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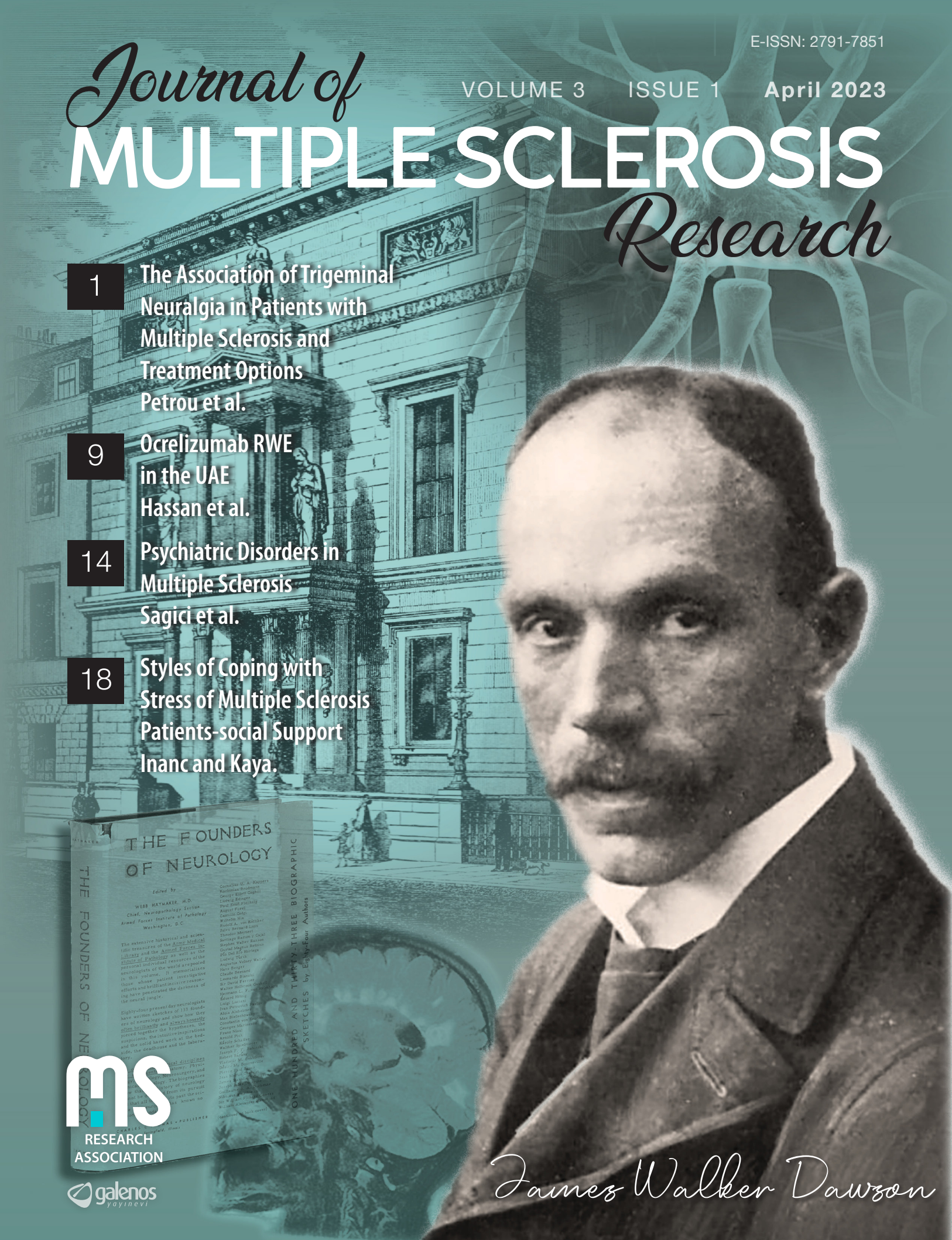

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ABOUT US

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

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

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

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

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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).

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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.

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

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

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

Abstract

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

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

Materials and Methods: Important methods should be written respectively.

Results: Important findings and results should be provided here.

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

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

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

1. Original Articles:

An article is considered original research if;

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

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

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Original articles should have the following sections:

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

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

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

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

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

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

Conclusion: The conclusion of the study should be highlighted.

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

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

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

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

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

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.

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

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

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

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All authors are responsible for the manuscript's content.

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

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

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

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

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

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

Ethics

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

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REVİEW

RESEARCH ARTICLES

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Journal of Multiple Sclerosis Research 2023;3(1):1-8

REVIEW

Association of Trigeminal Neuralgia with Multiple Sclerosis: A Comprehensive Review of Neuropathic Pain Treatment

Chrysoula Petrou[1], Anestakis Doxakis[2], Marissa A. Barrera[3], Polyanthi Konstantinidou[4]

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Abstract

This comprehensive review aimed to evaluate the association between trigeminal neuralgia and multiple sclerosis (MS). Neuropathic pain was analyzed, and trigeminal neuralgia and MS were compared. Pharmacological and surgical treatments for trigeminal neuralgia in patients with MS were explored in detail. The inclusion criteria were as follows: (1) studies of (2) adult participants with trigeminal neuralgia caused by MS, (3) employing pharmacological or surgical interventions and (4) evaluating outcomes related to pain reduction. Carbamazepine or oxcarbazepine is the first-line drug, and lamotrigine, baclofen, gabapentin, and pregabalin are second-line drugs. If the drug cannot control the pain, surgical options must be considered. The surgical procedures include surgical removal of peripheral lesions that are distal to the ganglion, percutaneous gasserian ganglion surgery, stereotactic radiosurgery, and microvascular decompression in the posterior fossa. Owing to the scarcity of data, medical treatment of a patient with MS-related trigeminal neuralgia is challenging. Initiating pharmacological therapy, followed by surgery, is recommended.

Keywords: Multiple sclerosis, neuropathic pain, pharmacological treatment, trigeminal neuralgia

Introduction

Multiple sclerosis (MS) is a disorder that affects the central nervous system, which is characterized by volatile elaboration and contrasting clinical instantiations. Even if pain is one of the most frequent complications of MS, the existence of trigeminal neuralgia (TN) is rare. This review aimed to evaluate the association between TN and MS. Although analogous studies have been conducted in recent times, it is precious to note new data on remedial and clinical approaches as the wisdom is fleetly evolving.

MS

MS is a degenerative disease that causes nerve fiber demyelination and axonal damage (1). The progression of damaged lesions and plaques in the brain leads to not only motor but also sensory and cognitive-communication impairments (2).

In 2013, 2.3 million people were living with MS globally, whereas in 2020, 2.8 million cases were reported (3). MS has four subtypes: relapsing-remitting (RR), secondary progressive, primary progressive, and progressive-remitting types (4). RRMS occurs in approximately 85% of cases. In addition, >50 signs are related to MS. These symptoms can vary not only in duration but also in severity (4,5). Common symptoms include numbness or weakness in one or more limbs, usually occurring on one side of the body at a time, tingling, electric shock sensation that occurs with certain neck movements, especially when the neck is bent forward (Lhermitte sign), lack of coordination, unsteady gait or inability to walk, and blurred vision. The most prominent signs of MS include intense exhaustion; unhappiness; deficits in bladder, bowel, and sexual function; insensibility and/or sensory excitement in the hands and legs; aches; dizziness; increased muscle tone; agitation; and visual, cognitive, speech, and swallowing problems (4,6,7).

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Many MS-related signs may be managed with medical remedies and multidisciplinary care from a team consisting of neurologists, psychologists, physical, occupational, and speech-language therapists (5). Interferons (IFNs) and glatiramer acetate, which are the first approved treatments, are widely used drugs that relatively reduce the frequency of MS relapses (8). Commonly used complaint-modifying curative agents for MS include ocrelizumab, natalizumab, dimethyl fumarate, teriflunomide, IFN-β, and glatiramer acetate. Mitoxantrone (9) is one of the rarely used complaint-modifying treatments for RMS in recent times, whereas alemtuzumab (10-12) and cladribine (13) are recently approved treatment options and are increasingly used.

Neuropathic Pain

According to the International Association for the Study of Pain, neuropathic pain results from a deficit in the somatosensory nervous system (14). The frequency of habitual pain ranges from 3-17. The prevalence ranges from 3.9 to 42.0/100,000 person-times in patients with post-herpetic neuralgia, from 12.6 to 28.9/100,000 person-times in patients with TN, from 15.3 to 72.3/100,000 person-times in patients with diabetic neuralgia, and from 0.2 to 0.4/100,000 person-times for patients with lingual pharyngeal neuralgia. In addition, neuropathic pain was more common in women (60.5% of cases), peaked at the age of 50-64 years, and was more constantly reported by workers and people from pastoral areas (15).

According to Finnerup en al. (16), the vast majority of patients diagnosed with neuropathic pain complain of continuous or sporadic impulsive pain. Neuropathic pain is often characterized as flaming, shooting, stabbing, pressing, or freezing pain (17,18). Neuropathic pain is typically categorized according to its causative condition. The latest ICD 11th edition classified neuropathic pain into peripheral and central neuropathic pain according to the state of damage or condition, which may be located in the peripheral or central somatosensory nervous system (19).

Tricyclic antidepressants, gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors (duloxetine, and venlafaxine) are the first-line medications. Capsaicin patches, lidocaine patches, and subcutaneous botulinum toxin type A injections are recommended only for peripheral neuropathic pain with mild severity (20). Tramadol and opioids are quite tolerable drugs; however, in general, they are not prescribed to patients with chronic pain (21,22). Most medical treatments often have side effects. Thus, many cases do not progress in the pain scale when receiving these medicines at tolerated doses (20). When monotherapy is partially effective, physicians proceed to combination treatment.

TN

The trigeminal nerve is the fifth cranial nerve. Its main function is to innervate sensory and motor sensations in the face. TN is described as a one-sided, abrupt, shock-like pain in one or more parts of areas innervated by the trigeminal nerve are touched.

TN is divided into classic TN and secondary TN (23). The incidence of TN ranges from 0.03 to 0.3 (24-27). In addition, 2-4% of patients with MS (pwMS) may present with trigeminal symptoms and may be the main feature of the disease in 1-5% of patients. By contrast, 2-14% of patients with TN are also diagnosed with MS (23,24,28-36).

The origin of pain is the trigeminal nerve or the region around it. In 80-90% of cases, the pain is caused by vessels that compress the nerve root in the posterior fossa (37-39). Other conditions may also cause pain, for example, MS causes pain in the root entry zone (REZ) of the trigeminal nerve (40). Initial treatment of TN includes drug treatment with anticonvulsants [carbamazepine (CBZ), oxcarbazepine (OXC), phenytoin, fosphenytoin, baclofen, lamotrigine, pimozide, levetiracetam, gabapentin, pregabalin, clonazepam, valproate, and misoprostol]. If drug treatment fails, the pain persists, or the side effects are unacceptable, the physician needs to consider percutaneous radiation therapy or open surgery (Figure 1). In essence, percutaneous, radiosurgical, and open incisional treatments are more effective in patients with TN type 1. Compared with patients with type 1 TN, those with TN type 2 are more likely to have pain recurrence and a shorter pain-free interval. Patients with secondary AI (e.g., tumors) should be treated for underlying pathology (e.g., resection and tumor decompression) to be relieved from pain. In patients who are not candidates for surgery, drug treatment of secondary TN may be offered for symptom control (41).

MS, TN, and Neuropathic Pain

According to the International Classification of Headache Disorders (42) and the TN classification as presented by the Special Interest Group on Neuropathic Pain, classic TN, caused by vascular contraction leading to morphological acclimation in the trigeminal root, is distinguished by secondary TN, due to an identifiable underpinning neurological complaint and idiopathic TN (43).

Over 15% of cases with TN are classified as secondary TN (44-46) and are analyzed in the presence of anatomical abnormalities stirring the trigeminal nerve in addition to vascular compression, in conjunction with plaques caused by MS, tumors, and cranial base abnormalities. The most commonly comprehensible anomalies are plaques caused by MS. PwMS are 20 times more likely to develop TN (32). This neuropathic pain status is observed in 1.9-4.9% of pwMS (47-51), regardless of the MS type. By contrast, only 2-14% of patients with TN are also diagnosed with MS (49).

Secondary TN caused by MS, like classic and idiopathic traumatic brain injury, presents with abrupt, usually one-sided, sharp, or electric shock-like recurrent pain, which is distributed in one or more branches of the trigeminal nerve. The rough attacks,

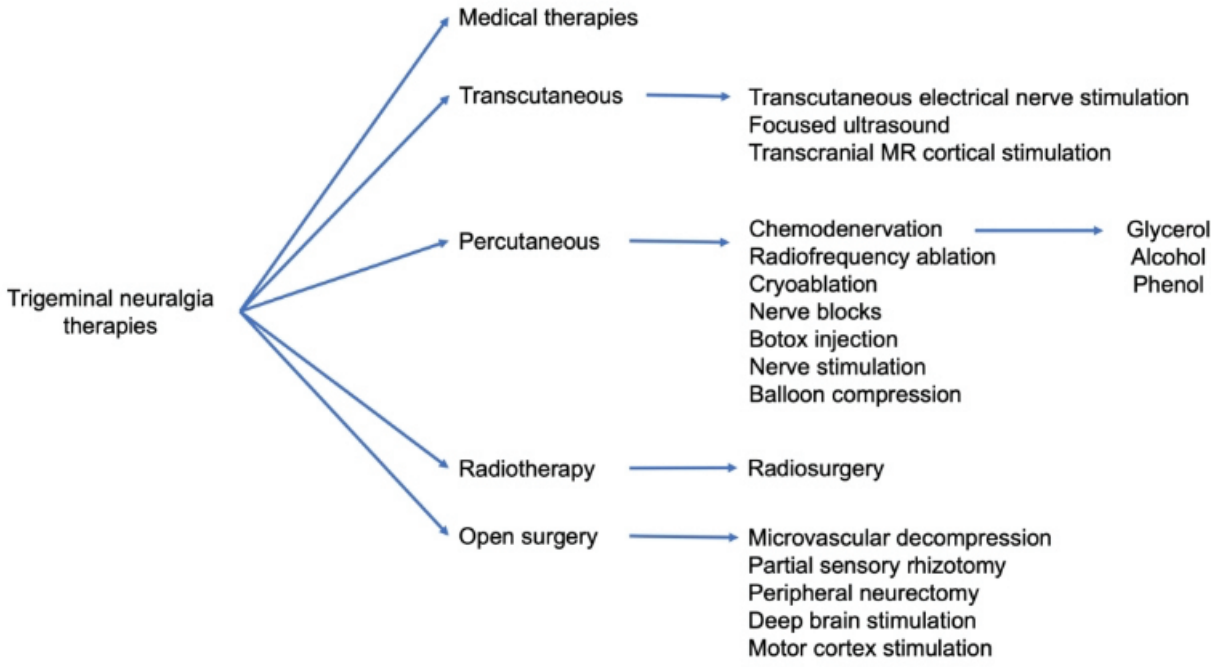

Figure 1. Chart of treatment options for trigeminal neuralgia

which may last from a fraction of a second to 2 min, are usually caused by stimulation of cutaneous or mucosal areas of the trigeminal ganglion called fire chambers.

MS-related TN mostly affects women more than men and mostly on the right side than on the left side (36,52). Still, MS-related TN occurs at a young age in pwMS, with the age of onset between 40 and 50 years (36,52). In MS-related TN, only the first branch may be affected, although the alternate and/or third branch may be affected in approximately 90% of patients (45,46,52). Although signs of MS-related TN resemble those of classic TN, pwMS more often experience bilateral pain. In particular, 18% of pwMS exhibit bilateral TN (36,52). Clinical preferences in sensitive places, which are clear locations of secondary TN, were observed in 37 patients with secondary TN (45,47). Although a younger age and trigeminal sensitivity are related to a high risk of secondary TN and should be regarded as helpful in differentiating secondary TN from classic TN, the lack of these clinical signs does not count TN secondary to MS (53,47). Secondary TN in MS is considered associated with murine demyelinating plaque.

Methods

This review addressed the question of whether pharmacological or surgical treatment is more beneficial in pwMS and TN. Fifty-seven studies were included (17 focused on pharmacological treatment and 40 on surgical treatment). Literature studies were searched in PubMed, Springer Link, Neurology.org, JAMA Neurology, and Journal of Neurosurgery databases. Data recorded between 1966 and 2022 were collected, and the following keywords were also used in the search: neuropathic pain, MS, medications for TN, and surgeries for TN.

So far, no placebo-controlled trials have been conducted. Current studies include small, open-label trials focused on therapies with gabapentin, topiramate, CBZ, misoprostol, lamotrigine, or their combination (23,24,30,32,54-66). These reported cases imply the efficacy of lamotrigine as monotherapy or in combination with gabapentin or CBZ, topiramate, and gabapentin (32). Initial treatment, as in classical and idiopathic TN, is grounded on the use of sodium-channel blockers, namely, CBZ and OXC (67,68).

For pwMS in whom pharmacologic therapy failed, percutaneous, surgical, and radiosurgical options are available. Surgical procedures include surgical removal of peripheral lesions distal to the ganglion, percutaneous techniques at the gasserian ganglion, stereotactic radiosurgery (SRS), and microvascular decompression (MVD) in the posterior fossa (69-71). The main surgical methods include surgical removal of peripheral lesions of the terminal trigeminal nerves at their exit from the facial bones: neurectomy, alcohol injection, radiofrequency thermocoagulation (RFT), or cryosurgery. Transcutaneous ganglion lesions include RFT, chemical lesions by injection of highly concentrated glycerol, and mechanical compression by balloon inflation. Several studies with more than 1 year of follow-up have examined the role of surgical procedures in repairing damage to the gasserian ganglion. The procedures were performed chemically with glycerol injections (72-75), mechanically with balloon compression (76-79), or thermally

with RFT (70,80-82). Although most of the patients reported complete acute pain relief after the lesion procedures, the recurrence rate during follow-up and the incidence of adverse events varied widely.

In the case series by Mohammad-Mohammadi et al. (83), 96 patients underwent 277 procedures to treat TN secondary to MS, including percutaneous glycerin infusion, balloon compression, SRS, RFT, and MVD. Symptoms recurred in 66% of the patients, and 181 procedures were performed for symptom recurrence. Balloon compression was the first procedure to have the highest initial pain-free rate and the longest median pain-free interval, followed by glycerin infusion (83).

Other studies with more than 1 year of follow-up examined the role of SRS in patients with TN of secondary MS (71,84-87). The likelihood of remaining pain-free without resorting to medication after 5 years and the incidence of adverse events are still unclear (32).

In a case series of patients with TN and MS who underwent SRS, only 38% of the patients were still pain-free without medication after 5 years. The incidence of complications, consisting of sensory disturbances of the trigeminal nerve, ranged from 5% to 57% (88). A recent retrospective review of long-term outcomes in 42 patients showed that the incidence rates of cases with pain relief after SRS were 62%, 29%, 22%, and 13% after 1, 3, 5, and 7 years, respectively (89). Retrospective studies have compared the efficacy of SRS with gasserian ganglion surgery (74-90). These studies have shown that patients who underwent gasserian ganglion surgery experience immediate pain relief and no longer need to resort to AI therapies than patients treated with SRS.

In a recent study of a small sample of cases, RFT and SRS originally provided pain relief in 71 cases. Over time, further interventions were needed to achieve satisfactory pain relief in 60 and 29 of the cases with RFT and SRS, respectively (91). MS has long been considered a contraindication of MVD because it affects demyelinating pillars in the central trigeminal pathways (92) or in the REZ of the trigeminal pathway (93).

In the literature, only a few pwMS had undergone MVD for TN, and the results are inconsistent (94,95).

In one series, 5 of 10 patients fared well at a follow-up of 12-39 months. Although the small series and short follow-up time do not allow definitive conclusions, the results suggest that it may be worthwhile not to withhold potential treatment from pwMS (69).

Truini et al. (36) screened 1628 pwMS and found that the incidence of neurovascular compression and its association with demyelinating pontine plaques were higher on the affected side than on the unaffected side (54% vs 0%, p=0.0001). The authors suggested that neurovascular compression with murine demyelinating plaques in combination may represent a dual mechanism underlying the pathophysiology of TN in pwMS.

Some studies support vascular contraction in MS (69,96,97). Neurovascular contraction may act as an attendant medium leading to focal demyelination of primary afferents near the entrance of the trigeminal root into the pons. This thesis is supported by the finding that severe neurovascular contraction in the trigeminal REZ is noted in most cases during surgery (50-100 of cases with TN secondary to MS) (98-100).

MVD in patients with classic TN results in immediate pain relief in most patients. However, this technique is generally described as less effective in patients with MS-related TN than in patients with classic TN. After 5 years, <50% of patients in the case series described by Broggi et al. (69) and 15% in the case series described by Aria et al. (99) were still pain-free compared with approximately 80% of patients who were pain-free after surgery for classic TN. The rate of adverse events during MVD is very low. In the above two case series, only one patient suffered long-term morbidity (facial nerve palsy). Two studies (100,69) reported issues after MVD and one after partial sensory rhizotomy (PSR) (101) in an aggregate of 77 pwTNMS. After MVD, 73% of cases reported pain relief, whereas in one PSR study, 87% reported pain relief, and the rush rates were 39% after MVD and 21.7% after PSR. Impassiveness occurred in 22/23 cases after PSR, including one with dolorosa anesthesia, and this also occurred in 2/105 cases in the MVD group. Hearing impairment was observed in two cases after MVD.

In six studies (74,83,86-88,102), an aggregate of 180 pwTNMS had undergone SRS. The mean age of 60 years was significantly advanced when compared with that of patients with MVD/PSR (52 years). Pain was relieved in 83.6% of cases after the procedure; however, 51.1% experienced recurrence during the follow-up period. Facial numbness, loss of sensation, and paresthesias were reported in 11.7% of the patients.

Eight studies have reported the use of percutaneous glycerol rhizotomy in 299 pwTNMS whose mean age was 51 years (73,76,83,103-105). The standard follow-up time was 42 months, 77.3% of the patients had good pain relief after the treatment, and 53.4% experienced recurrence during the follow-up period. In these patients, the median time to recurrence was 20.3 months, which was significantly shorter than that in patients who underwent SRS (30.4 months).

A total of 74 pwTNMS had undergone balloon microcompression (BC) (78,79,83,106), and 58 had undergone RFT (70,81,92,107), with 86.4% of those who underwent BC and 97.8% of those who underwent RFT reporting good pain relief. However, those who underwent BC reported the highest recurrence rate of 67.0%, whereas those who underwent RFT reported the lowest recurrence rate of 27.5%. For all procedures, recurrence

was reported in 50% of pwTNMS after 2.5 years, and studies providing comparative data with non-pwTNMS showed better outcomes for the latter. The only non-destructive procedure was MVD, an important neurosurgical procedure for which studies are limited. Destructive (ablative) procedures were frequently reported either in the REZ or at the gasserian ganglion.

Deep-brain stimulation of the posterior hypothalamus can be appraised as an ancillary procedure for resistant first-division TN (108), principally in MS (109). TN after failed MVD, significant medical multimorbidity, and MS are generally recommended to undergo gamma knife radiosurgery (110).

Results

Owing to the lack of data, the medical treatment of a patient with pwTNMS is burdensome. It is widely recommended to start with pharmacological therapy and then proceed to surgery. Pharmacological treatment of MS-related TN is demanding because of indigent drug tolerance and lack of evidence-based information (96). CBZ or OXC is the first-line drug, and second-line drugs include lamotrigine, baclofen, gabapentin, and pregabalin (111,112).

If medications cannot control the pain, the physician should consider surgical options. Surgical procedures include surgical removal of peripheral lesions distal to the ganglion, percutaneous gasserian ganglion surgery, SRS, and MVD in the posterior fossa (69-71). These procedures are usually well tolerated; however, none of these methods have ever been supported by studies adequately (113).

Studies of surgical procedures in patients with MS-related TN did not describe in detail short-term and long-term outcomes. In general, both percutaneous and surgical interventions are less effective in terms of postoperative pain enhancement and sustained pain relief rates (23,24,32,83,36).

Discussion

MS is one of the most common chronic neurological conditions; however, its cause is unknown, and its course is unpredictable (114).

TN is characterized by unilateral, touch-induced, brief, ferocious shock-like pain in one or more parts of the trigeminal nerve. Secondary TN in MS is characterized, like classical and idiopathic TN, by unforeseen, generally unilateral, brief, knife- or electric shock-induced, recurrent pain with a distribution consistent with one or more parts of the fifth cranial nerve (43). Established knowledge assumes that MS-related TN is associated with demyelinating pontine plaques.

Initiating pharmacological therapy, followed by surgery, is widely recommended. CBZ or OXC is the first-line drug, and second-line drugs include lamotrigine, baclofen, gabapentin, and pregabalin (111,112). The drugs should be administered slowly, the dosage should be increased gradually, and the patient should be monitored for side effects and possible worsening of existing MS symptoms (115). If medications cannot control the pain, the physician should consider surgical options. Surgical procedures include surgical removal of peripheral lesions distal to the ganglion, percutaneous gasserian ganglion surgery, SRS, and MVD in the posterior fossa (69-71). These procedures are usually well tolerated; however, none of these methods have ever been supported by adequate studies (113).

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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RESEARCH ARTICLE

Real-world Results of Ocrelizumab in the Treatment of Multiple Sclerosis: A Gulf Region Single-center Experience

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Abstract

Objective: This study aimed to describe the real-world effectiveness and tolerability of ocrelizumab treatment at MS Clinic, Tawam Hospital.

Materials and Methods: This retrospective, observational, single-center study analyzed the medical records of patients with multiple sclerosis (MS) receiving the standard dose of ocrelizumab.

Results: After starting ocrelizumab, 3 of the 19 patients included in the study experienced disease progression, 3 showed disability improvement, and the remaining 13 had stable status. None of the 15 patients with relapsing-remitting MS experienced a relapse. The average expanded disability status scale of all patients dropped from 2.32 to 2.22, when switched to ocrelizumab. After the follow-up period, 16 (84.21%) patients did not have any magnetic resonance imaging activity.

Conclusion: As an MS treatment, ocrelizumab is associated with a favorable response in terms of both efficacy and safety in clinical practice settings. The efficacy and safety demonstrated must be further evaluated to provide real-world evidence for the use of ocrelizumab.

Keywords: Multiple sclerosis, ocrelizumab, Gulf region

Introduction

Multiple sclerosis (MS) is a chronic inflammatory, immune-mediated disease affecting the myelin sheath of the nerves within the central nervous system (1). It is defined pathologically by the accumulation of demyelinating lesions in the white and gray matter of the brain and spinal cord. These lesions invade peripheral immune cells and cause leakages in the blood-brain barrier, with mechanisms involved in the direct effects of pro-inflammatory cytokines and chemokines produced by resident and endothelial cells in addition to indirect cytokine-dependent and chemokine-dependent leukocyte-mediated injury (2,3). However, the exact mechanisms are still not completely understood.

MS has a highly variable and unpredictable clinical presentation; however, it is often characterized by initial episodes of reversible neurological deficits, followed by gradual neurological deterioration as the disease progresses (4). The etiology of the disease remains unknown (1). Patients with MS can be classified according to MS phenotypes. Patients with accumulating neurological deficits, with no phases of relapse or remission, are said to have primary progressive MS (PPMS). This phenotype represents approximately 10% of patients with MS (5). Other phenotypes often manifest in patients with MS as a continuum, where patients commonly experience an initial phase of relapsing-remitting MS (RRMS), followed by a gradual conversion to secondary progressive MS in a phase referred to as transitional MS (6,7).

Accordingly, RRMS is the most common form, accounting for approximately 87% of patients with MS (1). The diagnosis of MS is based on clinical symptoms and supported by neuroradiological findings using magnetic resonance imaging

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(MRI) and the McDonald criteria, which comprise a clinically validated tool for early and accurate diagnosis (8).

The prevalence of MS is increasing worldwide, with the latest evidence from the MS International Federation revealing that approximately 2.8 million people are living with MS globally (9). Approximately twice as many women are affected than men, and the disease is commonly diagnosed in adults aged 20-45 years (2). The significant disabling effect on young adults results in the deterioration of health over time, in which approximately 50% of the patients require help when walking within 15 years of disease onset (10). This requires long-term rehabilitation, which places a significant economic burden on healthcare providers (11,12).

In the Middle East and North Africa, epidemiological studies reported that the prevalence of MS ranges from 30 to 38/100,000 people (13). These rates have risen over the first decade of the twenty-first century; however, they remain below the rates reported in North America and Europe (14). Data on the prevalence of MS in the United Arab Emirates (UAE) are limited. According to a 2011 study by Inshasi and Thakre (15), the estimated prevalence of MS in Dubai in 2007 was approximately 54.77/100,000, with an annual incidence rate of 6.8/100,00; however, of the patients identified, only 55.6% were Dubai natives and 44.4% were immigrants. A more recent study by Schiess et al. (16) determined the total crude prevalence of MS in Abu Dhabi to be 18/100,000 in Emiratis and expatriates combined. Age-/sex-standardized prevalence in the Abu Dhabi Emirati population is one of the highest and most reliable in the Arabian peninsula at 64.44/100,000 (16).

Recent treatment strategies for MS have revolved around disease-modifying therapy (DMT), with a large expansion in therapeutic options in recent years revolutionizing the care of patients with a relapsing disease (1). These medications help control the underlying disease process, aiming to shorten the duration and frequency of acute exacerbations and providing symptomatic relief (2). Ocrelizumab is a humanized anti-CD20 B-cell antibody that depletes immature and mature B-cells, but spares CD20-negative plasma cells (17). This drug slows the clinical and imaging-based progression of both relapsing and primary progressive forms of MS. As a result, ocrelizumab has been approved by both the US Food and Drug Administration in 2017 and the European Medicines Agency in 2018 (18,19). Real-world evidence of patients treated with ocrelizumab has been reported in North American, Latin American, and European patient populations (20-26). To our knowledge, this is the first report of real-world results of ocrelizumab treatment for patients with MS in the Middle East. Thus, this study aimed to describe the real-world effectiveness and tolerability of ocrelizumab treatment in patients with RRMS and PPMS in the Middle East.

Materials and Methods

Patients and Study Design

This retrospective, observational, single-center study analyzed the medical records of patients with MS at MS Clinic, Tawam Hospital. The main inclusion criterion was at least one infusion of ocrelizumab between January 1, 2018, and February 28, 2021. Patients were diagnosed with MS according to the most recent 2017 revision of the McDonald criteria (8). The indication for ocrelizumab therapy was determined based on disease activity and the MS type. A high disease activity, defined as high lesion load, was required, with patients either being treatment naive or shifted from another DMT because of disease activity, side effects, or safety concerns [namely, positive John Cunningham virus (JCV) antibodies on natalizumab]. Once determined, patients underwent screening for hepatitis B, human immunodeficiency virus, varicella antibodies, and tuberculosis, as per recommendations. In addition, any history of malignancy in the patients or their families was reviewed, with referral to screening programs if required, particularly for breast cancer in older female patients. Disease progression was defined as the deterioration of the expanded disability status scale (EDSS) score compared with baseline. The study was approved by the institutional ethics committee of Tawam Hospital (reference no: AA/AJ/682, date: 19.01.2021). All procedures were completed in accordance with the guidelines of the Declaration of Helsinki for research practice. As this study only used historically, routinely observed information from clinical practice, informed consent was not required. All data were documented anonymously and safely stored.

Treatment Protocol

Ocrelizumab (Ocrevus) was administered at a standard dose of 600 mg every 6 months. The first dose was divided into two, with each 300 mg dose separated by 2 weeks. All doses were preceded by premedication of 125 mg of intravenous methylprednisolone and 50 mg of Diphenhydramine HCl 30 min before ocrelizumab. Paracetamol and metoclopramide were administered as needed to ease any symptoms of nausea, headache, or fever. Patient data at months 6, 12, 18, and 24 were collected for the clinical review. Neuroimaging follow-up was conducted annually in asymptomatic cases according to recommendations and as soon as possible in patients who developed symptoms of disease progression.

Clinical and Radiological Outcome Measures

The following baseline patient data were collected: patient demographics, MS subtype, annualized relapse rate (ARR), DMTs before ocrelizumab administration, EDSS score, MRI activity before ocrelizumab initiation, reason for switching to ocrelizumab, emergency room (ER) visits while on prior DMT, adverse events while on prior DMT, and treatment compliance. The variables and outcomes assessed during the follow-up

period included ARR, EDSS, MRI activity, ER visits due to MS, adverse events, and treatment compliance.

Statistical Analysis

Descriptive analysis for quantitative data included the mean and standard deviations for normally distributed variables. When variables deviated from the normal distribution, the median and interquartile ranges were used instead. For qualitative categorical variables, frequency, percentage, and 95% confidence intervals were applied.

Results

Patient Baseline Characteristics

Of the 295 patients with MS included in the center's database, those who were receiving ocrelizumab during the study period were enrolled. After the study period (February 2021), a total of 20 patients were enrolled in the study. Only one patient received the first full dose of ocrelizumab and was lost to follow-up. Four patients of the remaining patients were diagnosed with PPMS and 15 with RRMS. The baseline characteristics of the patients are provided in Table 1.

The most common reason for switching to ocrelizumab was seropositivity, identified through a positive JCV test (n=11), followed by radiological and clinical activity (n=3), clinical activity alone (n=3), radiological activity alone (n=1), change of diagnosis to PPMS (n=1), and change in social status (n=1). Three of the patients were treatment-naive.

Clinical and Radiological Outcomes

While being on ocrelizumab therapy, patients' clinical conditions were monitored over a mean period of 27.4 (range, 18-41) months, during which an average of 4.4 (range, 1-7) doses were administered. After starting ocrelizumab therapy, none of the 15 patients with RRMS experienced a relapse, whereas the average ARR for this group before starting ocrelizumab was 0.63. The average EDSS of all patients dropped from 2.32 to 2.22 when switched to ocrelizumab.

Table 1. Baseline patient characteristics

	Total patients (n=19)
Male sex (%)	10 (52.63)
Mean age, years (range)	33.89 (21-54)
RRMS (%)	15 (78.94)
Family history of MS (%)	1 (5.26)
Previous DMTs, mean None (%) One (%) Two (%) Three (%) Four (%)	2.11 3 (15.79) 3 (15.79) 6 (31.58) 3 (15.79) 4 (21.05)
Baseline EDSS, mean (range)	2.32 (0-7)
ARR for previous years, mean (range)	0.63 (0-2)
Heavy MRI activity (%)	19 (100)

ARR: Annual relapse rate, DMT: Disease-modifying therapy, EDSS: Expanded disability status scale, MRI: Magnetic resonance imaging, MS: Multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis

Among the combined 19 patients, 3 (15.79%) experienced disease progression, of which 2 were diagnosed with RRMS and 1 with PPMS. Three patients showed disability improvement while on ocrelizumab therapy (2 RRMS and 1 PPMS), and the remaining 13 patients had a stable status.

After the follow-up period, 16 (84.21%) patients did not have any MRI activity; 2 (10.53%) patients showed MRI activity; however, one of these patients received their first dose of ocrelizumab only two weeks prior. This patient had another MRI follow-up after 1 year of treatment, which showed no new or enlarged T2 lesions. Follow-up imaging after starting the drug had not been performed for one patient.

Safety and Compliance

Two patients (10.53%) reported adverse events. One patient experienced a mild infusion reaction. Another patient reported skin discoloration, muscle pain, and fatigue for 1 month following the administration of the first ocrelizumab dose. Most patients did not report adverse events (n=17, 89.47%) or visit the ER because of their MS (n=16, 84.21%) while on ocrelizumab treatment. Patients were deemed compliant if no scheduled clinical follow-ups and treatments were missed. Seventeen (89.47%) of the 19 patients complied with their ocrelizumab treatment.

Discussion

To the best of our knowledge, this is the first single-center, retrospective, observational study to provide real-world evidence of ocrelizumab treatment in the UAE before and after the coronavirus disease-2019 pandemic. The results of this study show that ocrelizumab therapy was associated with an expected reduction in the ARR in patients with RRMS and no evidence of MRI activity in patients with MS with a high baseline lesion load. Ocrelizumab was generally well tolerated, and the compliance rates were high.

The results of this study support those of the initial OPERA I and II phase 3 clinical trials on RRMS and the ORATORIO phase 3 trial on PPMS. These trials found lower rates of disease activity and progression under ocrelizumab therapy than those under interferon beta-1a and placebo for 96-120 weeks (27,28). The proportion of infusion-related reactions in these trials (34.3%) was higher than the rate in the present study (n=1, 5.24%), suggesting that further research on infusion management in clinical practice is warranted. Further positive results can be seen in other real-world studies on ocrelizumab treatment. Daniels

et al. (22) showed clinically relevant improvement in disability status following ocrelizumab treatment in patients with PPMS. Similarly, a recent study by Fernandez-Diaz et al. (20) presented a suppressed disease activity in patients with MS treated with ocrelizumab, while exhibiting a favorable safety profile. The growing evidence base of positive clinical outcomes supports the inclusion of ocrelizumab in MS treatment.

Study Limitations

This study is subject to the limitations of the observational, retrospective study design, such as the absence of a control group and interpretation errors when analyzing medical records. The relatively small sample size of the study meant that the sample had insufficient power to perform subgroup analyses.

Conclusions

Although the study was not powered to assess the efficacy and safety of ocrelizumab, it provides insights into the effectiveness and tolerability of this DMT in a clinical practice setting. Moreover, the clinical course presented in this study is the longest in a real-world setting for ocrelizumab, with a mean period of 27.4 months. To validate our results, further research using real-world evidence from a larger sample size is necessary. Additional studies with a longer follow-up could clarify the long-term safety of ocrelizumab infusion in a real-world patient population.

Ethics

Ethics Committee Approval: The study was approved by the institutional ethics committee of Tawam Hospital (reference no: AA/AJ/682, date: 19.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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RESEARCH ARTICLE

Demographic and Clinical Characteristics of Persons with Multiple Sclerosis with Psychiatric Disorders

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Abstract

Objective: Psychiatric syndromes (PS) are among the most common comorbidities seen in multiple sclerosis (MS). It has been demonstrated that PS, such as depression, anxiety, and bipolar disorder, are more common in people with MS (pwMS) than in the general population. However, the reasons for this remain unknown. We aimed to identify the demographic and clinical characteristics of pwMS with PS and compare them with pwMS without PS.

Materials and Methods: In total, 2,732 (1,886 female; 846 male) pwMS attending the outpatient MS Clinic of Dokuz Eylul University Hospital were included in the study. We recorded the age, gender, disease duration, duration of PS diagnosis, age of onset, and MS course of the pwMS.

Results: PS had been diagnosed in 383 (14%) of pwMS, and in 352 of those it were diagnosed after their MS. There was no significant difference between the two groups in terms of disease duration and duration of diagnosis. There were significant differences regarding age, gender, age of onset, and MS classification between the two groups. The age and age of onset of PS in pwMS (45.89±11.50 and 30.42±9.81, respectively) were higher than in pwMS without a PS (44.09±12.57 and 29.29±9.74, respectively). The rate of female pwMS with a PS (76.4%) was higher than female pwMS without a PS (67.8%). Regarding the MS type, whereas 81% of those who had PS had relapsing-remitting MS (RRMS), 15.6% had secondary progressive MS (SPMS), and 3.4% had primary progressive MS (PPMS). Furthermore, 85.4% of those who had no PS were RRMS, 11% were SPMS, and 3.6% were PPMS.

Conclusion: In this study, the most related factors were age, gender, age of onset, and MS course for PS in MS. Studies involving other clinical features and cognitive functions are needed to better understand PS in MS.

Keywords: Multiple sclerosis, psychiatric syndrome, depression

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by central nervous system inflammation, demyelination, and axonal loss. Symptoms occur even in the early stages of the disease (1). MS is one of the most common causes of neurological disability in young and middle-aged adults and negatively affects their productivity and quality of life. Symptoms in MS differ according to the areas of involvement, and motor, sensory, cognitive, and neuropsychiatric symptoms are often observed (2,3).

Charcot first described the psychiatric syndrome (PS) seen in people with MS (pwMS) over a century ago (4). Recently, PS in MS has been discussed from epidemiological, clinical, and radiological perspectives (5).

Psychiatric symptoms are more frequent in pwMS than in people without it. Mood disorders, such as depression and anxiety are 20% more common. PS is often seen at the time of MS diagnosis and become more severe during the disease (6). Reports estimated that, on average, of pwMS with PS, 30% have depression, 22% anxiety, 13% bipolar mood disorder, 4% psychotic disorder, and 31% obsessive-compulsive disorder. These rates are high compared with the general population (7).

Considering the effects of psychiatric symptoms on cognitive performance, physical disability, and fatigue, early diagnosis

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of PS in pwMS improves their quality of life and increases compliance with treatment (5). In this study, we aimed to identify the demographic and clinical characteristics of pwMS with PS and compare them with pwMS without PS.

Materials and Methods

Study Design

This retrospective study was performed at the MS Clinic Dokuz Eylul University Hospital, Izmir, Turkey. This work has been approved by the Dokuz Eylul University Non-Invasive Research Ethics Committee (approval number: 2016/27-08, date: 20.10.2016). Informed consent was obtained from all participants.

Participants

The data of the participants who were diagnosed with MS were retrieved from the registry database, iMed (version 7.0.0; MSBase Foundation), and all participants were included in the study.

Outcome Measures

Demographic (gender, age, education level, marital status, employment status) and clinical data (date of onset, date of diagnosis, course of disease, age of onset of PS, and date of onset of PS) of pwMS were obtained from the medical records.

Statistical Analysis

The normal distribution of data was checked with the Kolmogorov-Smirnov test and histograms. Descriptive analyses are presented with mean and standard deviation for continuous variables and percentages for categorical variables. Logistic regression was performed to determine the risk factors for the participants with psychiatric disorders in pwMS. Statistical significance was set at $p<0.05$. Data were analyzed using the IBM SPSS Statistics software (Version25.0. Armonk, NY: IBM Corp.).

Results

In total, 383 (14%) of pwMS had a diagnosis of PS, and 352 of those were diagnosed with PS after their MS. There was no significant difference between the two groups in terms of disease duration and duration of diagnosis. There were significant differences regarding age, age of onset, gender, employment status, marital status, and MS classification between the two groups. The age and age of onset for pwMS with a PS were higher than that for those without a PS. The rate of female pwMS with a PS was higher than female pwMS without a PS. Regarding the MS type, while relapsing-remitting MS (RRMS) was more frequent in the pwMS with a PS, secondary progressive MS (SPMS) was more frequent in the pwMS without a PS (Table 1).

Logistic regression was performed to determine the effects of age, age of onset, gender, employment status, marital status, and MS classification on the likelihood that pwMS would have PS. The logistic regression model was statistically significant: $x^2(6)=9.557$, $p<0.001$. The model explained 2.7% (Nagelkerke R^2) of the variance in having PS and correctly classified 85.3% of participants. The pwMS who were divorced and retired were 1.77 and 1.73 times, respectively, more likely to have a PS (Table 2).

Discussion

This study found a relationship between the diagnosis of PS in pwMS and age, age at onset, gender, employment status, marital status, and disease course. In all, 14% of our cohort received a PS diagnosis, most of which were made after the MS diagnosis.

Some studies have found no relationship between the duration of illness and PS diagnosis, consistent with the finding of this study. However, age and gender were not correlated, contrary to our results (8-10). We hypothesize that the high age and age at onset in the PS group may be due to it being more difficult to diagnose patients in this group.

The relationship between MS and PS diagnosis is complex. A pwMS may develop a PS because of the neuropathological process of MS or as a reaction to being diagnosed with MS (11). The etiology remains unclear. In this study, most pwMS who were diagnosed with PS received a psychiatric diagnosis later.

The rate of PS was higher in female pwMS than in males. Considering that PS such as depression are seen twice as often in society and the rate of women in MS is higher, this may be why the rate was higher in women (1,12). The rate of PS was higher in those with SPMS with higher disability. However, there are different results in the literature regarding the relationship between disability and PS (8,10).

Divorced pwMS was 1.77 times more likely to have a PS. Our study is consistent with reports that people with PS are more often single or divorced (13). Breslau et al. (14) showed that PS is related to divorce, and Landfeldt et al. (15) demonstrated that men with MS have an increased risk of divorce. In our cohort, the diagnosis of MS may have caused the divorce and triggered the PS. Another result of this study was that retired pwMS was 1.73 times more likely to have a PS. Considering the possibility of pwMS retiring early because of physical or psychiatric conditions, the increased risk may be due to this disease (16).

Study Limitations

The most important limitation of this study was that the PS were processed according to medical records. The study could have been made more robust by applying PS tests to the pwMS and evaluating their cognitive functions. However, this would have been difficult in such a large group of patients. Another

Table 1. Demographic characteristics of the participants (n=2732)			
	PwMS with a psychiatric syndrome (n=383)	PwMS without a psychiatric syndrome (n=2349)	p-value
Age (years)	45.89±11.50	44.09±12.57	0.003
Age of onset (years)	30.42±9.81	29.29±9.74	0.038
Disease duration (years)	14.83±8.42	14.20±9.03	0.063
Time from symptom onset to diagnosis (days)	1174.60 (1644.30)	1153.28 (1686.59)	0.673
Gender			
Female	294 (76.8%)	1592 (67.8%)	<0.001
Male	89 (23.2%)	757 (32.2%)	
Employment status			
Unemployed	109 (36.7%)	600 (34.7%)	0.003
Employed	130 (43.8%)	848 (49.0%)	
Retired	41 (13.8%)	136 (7.9%)	
Student	17 (5.7%)	145 (8.4%)	
Level of education			
Primary school	75 (25.3%)	464 (27.2%)	0.675
High school	89 (30.0%)	474 (27.8%)	
College or university	133 (44.8%)	767 (45.0%)	
Marriage status			
Single	77 (26.1%)	479 (26.8%)	<0.001
Married	184 (62.4%)	1213 (68.0%)	
Divorced	34 (11.5%)	92 (5.2%)	
MS classification			
RRMS	311 (81.2%)	2005 (85.4%)	0.031
SPMS	60 (15.7%)	259 (11.0%)	
PPMS	12 (3.1%)	85 (3.6%)	

RRMS: Relapsing remitting multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, PPMS: Primary progressive multiple sclerosis, PwMS: Person with multiple sclerosis

Table 2. Risk factors for having psychiatric syndromes in pwMS			
Risk factors	OR	95% CI	p-value
Age (years)	0.998	0.981-1.015	0.803
Age of onset (years)	1.003	0.985-1.022	0.736
Gender (ref = female)			
Male	0.805	0.587-1.103	0.177
Employment status (ref = unemployed)			
Employed	1.087	0.791-1.494	0.608
Retired	1.729	1.083-2.761	**0.022**
Student	0.649	0.355-1.186	0.160
Marriage status (ref = single)			
Married	0.764	0.536-1.088	0.136
Divorced	1.768	1.046-2.987	**0.033**
Classification (ref = RRMS)			
SPMS	1.205	0.803-1.809	0.368
PPMS	0.924	0.448-1.908	0.831

Significant p-values are presented in bold. CI: Confidence interval, OR: Odds ratio, RRMS: Relapsing remitting multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, PPMS: Primary progressive multiple sclerosis, PwMS: Person with multiple sclerosis, ref: reference variable

limitation is that the treatments of the patients were excluded from the study, since some MS treatments may trigger PS.

Conclusion

This study showed that several demographic and clinical factors are associated with a psychiatric diagnosis in pwMS. It also found that being retired and divorced increased the risk. The diagnosis and treatment of PS in pwMS is important to minimize the risk of adding another disease to their chronic condition and further impacting their quality of life.

Ethics

Ethics Committee Approval: This work has been approved by the Dokuz Eylul University Non-Invasive Research Ethics Committee (approval number: 2016/27-08, date: 20.10.2016).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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RESEARCH ARTICLE

The Relationship Between the Styles of Coping with Stress of Multiple Sclerosis Patients and the Perception of Social Support

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Abstract

Objective: This study examined the effect of perceived social support on the coping styles of patients with multiple sclerosis (pwMS) and their relationship with disability.

Materials and Methods: In total, 100 pwMS who applied to the Neurology Outpatient Clinic of Kahramanmaras Sutcu Imam University Medical Faculty Hospital and 100 healthy controls were included in the study. Disease duration, MS type, and Expanded Disability Status Scale (EDSS) scores for pwMS were evaluated. The socio-demographic information form, multidimensional scale of perceived social support, scale for coping with stress, and Beck depression inventory were used.

Results: The family, friend, and special person subdimensions of the perceived social support mechanism among pwMS and the helpless, optimistic, submissive, and self-confident approaches from the stress-coping subdimensions were positively correlated. However, the social support-seeking factor subdimension was negatively correlated. In the analysis of the effect of the social support level and coping mechanisms on each other in pwMS, a positive and significant correlation was found between the family and special person subdimensions and the optimistic approach. Moreover, pwMS had a mean score of 19.6±6.1 in the family subdimension of the perceived social support scale, 16.8±7.6 in the friend subdimension, and 19.5±6.1 in the special person subdimension. The helpless, submissive approach, and social support-seeking scores were 2.4±0.6, 2.4±0.6, and 3.1±0.5, respectively. In the analysis of the average of the scores obtained from the depression inventory, pwMS had an average score of 22±14, and the control group had an average score of 14.1±10.8. The mean scores of the pwMS in the helpless approach ($p<0.05$), submissive approach ($p<0.05$), and depression ($p<0.05$) inventory were significantly higher than those in the control group ($p>0.05$). The mean scores of the helpless approach ($p<0.05$) and the submissive approach ($p<0.05$) of pwMS with an EDSS score of >3 were significantly higher than those of pwMS with an EDSS score of ≤3.

Conclusion: Coping strategies change throughout the disease. Specifically, patients with moderate-to-severe disabilities will need help coping with their existing disorder. As disability increases, the social support provided by family, friends, or spouses becomes more important.

Keywords: Multiple sclerosis, perceived social support, coping with stress

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory and neurodegenerative disease of the central nervous system. Young adults are usually affected, and 20-40 years is the most common age range. Most patients have a relapsing form characterized by relapsing-remitting MS; however, over time, the disease may progress in the clinical process and become a secondary progressive MS. Approximately 15% of patients have progressive disease from the onset (1-3).

In addition to physical disability, cognitive and psychological findings can be seen in patients with MS (pwMS) in the initial or advanced disease stages. Psychiatric findings, which are comorbidly found in pwMS, significantly affect the quality of life of the patients. Thus, providing support to patients is important

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to prevent these problems or ensure that they experienced a milder disease form.

The social support that individuals receive from family members, relatives, or friends is an important factor in coping with difficult processes. Social support, as a result of stressful situations in which people feel inadequate or are exhausted, provides the satisfaction of needs such as being loved, respected, compassionate, and belonging, contributes to positive thinking, and affects mental and physical health positively (4,5). Since MS is a chronic neurological disease, the lack of support may affect the mental and physical conditions of pwMS and may exacerbate the clinical course of the disease (6,7). Studies examining the effect of social support on the mental health of pwMS have concluded that the presence of social support contributed significantly to the quality of life and, accordingly, to the mental health dimension (8).

Throughout their lives, individuals may encounter many life events that will disrupt their physiological and psychological balance. As a result of these life events, which are called stress factors, individuals take some functional and non-functional actions against these disturbing events. With these actions, they try to adapt to stress by regulating their mood in the face of the stressor, changing their behavior toward resolving the stress-inducing events, or regulating their thoughts about the source of stress (9). This adaptation process is called coping. Coping strategies can be divided into problem-focused coping, in which negative emotions are due to changes in person-environment events, and emotion-focused coping, which aims to change how the emerging event is evaluated (10). While the self-confident, optimistic, and social support-seeking approaches are seen as functional coping styles, submissiveness and helpless approach are considered dysfunctional coping styles (11).

This shows that continuous social support has an important role in the development of coping behaviors, perceived social support motivates the individual to evaluate him-/herself and his/her environment more positively and functionally, and individuals with high social support have more functional coping skills in stressful situations (12).

The state of being healthy in pwMS is evaluated as a whole, and it should be evaluated not only as the absence of disease symptoms but also the individual's social and mental well-being (13) When approached from this point of view, the effect of the social environment on patients' coping with stress should not be ignored. However, studies emphasizing the social factors that affect pwMS' levels of coping with stress appear limited. Therefore, in this study, we aimed to determine the relationship between the perceived social support mechanisms and coping styles of pwMS.

Materials and Methods

The study was performed in the MS Outpatient Clinic of Kahramanmaras Sutcu Imam University Medical Faculty Hospital. Ethical approval was obtained at decision number 01 (date: 20.09.2022) in Kahramanmaras Sutcu Imam University Faculty of Medicine. The study consisted of 100 patients treated for MS in the neurology outpatient clinic and 100 matched healthy controls. For data collection, the information form created by the researchers, styles of coping with stress scale, multidimensional scale of perceived social support, and the Beck depression inventory were used. Data were collected through face-to-face interviews. In the information form, questions intended to determine the characteristics of the sample group, such as age, marital status, educational status, place of residence, employment status, disease duration, MS type, and Expanded Disability Status Scale (EDSS) scores of pwMS.

Statistical Analysis

The IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) was used for the statistical evaluation of data. Continuous data were summarized as mean and standard deviation, whereas categorical data were summarized as numbers and percentages.

Stress-coping styles scale: The scale was developed by Lazarus and Folkman (14), and it measures the actions and way of thinking of individuals following stressful events. The Turkish validity and reliability tests of the scale were conducted by Şahin and Durak in 1995 (14). The scale consists of 30 items, and each item is scored between 0 and 3. It consists of five subscales: self-confident, optimistic, helpless, submissive, and social support-seeking approaches. The self-confident, optimistic, and social support-seeking approaches are functional coping methods focused on problem solving, and the helpless and submissive approaches show dysfunctional coping ways that focus on emotions. The high scores obtained from the subscales, which do not have a total score, indicate that the individual prefers the coping method much more.

Multidimensional scale of perceived social support: The scale was developed by Zimet et al. (15). It measures the adequacy of social support provided by three social sources. The scale, which was adapted into Turkish by Eker et al. (16), consists of 12 items and has three subscales: family, friend, and special person. The lowest score that can be obtained from the family (items 1, 2, 7, and 10), friend (items 3, 4, 8, and 12), and special person (items 5, 6, 9, and 11) subscales is 4, and the lowest total score obtained by adding the scores from the subscales is 12; a high score indicates high perceived social support (16).

Beck depression inventory: This depression-rating scale consists of 21 questions in total, evaluated by adding the scores between 0 and 3 obtained from each answer. In line with the

corresponding score ranges, the scale was classified as normal when the score is within 1-10; moderate mood disorder, 11-16, clinical depression, 17-20; moderate depression, 21-30; severe depression, 31-40. A score between 41 and 63 is considered severe depression. The Turkish validity and reliability tests of the scale were conducted by Hisli (17,18).

Results

Considering the demographic characteristics of pwMS, the mean age was 34.9±9.9, and the majority of them were female (75%), high school (35%), and university graduate (35%). The mean disease duration was 5.9±8.1. The mean EDSS score was 1.8±1.6, and 97% of the patients had RRMS. Regarding the demographic characteristics of the control group, the mean age was 28.1±8.2, the majority of them were women (55%), and they were university graduates (79%) (Table 1).

When the perceived social support, coping with stress, and Beck depression inventory scale scores of pwMS and the control group were examined, pwMS were found to have mean scores of 19.6±6.1, 16.8±7.6, and 19.5±6.1 in the family, friend, and special person subdimensions of the perceived social support scale. The helpless, submissive, and social support-seeking approach scores were 2.4±0.6, 2.4±0.6, and 3.1±0.5, respectively. In the control group, the scale of perceived social support had mean scores of 20±6.03, 18.4±6.5, and 20.6±6.2 in the family, friend, and special person subdimensions. The helpless, submissive, and social support-seeking approach scores were 2.1±0.5, 2.2±0.5, and 2.9±0.5, respectively. In the analysis of the average of the scores obtained from the depression inventory, pwMS had an average of 22.1±14, and the control group had an average of 14.1±10.8. The mean scores of pwMS in the helpless approach, submissive approach, and depression inventory

Table 1. Demographic characteristics of the participants

Variables		pwMS		Healthy	
		Mean ± SD		Mean ± SD	
Age		34.9±9.9		28.1±8.2	
		n	%	n	%
Sex	Male	25	25	45	45
	Female	75	75	55	55
Education	Primary	22	22	4	4
	Secondary	8	8	2	2
	High	35	35	15	15
	University	35	35	79	79
Marital status	Single	33	33	66	66
	Married	67	67	34	34
Living in	Village	7	7	13	13
	District	29	29	15	15
	City	64	64	72	72
Working status	Officer	9	9	9	9
	Worker	10	10	27	27
	House wife	47	47	2	2
	Unemployed	15	15	2	2
	Retired	3	3	0	0
	Freelancer	5	5	3	3
	Student	11	11	54	54
MS type	RRMS	97	97	-	-
	SPMS	2	2	-	-
	PPMS	1	1	-	-
Illness duration (year)		5.97	-	-	-
Medium EDSS		1.8±1.6	-	-	-
EDSS ≤3		87	87	-	-
EDSS ≥3		13	13	-	-

pwMS: People with multiple sclerosis, SD: Standard deviation, RRMS: Relapsing-remitting multiple sclerosis, PPMS: Primary progressive multiple sclerosis, EDSS: Expanded Disability Status Scale

(p<0.05; p<0.05; and p<0.05) were significantly higher than that in the control group (p>0.05) (Table 2).

According to the EDSS scores, pwMS with an EDSS score of ≤3 had mean scores of 19.5±6, 17.1±7.6, and 19.4±6.2 in the family, friend, and special person subdimensions of the perceived social support scale. The optimistic, helpless, submissive, and social support-seeking approach scores were 2.8±0.6, 2.3±0.6, 2.4±0.6, and 3±0.4, respectively. In pwMS with an EDSS score of >3, the mean scores in the family, friend, and special person subdimensions of perceived social support scale were 19.6±3.4, 15.5±7.9, and 20.2±5.7, respectively. The optimistic, helpless, submissive, and social support-seeking approach scores were 2.9±0.7, 2.9±0.7, 2.9±0.7, and 2.9±0.5, respectively. The mean scores of the helpless approach (p<0.05) and the submissive approach (p<0.05) of pwMS with an EDSS score of >3 were significantly higher than those of pwMS with an EDSS score of <3 (Table 3).

The results revealed that the family, friend, and special person subdimensions of the perceived social support mechanism in pwMS and the helpless, optimistic, submissive, and self-confident approaches from the stress-coping subdimensions were positively correlated. However, the social support-seeking subdimension was negatively correlated. In the analysis of the effect of the social support level and coping mechanisms on each other in pwMS, a positive and significant correlation was found between the family and special person subdimensions and the optimistic approach (family-optimistic approach, r=0.261, p=0.009; special human-optimistic approach, r=0.300, p=0.003) (Table 4).

Table 2. Comparison of perceived social support, coping with stress, and depression scores between the MS group and the healthy control group

	MS	Healthy	
	Mean ± SD	Mean ± SD	p-value
Perceived social support			
Family	19.6±6.1	20.1±6.03	0.594
Friend	16.8±7.6	18.4±6.5	0.11
Special person	19.5±6.1	20.6±6.2	0.21
Coping with stress			
Confident approach	3.0±0.6	3.1±0.6	0.1
Optimistic approach	2.8±0.6	2.7±0.7	0.1
Helpless approach	2.4±0.6	2.1±0.5	0.02
Submissive approach	2.4±0.6	2.2±0.5	0.02
Seeking social support	3.1±0.5	2.9±0.5	0.2
Depression	22.1±14.1	14.1±10.8	0.005

MS: Multiple sclerosis, SD: Standard deviation

Discussion

MS is the most common chronic inflammatory disease of the central nervous system in young adults. Social support from family members, relatives, or friends is an important factor in the coping of pwMS with difficult processes due to disease-related disability and psychological and comorbid conditions. This study focuses on the social support perceptions and levels of "coping with stress" of pwMS, examines the relationship with the level of disability, and compares the scores obtained from the scales in the control group. According to the findings, a

Table 3. Comparison of EDSS, perceived social support, and coping with stress subscale scores in the MS group

	EDSS ≤3	EDSS >3	
	Mean ± SD	Mean ± SD	p-value
Perceived social support			
Family	19.5±6.1	19.6±5.4	0.4
Friend	17.1±7.6	15.5±7.9	0.1
Special person	19.4±6.2	20.2±5.7	0.2
Coping with stress			
Confident approach	3.1±0.6	3.1±0.6	0.1
Optimistic approach	2.8±0.6	2.9±0.7	0.1
Helpless approach	2.3±0.6	2.9±0.7	0.015
Submissive approach	2.4±0.6	2.9±0.7	0.023
Seeking social support	3.1±0.4	2.9±0.5	0.2

EDSS: Expanded Disability Status Scale, SD: Standard deviation

Table 4. Comparison of perceived social support and coping with stress subscale scores in the MS group

	Coping with stress mechanism					
Perceived social support	Helpless approach		Optimistic approach	Submissive approach	Seeking social support	Confident approach
Family	r	0.102	0.261	0.054	-0.095	0.121
	p	0.316	0.009	0.593	0.352	0.233
Friend	r	0.213	0.122	0.187	-0.153	0.140
	p	0.34	0.229	0.064	0.132	0.166
Special person	r	0.072	0.300	0.030	-0.107	0.089
	p	0.482	0.003	0.768	0.292	0.380

MS: Multiple sclerosis, r: Pearson correlation coefficient

positive correlation was found between the helpless, optimistic, submissive, and self-confident approaches and the social support scale subdimensions of family, friends, and special people in pwMS, and a significant relationship was found.

In the study, the levels of using the self-confident, optimistic, and social support-seeking approaches, which are the subdimensions of the stress-coping attitudes scale, were higher than the levels of using the helpless and submissive approaches. Patients with an EDSS score >3 used the submissive and helpless approach significantly more than patients with an EDSS score of ≤3. When compared with the healthy control group, the depression level and submissive and helpless approaches, which are the subdimensions of the approach to emotion, were significantly higher in pwMS than in the control group.

Social support is the emotional and physical experiences of the individual that given by either the inner or outer circles (19). Social support is a kind of shock absorber against the physical and psychological problems of the individual and has important results for individuals at every stage of life (20,21).

In this study, pwMS had a high perception of social support in all three dimensions. The patients stated that they mostly received support from their families and special people. The level of social support in pwMS was high because the majority of the participants (67%) were married. A study conducted in 2017 revealed that marriage potentiates the perception of social support (22). In a study working on the relationship between psychological factors and chronic pain among handicapped people, the perception of social support resulted in lower pain levels and a better psychological mood (23).

The MS process usually causes disability and brings new problems and stress factors in view (24,25). A study stated that stressful life events and family problems were more common in pwMS than in the control group (26). In the present study, in accordance with the literature data, the depression level in pwMS was significantly higher than that in the control group.

In the study, the levels of using the self-confident, optimistic, and seeking social support approaches, which are the subdimensions of the stress-coping attitudes scale, were higher than the levels of using the helpless and submissive approaches. This result shows that pwMS prefer problem-oriented approaches more than emotion-oriented approaches based on their styles of coping with stress. The depression level and submissive and helpless approaches, which are the subdimensions of the approach to emotion, were significantly higher in pwMS than in the control group. In a meta-analysis study on the coping styles of pwMS, patients mostly preferred emotion-oriented and avoidance strategies and used problem-oriented active coping approaches at a lower rate than the general population (27). Similarly, in another study, pwMS has a higher risk of experiencing depression than the control group (28). Thus, depression comes along with disability and ineffective coping methods (29,30).

Patients with an EDSS score of >3 used the submissive and helpless approaches significantly more than patients with an EDSS score of <3. Considering that patients with an EDSS score of ≥3 need physical support and permanent disability progresses, the rate of using helpless and submissive approaches increases due to the increase in cognitive losses, dependence on the environment, and inability to meet their needs. PwMS experience exhaustion with an increasing disability; this symptom is accompanied by depression, and they have difficulty even doing house chores in daily life (31). The majority of the pwMS were women (75%) and married (67%; they also have responsibilities related to their children and housework, if any, apart from their own care), and patients are coping with problems in fulfilling these roles because of MS symptoms. It increases the orientation toward dysfunctional and emotion-focused strategies.

Study Limitations

Social support mechanisms are a way of coping with adversity, are accepted as problem-focused coping strategies, and effectively reduce stress (32). In this study, the analysis of the effect of the social support level and coping mechanisms on each other in pwMS revealed a positive and significant correlation between the family and private person subdimension and the optimistic approach. Social support mechanisms can be offered directly or indirectly to an individual according to the support request, and individual needs must be provided to help them use coping strategies more effectively in difficult situations (33).

Conclusion

Coping strategies change throughout the disease course. Patients with moderate-to-severe disabilities will need help in coping with their existing disorders. As the disability progresses, social support from family, friends, or spouse becomes more important. Neuropsychological aspects must be considered, particularly during disease onset and later stages of disability.

Ethics

Ethics Committee Approval: Ethical approval was obtained at decision number 01 (date: 20.09.2022) in Kahramanmaras Sutcu Imam University Faculty of Medicine.

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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