SL, Brown CR, Taylor KL, Khan F, Jelinek GA. Pain in People with Multiple Sclerosis: Associations with Modifiable Lifestyle Factors, Fatigue, Depression, Anxiety, and Mental Health Quality of Life. Front Neurol 2017;8:461.
39. Solaro C, Gamberini G, Masuccio FG. Depression in Multiple Sclerosis: Epidemiology, Aetiology, Diagnosis and Treatment. CNS Drugs 2018;32:117-133.
40. Heitmann H, Haller B, Tiemann L, Mühlau M, Berthele A, Tölle TR, Salmen A, Ambrosius B, Bayas A, Asseyer S, Hartung HP, Heesen C, Stangel M, Wildemann B, Haars S, Groppa S, Luessi F, Kümpfel T, Nischwitz S, Meuth SG, Klotz L, Linker RA, Zettl UK, Ziemann U, Tumani H, Tackenberg B, Zipp F, Wiendl H, Gold R, Hemmer B, Ploner M; German Competence Network Multiple Sclerosis (KKNMS). Longitudinal prevalence and determinants of pain in multiple sclerosis: results from the German National Multiple Sclerosis Cohort study. Pain 2020;161:787-796.
41. Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. Mult Scler 2006;12:629-638.
42. Fasick V, Spengler RN, Samankan S, Nader ND, Ignatowski TA. The hippocampus and TNF: Common links between chronic pain and depression. Neurosci Biobehav Rev 2015;53:139-159.
43. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. JAMA 1998;280:147-151.
44. Toosy A, Ciccarelli O, Thompson A. Symptomatic treatment and management of multiple sclerosis. Handb Clin Neurol 2014;122:513-562.

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BRIEF REPORT

# Neuromyelitis Optica Following COVID-19 Infection

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## Abstract

The coronavirus disease-2019 (COVID-19) may be a trigger for acquired demyelinating central or peripheral nervous system disorders like other viral infections. We present a clinical image of a patient who was diagnosed with neuromyelitis optica (NMO) following COVID-19 infection. A 25-year-old woman presented with progressive loss of strength and numbness in her left upper extremity and bilateral lower extremities and sphincter involvement on the second week of isolation. Spinal magnetic resonance imaging revealed extensive long-segment demyelinating lesion. NMO-immunoglobulin G antibody was positive. It is one of the first cases of long extensive transverse myelitis with seropositivity among the long-segment myelitis cases in the literature.

**Keywords:** COVID-19, longitudinally extensive transverse myelitis, neuromyelitis optica

## Clinical Image

A 25-year-old woman was admitted to our emergency department for evaluation, with a 1-week history of progressive loss of strength and numbness in her left upper extremity and bilateral lower extremities and urinary retention. Her past medical history was remarkable for 5-day hospital admission and an isolation period at home for 2 weeks because of COVID-19 infection. Her neurological symptoms appeared in the second week of self-isolation. Thoracic computed tomography revealed diffuse infiltration areas and ground-glass opacities of both lungs (Figure 1).

At the time of assessment, she was alert and fully oriented. All cranial nerve functions were intact. Motor system examination was significant for left hemiparesis, hyperreflexia in the lower extremities with a positive Hoffman sign on the right side, and bilaterally positive Babinski sign. She had diminished sensation in the lower extremities, which was more prominent on the left side. A Foley catheter was inserted, and a half-liter of urine was drained. Her complete blood count, routine biochemistry, and C-reactive protein were all normal. Brain magnetic resonance imaging (MRI) findings were normal. Spinal MRI revealed long-segment signal alteration and cord expansion from C2 to C8 in T2-weighted sequences (Figure 2 A, B), consistent with longitudinally extensive transverse myelitis (LETM). A thorough workup was performed for possible causes of LETM. Lumbar puncture revealed lymphocytic pleocytosis with white blood cell count of 323 and high protein levels (149.1 mg/dL; normal range, up to 45 mg/dL). Infectious workups all returned negative. The immunoglobulin G (IgG) index was negative, and oligoclonal bands were absent. Laboratory studies used during workups for vasculitis and paraneoplastic diseases

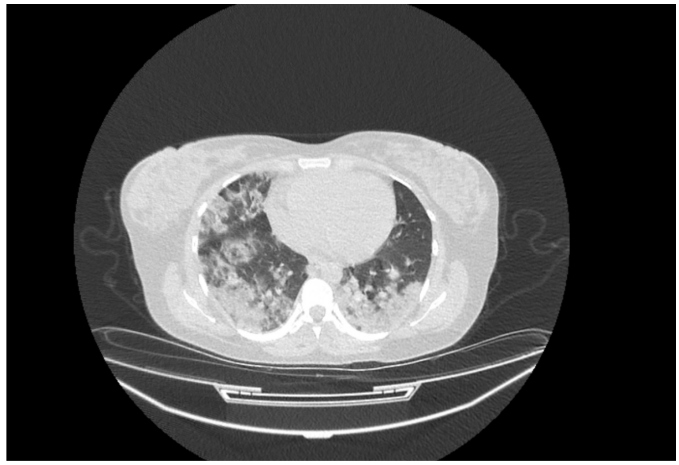

**Figure 1.** Infiltrations compatible with COVID-19 in thoracic computed tomography

COVID-19: Coronavirus disease-2019

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**Received:** 01.04.2022 **Accepted:** 13.06.2022

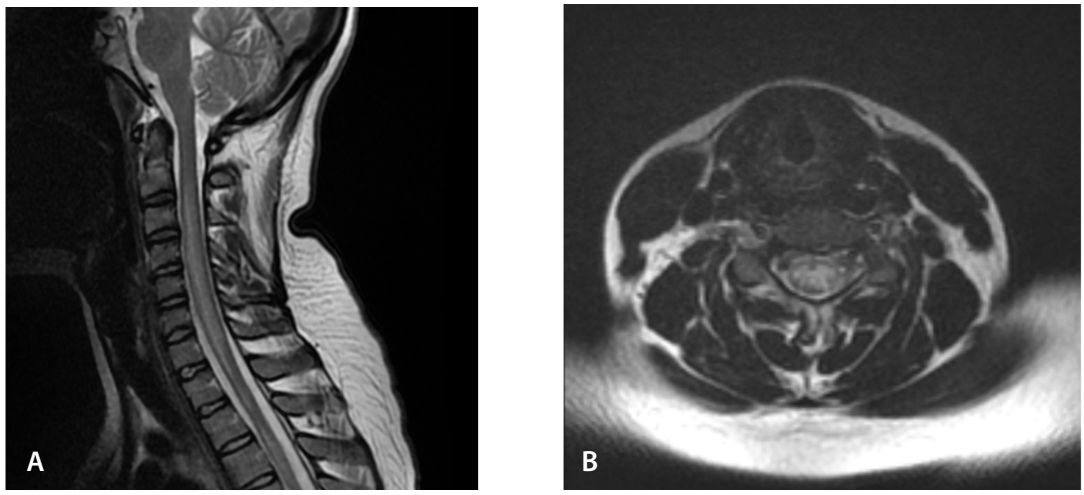


**Figure 2.** T2-weighted sequences: (A) sagittal plane and (B) axial plane of longitudinally extensive lesion from C2 to C8 vertebrae

were negative. The test for neuromyelitis optica-IgG (NMO-IgG) antibody was positive, whereas MOG-IgG antibody was negative.

Her diagnosis was based on NMO spectrum disorder diagnostic criteria by having LETM confirmed by MRI and high NMO-IgG antibody levels. Subsequently, she was started on a high-dose (1 g/day) intravenous methylprednisolone (IVMP) regimen. On day 2 of IVMP infusion, she developed quadriplegia and was taken up for plasmapheresis. In total, five sessions of plasmapheresis were performed (every other day). IVMP infusion was also given for 10 days, followed by an oral regimen with progressive improvement of muscle strength. Rituximab maintenance therapy was initiated during follow-up.

Considerable neurological manifestations of COVID-19 are reported in the literature during the pandemic (1). Among these manifestations, spinal cord demyelination is an under-recognized neurological complication (2,3). To the best of our knowledge, this is the third report of an LETM case with seropositivity in favor of NMO among few long-segment myelitis cases in the literature (4,5). In this case, the interval of 3 weeks between the onset of COVID-19 symptoms and neurological symptoms supports post-COVID NMO reactivity in terms of secondary immunogenic reaction.

Several pathogenetic mechanisms are hypothesized for the pathogenesis of parainfectious NMO, such as molecular mimicry, bystander activation, and exacerbation of subclinical disease by systemic infection. In the case of molecular mimicry, antibodies that recognize both the microbial and self-epitopes are produced by activated B cells. In bystander activation, aquaporin-4 (AQP4) (which is the target antigen of NMO-IgG)-specific T and B cells are activated because AQP4-rich tissues are destroyed by microbes and increased self-antigen presentation (6). This mechanism is likely for seropositive parainfectious NMO cases.

In conclusion, NMO should be considered in the differential diagnosis for patients with COVID-19 who present with LETM or vice versa. Establishing an early diagnosis and treatment strategy for improved outcomes is critical.

### Ethics

**Peer-review:** Externally peer-reviewed.

**Informed Consent:** Informed consent was obtained from the patient included the study.

### Authorship Contributions

Surgical and Medical Practices: D.C.T., I.G.D., S.D., Concept: D.C.T., I.G.D., Design: D.C.T., S.D., Data Collection or Processing: D.C.T., I.G.D., Literature Search: D.C.T., I.G.D., S.D., Writing: D.C.T., I.G.D.

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

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## References

1. Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol 2021;268:3059-3071.
2. Mondal R, Deb S, Shome G, Ganguly U, Lahiri D, Benito-León J. COVID-19 and emerging spinal cord complications: A systematic review. Mult Scler Relat Disord 2021;51:102917.
3. Arslan D, Acar-Ozen P, Gocmen R, Elibol B, Karabudak R, Tuncer A. Post-COVID-19 longitudinally extensive transverse myelitis: is it a new entity? Neurol Sci 2022;43:1569-1573.
4. Shaw VC, Chander G, Puttanna A. Neuromyelitis optica spectrum disorder secondary to COVID-19. Br J Hosp Med (Lond) 2020;81(9):1-3.
5. Batum M, Kisabay Ak A, Mavioğlu H. Covid-19 infection-induced neuromyelitis optica: a case report. Int J Neurosci 2020;1-7.
6. Sellner J, Hemmer B, Mühlau M. The clinical spectrum and immunobiology of parainfectious neuromyelitis optica (Devic) syndromes. J Autoimmun 2010;34:371-379.

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CASE REPORT

# Altitudinal Visual Defect as the Initial Sign of Optic Neuritis: A Case Report

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## Abstract

Optic neuritis (ON) is the most common optic neuropathy in adults and is frequently seen together with multiple sclerosis, manifesting itself mainly as painful diffuse field loss or central scotomas. However, it could be encountered in various other inflammatory, demyelinating, infectious, and autoimmune conditions that could be broadly classified into two groups: typical and atypical ON. On the contrary, painless vision loss, especially altitudinal visual field defects (AVD), is commonly observed in ischemic optic neuropathies (ION), mostly in patients with vascular risk factors or history of giant cell arteritis. Although rare, AVD can be the initial sign of ON and inflammatory demyelinating process. Herein, we report a case of a 17-year-old patient with ON presenting with painless AVD and provide a brief review of the mechanisms involved in typical and atypical ON and ION.

**Keywords:** Optic neuritis, ischemic optic neuropathy, altitudinal visual defect

## Introduction

Optic neuritis (ON) is the most common optic neuropathy in young adults and is characterized by the inflammation of the optic nerve. ON is seen in various demyelinating, infectious, and inflammatory conditions. Typical ON is generally associated with multiple sclerosis (MS), which manifests as painful subacute vision loss. On the contrary, ischemic optic neuropathies (ION) result in painless monocular vision loss with altitudinal visual field defects (AVD), commonly seen in older people with vascular risk factors. Herein, we present the case of a young female patient with painless AVD as the initial sign of ON and provide a brief review of ON and ION.

## Case Report

A 17-year-old previously healthy female patient comes to the clinic due to blurry vision on her right eye that suddenly occurred two days ago. Eye movements were not painful, and she had no headache or any other neurological symptoms. She had no history of trauma and denied any recent infections, fever, or constitutional symptoms. Both her medical and family histories were unremarkable.

A detailed neurological examination was performed. Both direct and indirect pupillary light reflexes were normal; however, she had a mild relative afferent pupil defect on her right eye. Other cranial nerves and results of motor, sensory, and cerebellar examinations were normal. During the examination, she stated that for the last few days she would feel an electrical-like sensation extending down her spine when she flexed her neck, which was suggestive of Lhermitte's sign. On her ophthalmological examination, her intraocular pressure was normal, no signs of anterior compartment pathologies, retinitis, or vitritis were noted, and the optic disc was normal. Her visual acuity was 20/20 for both eyes on the Snellen chart. However, her visual field test revealed superior AVD in the right eye (Figure 1).

Complete blood count, $B_{12}$ levels, comprehensive metabolic panel, erythrocyte sedimentation rate, angiotensin-converting enzyme level, and urinalysis parameters were in the normal range. *Borrelia*, *Treponema*, human T-cell leukemia virus, and human immunodeficiency virus serology were negative. Results of a wide range of autoantibody tests were normal. Chest X-ray imaging excluded infections and connective tissue

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disorders, and the findings were normal. A lumbar puncture was performed. The cerebrospinal fluid (CSF) was clear, with a normal opening pressure. CSF biochemistry and cytology were normal. Anti-aquaporin-4 antibody was found to be negative both in the CSF and serum. Anti-myelin oligodendrocyte glycoprotein immunoglobulin G (IgG) was negative. Nonetheless, CSF electrophoresis revealed oligoclonal bands, and the IgG index was 0.78. Visual evoked potential (VEP) revealed delayed P100 latency of the right eye. Cranial magnetic resonance imaging (MRI) demonstrated single ovoid hyperintensity perpendicular to the corpus callosum and contrast enhancement of the retroorbital segment of the right optic nerve, compatible with ON (Figure 2). The patient was admitted to the inpatient clinic and received 5 days of intravenous methylprednisolone 1,000 mg/day. After one month, the patient's vision was fully recovered, and her ophthalmological examination was completely normal. She had no other neurological deficits. Six months later, the follow-up MRI revealed new non-contrast enhancing hyperintense lesions in the right parietal white matter and C3-C4 vertebral level. Written informed consent of the patient was obtained.

## Discussion

ON occurs through different mechanisms that could be categorized into two distinct groups: typical ON and atypical ON. The hallmark of typical ON is acute inflammatory demyelination, followed by axonal loss in the long term (1). It is mostly associated with MS; essentially, ON is the initial presentation in 20% of the MS, and 50% of patients with MS experienced ON during the disease course (2). Although its pathophysiological mechanism has not been fully elucidated, peripheral T-cell activation and migration toward the blood-brain barrier is thought to initiate this inflammatory process. This activation leads to a type 4 hypersensitivity-like reaction and results in myelin damage and axonal degeneration (3).

More than 90% of typical ON presents with painful monocular vision loss. Dyschromatopsia, reduced contrast acuity, and central visual defects are also among the common presentations of ON. According to the ON treatment trial, 97.5% of the patients experienced visual field defects, central scotomas being the most common entity, at some point of the disease course (4). Vision loss varies, ranging from mild to complete loss, can last up to 6 months, and mostly reaches its peak within two weeks after onset. It manifests mostly as retrobulbar neuritis in which the optic disc is normal or rarely as papillitis which involves the anterior optic nerve and results in disc swelling (5).

On the contrary, atypical ON is mostly caused by neuromyelitis optica spectrum disorders (NMOSD), other rare inflammatory conditions, and systemic diseases such as lupus, sarcoidosis, or Wegener's granulomatosis (3). NMOSD mostly presents with unilateral, sometimes bilateral rapidly sequential vision loss with painful eye movements. Although AVDs can be encountered in NMOSD, it is much more extensive, extending to the optic chiasm and optic tracts, and vision loss is much more persistent (6).

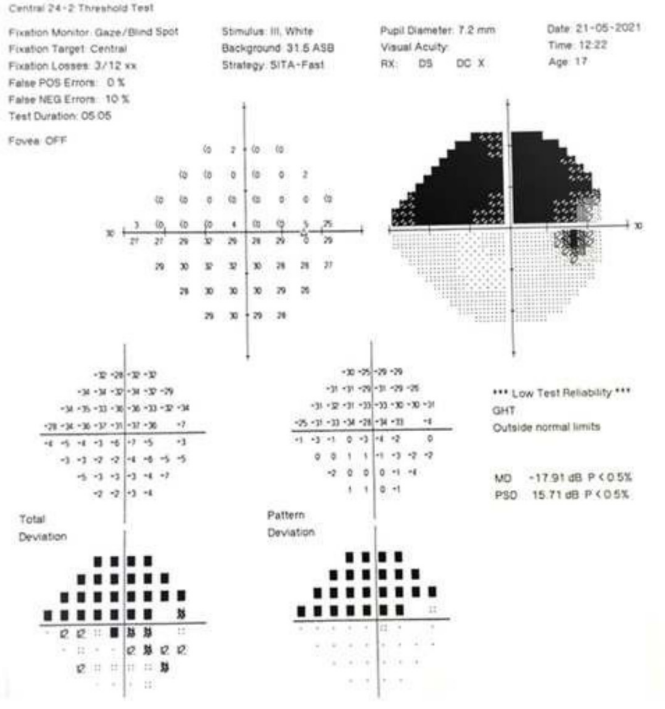


**Figure 1.** Visual field test revealing right superior altitudinal visual field defect

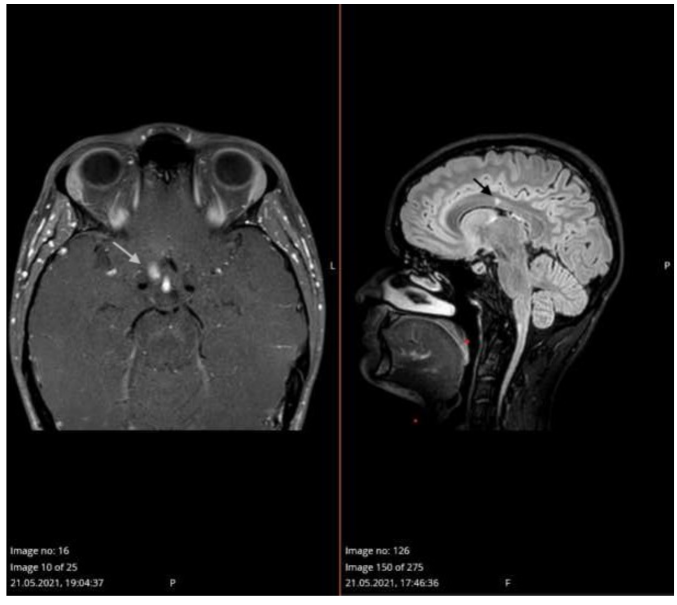


**Figure 2.** Orbital MRI showing contrast enhancing lesion in the right optic nerve (left) and cranial sagittal MRI showing single ovoid hyperintensity perpendicular to the corpus callosum (right) in T2-weighted images

MRI: Magnetic resonance imaging

Painless unilateral vision loss with AVD mostly suggests ION. Anterior ION (AION) is the most common cause of vision loss in older people and is divided into arteritic and non-arteritic (7). Arteritic AION is almost always seen with giant cell arteritis, whereas non-arteritic AION is seen in patients with vasculopathic risk factors such as diabetes, hypercholesterolemia, and hypertension. Fundoscopic examination typically reveals optic disc edema. Taken together, our patient's age, medical history, and fundoscopic examination are not compatible with AION. Although posterior ION presents with normal optic disc findings, as observed in our patient, the absence of recent ocular surgery or history of giant cell arteritis excludes this diagnosis (8).

At her initial admission, her MRI findings did not fulfill the McDonald criteria; however, the positive findings on her follow-up MRIs in the subsequent year, together with CSF, VEP, and laboratory findings, raised strong suspicion for MS.

## Conclusion

Although the painless nature of the visual loss and its characteristic findings mostly suggest an ischemic or vasculitis cause, our patient represents a rare phenomenon. This case emphasized that AVDs should be considered in the decision-making process and could be observed as the foremost findings of an inflammatory process.

### Ethics

**Informed Consent:** Written informed consent of the patient was obtained.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: R.C.A., H.S., Design: R.C.A., C.B., S.C., H.S., Data Collection or Processing: R.C.A., C.B., H.S., Analysis or Interpretation: R.C.A., H.S., Literature Search: R.C.A., C.B., H.S., Writing: R.C.A., S.C., H.S.

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## References

1. Toosy AT, Mason DF, Miller DH. Optic neuritis. Lancet Neurol 2014;13:83-99.
2. Kale N. Optic neuritis as an early sign of multiple sclerosis. Eye Brain 2016;8:195-202.
3. Pau D, Al Zubidi N, Yalamanchili S, Plant GT, Lee AG. Optic neuritis. Eye (Lond) 2011;25:833-842.
4. Frohman EM, Frohman TC, Zee DS, McColl R, Galetta S. The neuro-ophthalmology of multiple sclerosis. Lancet Neurol 2005;4:111-121.
5. Wilhelm H, Schabet M. The Diagnosis and Treatment of Optic Neuritis. Dtsch Arztebl Int 2015;112:616-625; quiz 626.
6. Levin MH, Bennett JL, Verkman AS. Optic neuritis in neuromyelitis optica. Prog Retin Eye Res 2013;36:159-171.
7. Morrow MJ. Ischemic Optic Neuropathy. Continuum (Minneap Minn) 2019;25:1215-1235.
8. Atkins EJ, Bruce BB, Newman NJ, Biousse V. Treatment of Nonarteritic Anterior ischemic optic neuropathy. Sur Ophthalmol 2010;55:47-63.