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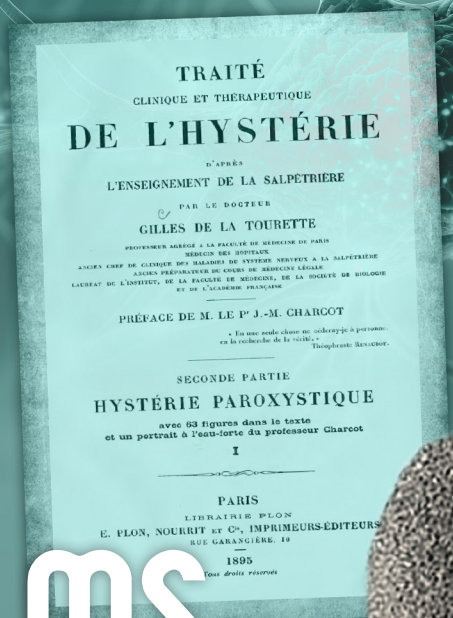
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Journal of MULTIPLE SCLEROSIS Research

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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.

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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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Manuscript Format and Style

Writing rules

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

a. Title

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

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

d. Copyright Transfer Form and Authorship Contribution Form

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

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

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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.

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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;

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- 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.

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

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

Conclusion: The conclusion of the study should be highlighted.

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

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

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

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

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

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

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

Examples of References

1. List All Authors

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

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

2. Organization as Author

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

3. Complete Book

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

4. Chapter in Book

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

5. Abstract

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

6. Letter to the Editor

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

7. Supplement

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

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

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

Authorship

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

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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.

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PEER REVIEW

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

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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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CONTENTS

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Journal of Multiple Sclerosis Research 2023;3(2):24-29

RESEARCH ARTICLE

Determination of *SIRT7, SEMA3A, SEMA3F* Gene Expressions in Patients with Multiple Sclerosis

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Abstract

Objective: In this study, we aimed to analyze the expression levels of specific genes that may contribute to the pathogenesis of multiple sclerosis (MS) in patients and explore the applicability of biomarkers. These biomarkers could serve as valuable diagnostic and prognostic tools, contributing to a better understanding of disease etiology, facilitating disease monitoring, and evaluating treatment efficacy.

Materials and Methods: We analyzed the expression levels of *SIRT7, SEMA3A,* and *SEMA3F* genes using samples obtained from both MS patients and healthy controls.

Results: Our research findings suggest that these genes have increased expression in the specific tissues of patients with MS, with blood samples showing the most pronounced increase in their expression levels.

Conclusion: Although these increases were not statistically significant, our study provides valuable insights for further research on gene expression in MS patients. This study demonstrates that potential biomarkers are essential in comprehending the molecular basis of MS. Additional research is needed to substantiate the findings presented in our study and enhance our understanding of the role of genes in the pathogenesis of MS.

Keywords: Multiple sclerosis, *SIRT7, SEMA3A, SEMA3F*

Introduction

Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system, marked by inflammation, demyelination, and axon damage. Damage occurs to the myelin sheaths, oligodendrocytes, and, to a lesser degree, the axons and nerve cells. The disease commonly manifests in young adults, with a prevalence ranging from 2 to 200 per 100,000 based on geographic location (1). The incidence of MS is 2-3 times higher in female patients than in male patients.

The exact cause of MS remains unknown (source). However, it is widely believed that genetic and environmental risk factors interact in a complex inheritance pattern. This disease is the leading cause of disability among non-traumatic neurological conditions in young adults. MS, defined as a chronic, neuroinflammatory, neurodegenerative disease, encompasses diverse clinical subtypes with complex pathogenesis and distinct prognoses (1). It is crucial to comprehend the molecular and chemical structure of *SIRT* genes to analyze their biological role, given the positive outcomes of recent studies in treating various health issues (2).

Sirtuins, a protein family involved in protein deacetylase and adenosine diphosphate-ribosyl transferase activities, were initially detected in yeast. Thus far, mammalian cells have been found to possess seven isoforms of sirtuins, namely *SIRT 1-7*. While *SIRT1* is located in both the cytoplasm and nucleus, *SIRT6* and *SIRT7* are strictly nuclear, and *SIRT3*, *SIRT4*, and *SIRT5* are

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confined to the mitochondria (3). These proteins are involved in numerous cellular functions, such as transcription, aging, inflammation, and apoptosis (4).

Recent studies suggest that *SIRT7* is involved in ribosome biogenesis, particularly in dividing cells, and may have implications for the development of thyroid and breast cancer (5). The *SIRT7* gene, which we intend to study, is located on chromosome 17q25.3 (6). It encodes a protein that belongs to class IV of the sirtuin family, homologous to yeast Sir2 protein (7). Similar to yeast sirtuin proteins, *SIRT7* is also involved in regulating epigenetic gene silencing and suppressing rDNA recombination.

SIRT7 expression is higher in metabolically active tissues, such as the liver and spleen, and lower in non-proliferating tissues, such as the heart and brain (8). The mammalian homolog of Sir2, *SIRT7*, serves as an activator of RNA polymerase I transcription (9).

Semaphorins were initially discovered in invertebrates in 1992 (10). Semaphorin 3A (*SEMA3A*) is the first member of this family identified in vertebrates and was initially isolated from extracts of poultry brains in 1993.

The *SEMA3A* gene is located on chromosome 7q21.11 (11), while *SEMA3F* is located on chromosome 3p21.3 (12). *SEMA3F* is regarded as a potential tumor suppressor gene (13). Both *SEMA3A* and *SEMA3F* are recognized for their significant involvement in directing certain CNS pathways and peripheral nerves during the development of the nervous system. In this study, our objective was to examine the expression levels *of SIRT7*, *SEMA3A*, and *SEMA3F* in the gene regions associated with RNAs (*SIRT7*, *SEMA3A*, *SEMA3F*) extracted from the CSF and blood of newly diagnosed, drug-free patients with MS and individuals in the control group. This investigation aims to reveal the correlation between these molecular changes and MS while offering guidance for future studies.

Materials and Methods

The study was conducted at T.C. Firat University Faculty of Medicine (approved by Firat University Medical Research Ethics Committee with decision number 14 dated 26.10.2017 and session number 2020/03-18 dated 02.06.2020) by the Helsinki Declaration rules.

A total of 59 individuals participated in the study conducted at the Department of Neurology at Firat University Faculty of Medicine. The patient group comprised 31 newly diagnosed individuals with relapsing-remitting MS (RRMS) who met the revised McDonald 2017 criteria, while the control group consisted of 28 individuals diagnosed with benign intracranial hypertension.

All participants in both the patient and control groups were given comprehensive details about the informed consent form, and written consent was obtained from each participant. The study was performed by the principles of the ethics committee.

A total of 5 mL of CSF and 2 mL of blood samples were collected from individuals in an ethylenediamine tetraacetic acid tube and subjected to further analysis at the Molecular Genetics Laboratory of the Faculty of Health Sciences at Firat University. The CSF was obtained from 16 patients with MS and 14 controls diagnosed with benign intracranial hypertension. Blood samples were collected from 15 patients diagnosed with MS and 14 patients in the control group diagnosed with benign intracranial hypertension. However, no serological or CSF indices of inflammation were detected in the control group diagnosed with intracranial hypertension.

We isolated RNA from both CSF and total blood using the EXTRACTME Total RNA Kit (BLIRT, EM09.1). We assessed the quality and quantity of the isolated RNA samples in our study using a Nanodrop device, evaluating their suitability for expression analysis. The RNA samples were stored at -20 ºC until the analysis of RNA expression. The high-capacity cDNA Synthesis Kit (WIZ Biosolutions, W2211) was utilized to synthesize cDNA from RNA.

Gene Expression Assay (GENEX-250, Suarge Biyoteknoloji, Turkey) was used to prepare quantitative polymerase chain reaction (PCR) experiments with Forward and Reverse Primers specific for *SIRT7*, *SEMA3A*, and *SEMA3F* genes while adhering to the AMPLIFYME SYBR Universal Mix (AM02, BLIRT, Poland) protocol. Finally, RNA expression levels were quantified using the StepOnePlus Real-Time PCR System (ThermoFisher Scientific, USA). RNA expression levels were determined using the ΔΔCt method normalized with ACTB as an endogenous control.

Statistical Analysis

The gene expression scores were analyzed using SPSS for Windows (version 21). The results were presented as mean ± standard deviation (SD). Analysis of variance was conducted to determine differences between the groups. The RT^2 Profiler Data Analysis Software, provided by Qiagen, was used for the analyses, with 2'Average delta CT values utilized. The 2-ΔΔCt method was employed for relative gene expression. The result was considered statistically significant if the p-value was <0.05.

Results

In this study, the patient group consisted of individuals diagnosed with MS and controls without MS. Total RNA was extracted from CSF and blood samples of these individuals, and gene expression levels for *ACTB*, *SEMA3A*, *SEMA3F*, and *SIRT7* were examined. A total of 59 participants were included in the study group, consisting of 31 patients and 28 controls. CSF

samples were obtained from 16 out of the 31 patients, while blood samples were obtained from the remaining 15 patients. Meanwhile, CSF samples were collected from 14 individuals in the control group, and blood samples were collected from the remaining 14 individuals. No additional subjective assessments were conducted in this section.

The age of the 31 patients ranged from 16 to 50 years with a mean age of 31.19 years (SD: 2.16). The gender distribution was four male and 27 female patients. The age of the 28 patients in the control group ranged from 19 to 82 years with a mean age of 50.17 years (SD: 2.16). The distribution included nine male and 19 female patients.

Table 1 summarizes the general characteristics of the patient and control groups based on CSF samples, while Table 2 summarizes the general characteristics based on blood samples. The comparison of CSF samples from patients and controls is presented in Table 3, and the results are shown in Figure 1. Abbreviations are explained upon first use.

Table 1. General characteristics of CSF sample

	Patient (16)	Control (14)
Age	31.62 (19-43)	44 (19-82)
Male	1 (6%)	4 (29%)
Female	15 (94%)	10 (71%)

CSF: Cerebrospinal fluid

Table 2. General characteristics of blood sample

	Patient (16)	Control (14)
Age	30.73 (16-50)	56.35 (25-82)
Male	3 (20%)	5 (36%)
Female	12 (80%)	9 (64%)

Table 3. Comparison of patient and control CSF samples

Gene	Control	Patient	
	2^[-Avg. Delta (Ct)]	2^[-Avg. Delta (Ct)]	Fold change
SEMA3A	0	-5,1818	36,299^
SEMA3F	0	-4,1698	17,998^
SIRT7	0	-2,3189	4,989^

CSF: Cerebrospinal fluid, Avg.: Average

Table 4. Comparison of *SEMA3A, SEMA3F,* and *SIRT7* in patient and control blood samples

Gene	Control	Patient	
	2^[-Avg. Delta (Ct)]	2^[-Avg. Delta (Ct)]	Fold change
SEMA3A	-7,2456	–7,3374	161,735^
SEMA3F	-7,7314	–6,1099	69,068^
SIRT7	0,7535	–0,8987	1,864^

Avg.: Average

The results show a significant increase in *SEMA3A* (36-fold), *SEMA3F* (17-fold), and *SIRT7* (5-fold) (upregulation) in the patient group when comparing the levels of *SEMA3A*, *SEMA3F*, and *SIRT7* in the CSF samples with those of the control group. The results of the *SEMA3A*, *SEMA3F*, and *SIRT7* comparison between patient and control blood samples are shown in Table 4. Meanwhile, Figure 2 shows the gene expression comparison of *SEMA3A*, *SEMA3F*, and *SIRT7* in patient and control blood samples.

SEMA3A was upregulated 151-fold in the control group and 161-fold in the patient group. *SEMA3F* increased 212-fold in the control group and 69-fold in the patient group (downregulation). *SIRT7* increased 0.59-fold in the control group and 1.86-fold in the patient group (upregulation).

Discussion

MS is a chronic, usually progressive disease characterized clinically by focal deterioration of the optic nerve, spinal cord, and brain, with varying degrees of improvement and relapse over the years. Typical features of MS include muscle weakness, paraparesis, paresthesias, visual loss, diplopia, nystagmus, dysarthria, tremor, ataxia, paresthesias, and bladder dysfunction.

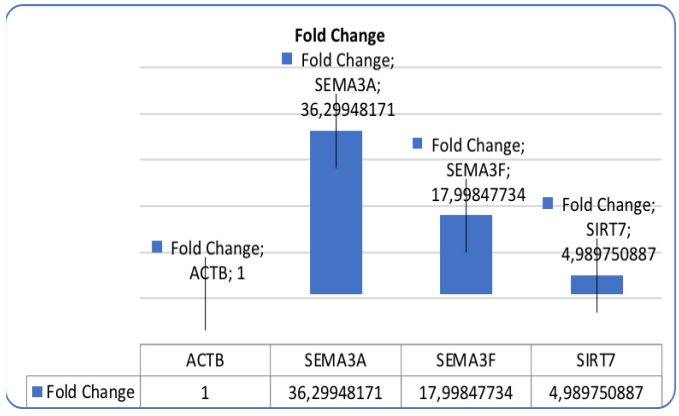

Figure 1. Comparison of patient and control CSF samples
CSF: Cerebrospinal fluid

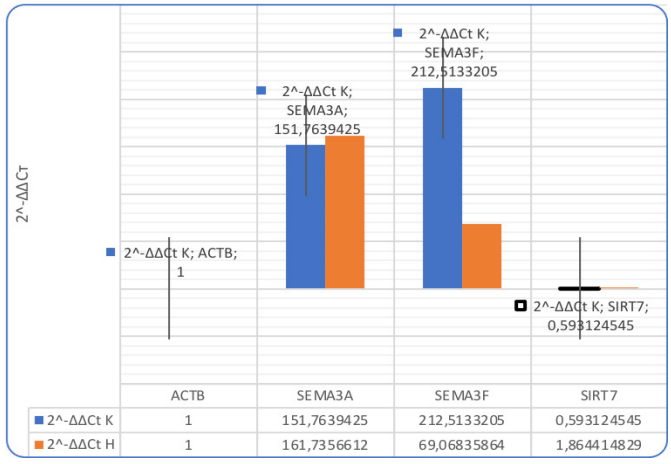

Figure 2. Comparison of patient and control blood sample

The disease is characterized by inflammation, demyelination, and axonal damage in the CNS. MS can be diagnosed both clinically and histopathologically (14). Clinical symptoms vary according to the location of the lesions and are often associated with the invasion of inflammatory cells across the blood-brain barrier, resulting in demyelination and edema (15).

The incidence of MS is 2-3 times higher in women than in men, although the exact cause is unknown, and the disease is typically observed in young individuals (16,17). However, it has been hypothesized that women are generally more susceptible to autoimmune and inflammatory diseases (18). In our study, the female-to-male ratio was also high (male/female: 4/27). The mean age of the patients was 31.19 years (16-50). MS results from a combination of both genetic predisposition and environmental factors. In other words, it is a multifactorial disease.

The objective of our study was to investigate the contribution of *SIRT7*, *SEMA3A*, and *SEMA3F* gene expression levels in CSF and blood samples of patients with MS to the pathogenesis of the disease. Magnetic resonance imaging is presently employed in the diagnostic criteria (19). Meeting these criteria can be challenging sometimes. Molecular biomarkers may help confirm the diagnosis, assess disease progression, and evaluate the efficacy of treatment (20).

The function of the sirtuin gene family is mostly related to protein acylation. Protein acylation is a post-translational modification that alters the surface charge of proteins, regulating protein conformation or protein-protein interactions, similar to phosphorylation. The implication of sirtuin genes in diabetes, metabolic syndrome, cancer, inflammation, neurodegenerative diseases, and similar chronic conditions has prompted extensive study of this gene family in these areas (21).

SIRT7 is the most enigmatic of the sirtuin isoforms. It is localized in the nucleolus and appears to be involved in the regulation of ribosomal gene expression via RNA polymerase-1, cell proliferation, and ribosome synthesis. *SIRT7* also protects cells under stress, such as endoplasmic reticulum stress, genotoxic stress, and oxidative stress induced by unfolded proteins (22). *SIRT7* is less abundant in the heart, brain, and skeletal muscle, whereas it is more abundant in proliferative tissues, such as the testis, spleen, and liver (23). However, information regarding its role in the CNS is limited. *SIRT7* gene expression is reduced in aged human stem cells, which are characterized by increased apoptosis. Decreased *SIRT7* gene expression is associated with various diseases, apoptosis, and increased DNA damage (24).

In our study, when comparing *SIRT7* gene expression levels in blood samples from the patient and control groups, a 1.86-fold increase was observed in the patient group (upregulated) (Table 4). Similarly, when comparing CSF samples from the patient and control groups, a 5-fold increase in *SIRT7* gene expression was observed in the patient group (upregulated) (Table 3). Although these increases were not statistically significant as $p>0.05$, further studies will provide a better understanding of this upregulation.

Semaphorins are the major oligodendrocyte progenitor cell (OPC) guidance molecules. Two members of the semaphorin family, *SEMA3A* and *SEMA3F*, have been shown to play important roles in OPC migration (25). Their expression varies depending on the lesion type and the degree of inflammation. In active lesions (ongoing remyelination and more inflammation) the chemoattractant *SEMA3F* is more abundant than *SEMA3A*. Conversely, in chronic lesions (less inflammation and less remyelination) the chemorepellent *SEMA3A* is more abundant than *SEMA3F* (26).

SEMA3A induces a reversible dose-dependent inhibition of OPC differentiation. Therefore, overproduction of *SEMA*3A may prevent OPCs from migrating to the demyelinated area and differentiating into myelin-synthesizing oligodendrocytes. The presence of *SEMA3A* in demyelinated lesions is associated with impaired remyelination (27). In the central nervous system, inhibiting *SEMA3A* may allow OPC migration to demyelinated areas and facilitate the remyelination process. Therefore, novel approaches are needed.

Semaphorins are aberrantly expressed in central nervous system neurons during pathogenesis. For example, *SEMA3A* is expressed at the neuromuscular junction in amyotrophic lateral sclerosis and in neurons in Alzheimer's disease (28). It has been observed that *SEMA3A* and *SEMA3F* are involved in OPC migration and their expression is increased around MS lesions. The abnormal expression of *SEMA3A* in central nervous system neurons of patients with MS (29) suggests that *SEMA3A* plays a role in oligodendrocyte or axon regeneration. In this study, we aimed to elucidate the contribution of these genes to the pathogenesis of the disease by examining their expression levels in patients with MS.

In our study, we compared the expression levels of *SEMA3A* and *SEMA3F* genes in CSF samples obtained from the patient and control groups with the control group. We found a 36-fold increase for *SEMA3A* and a 17-fold increase for *SEMA3F* in the patient group (Table 3). In the blood samples obtained from the patient and control groups, *SEMA3A* and *SEMA3F* gene expression levels were found to be increased by 161-fold (upregulated) and 69-fold (down-regulated), respectively, in the patient group compared to the control group (Table 4). Comparison of *SEMA3A*, *SEMA3F*, and *SIRT7* in patient and control blood samples showed increases in up- or down-regulated levels. However, these changes were not statistically significant. This may be due to the small number of patients and controls.

One notable aspect of this study is that the increase in gene expression was more pronounced in the blood. Furthermore, it is important to substantiate this increase with larger studies. Biomarkers can be used for diagnosis, staging, prognosis, and monitoring of treatment response (30). Another requirement is easy access to the biomarker. For example, body fluids serve as the access point for MS. These fluids can be CSF, blood, urine, and tears. It may be possible to monitor disease progression by examining the expression levels of these genes in blood samples, eliminating the need for an interventional CSF sample. As MS is a multifactorial disease, it is crucial to genetically understand the pathogenesis of the disease to contribute to disease progression and treatment approaches. *SIRT7*, *SEMA3A*, and *SEMA3F* were significantly upregulated in MS patients. However, larger studies are needed to clarify the relationship between *SIRT7*, *SEMA3A*, and *SEMA3F* gene functions and MS.

Study Limitations

This study has certain limitations. The primary constraint is within the inclusion and exclusion criteria. The inclusion criteria include a diagnosis of RRMS according to the revised McDonald 2017 criteria, the absence of any other neurological/autoimmune disease in the patient's history, and a diagnosis of benign intracranial hypertension. The exclusion criteria encompass a history of RRMS attack within the last 40 days, treatment for infection for any reason within the last 40 days, and receipt of high-dose anti-inflammatory treatment for any reason within the last 40 days.

In addition to the diagnosis of benign intracranial hypertension, the patient could have an additional disease that may be linked to the central nervous system. To overcome these limitations, examining the gene expression levels in blood samples, instead of the need to obtain CSF through interventional means, is a potential means to monitor the progression of the disease.

Conclusion

In this study, we aimed to investigate the expressions identified in the relevant gene regions of RNAs (*SIRT7*, *SEMA3A*, and *SEMA3F*) obtained from the CSF and blood of newly diagnosed, untreated patients with MS and control group individuals. The objective was to unveil any relationship between these expression changes and MS and to guide future studies. The study yielded significant findings.

In the present study, when comparing the gene expression levels of *SEMA3A* and *SEMA3F* in CSF samples from both the patient and control groups with the control group, a 36-fold increase for *SEMA3A* and a 17-fold increase for *SEMA3F* was observed in the patient group. These findings indicate a potential involvement of *SEMA3A* and *SEMA3F* in the pathology of the disease. Gene expression levels of *SEMA3A* and *SEMA3F* were found to be upregulated 161-fold and 69-fold, respectively, in the patient group compared to the control group, as demonstrated by blood samples.

Notably, gene expression increases were more pronounced in blood, emphasizing the necessity for larger studies to substantiate these findings. It may be feasible to trace the advancement of the disease by examining the expression levels of the genes in blood samples, eliminating the necessity for intervention-based CSF sample collection from patients.

Given the complexity of MS, it is vital to elucidate its genetic pathogenesis, as this contributes to an understanding of the disease's progression and treatment methodologies. Significant upregulation of *SIRT7*, *SEMA3A*, and *SEMA3F* genes was observed in patients with MS. However, further studies are needed to elucidate the relationship between *SIRT7*, *SEMA3A*, and *SEMA3F* gene functions and MS.

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Ethics

Ethics Committee Approval: The study was conducted at T.C. Firat University Faculty of Medicine (approved by Firat University Medical Research Ethics Committee with decision number 14 dated 26.10.2017 and session number 2020/03-18 dated 02.06.2020) by the Helsinki Declaration rules.

Informed Consent: All participants in both the patient and control groups were given comprehensive details about the informed consent form, and written consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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RESEARCH ARTICLE

Effect of Telerehabilitation on Verbal and Visual Memory in Multiple Sclerosis Patients: A 12-month Follow-up Study

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Abstract

Objective: Conditions such as chronic fatigue or physical disability, particularly regular work, limit the treatment options that require continuous participation in multiple sclerosis (MS) patients. The pandemic period highlighted the importance of home health services and increased interest in the current cognitive telerehabilitation (TR) applications. This study aims to determine the short and long-term effects of TR and the factors that influence it.

Materials and Methods: This study included 61 MS patients. During 6 months, 32 patients (mean age =41.21±11.57; females =23 and males =9) received structured TR, and 29 patients (mean age =37.62±6.95; females =20 and males =9) received unstructured mental exercises. After the 6-month intervention period, another evaluation was conducted at the end of the 6-month silent period to evaluate the protective effect of the exercises. The participants were administered with Rao's Brief Repeatable Battery of neuropsychological tests at the beginning of the study and at the 6th and 12th months. The repeated measures analysis of variance was used to evaluate performance changes over time, and the repeated measures ANCOVA test was used to assess the factors affecting these changes.

Results: On average, most participants (59.4%) used the TR application for less than 4 h each week. TR and unstructured exercises positively affected Spatial Recall Test-Total Learning/Con and Paced Auditory Serial Addition Test performances, and the total number of relapses affected these results. The total verbal learning Selective Reminding Test-Total Learning (SRT-TL), long-term storage (SRT-LTS), and delayed recall (SRT-DR) skills of all participants decreased at the end of the silent period. The factors affecting this deterioration are the duration of the disease, the total number of relapses, and the age of onset of the disease.

Conclusion: Our findings showed that TR and unstructured exercises had no differential effect on cognitive performance. In addition, the decrease in verbal memory performances in the silent period showed that the age of onset of the disease and the total number of relapses could be important evaluation criteria for cognitive involvement.

Keywords: Follow-up, multiple sclerosis, telerehabilitation, verbal memory, visual memory

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, degenerative disease of the central nervous system that causes demyelination and axonal transection (1). It is most often diagnosed in the early stages of life (between the ages of 20 and 30), and 20% of patients develop into the progressive phase of increased physical disability within an average of 15 years (2). In addition, approximately 50-60% of patients experience cognitive decline (3), which negatively affects many aspects of everyday life, including the ability to participate in society and maintain employment (4,5). Although there are several pharmacological treatment options for treating or reducing sensory and motor symptoms, there is no such method for treating cognitive impairments (6).

Telerehabilitation (TR) is the provision of therapy and rehabilitation services using various telecommunication mediums, most notably the Internet and computer networks. TR has the potential to reduce time and money and increase access and treatment adherence in groups with high or increasing disability (7,8). The advantages of TR include providing therapy

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to rural areas, expanding rehabilitation opportunities with computer-assisted systems, indirectly increasing the quality of life, and reducing medical expenses and travel time (9). According to Kairy et al., (10), a meta-analysis of the effects of TR on 28 studies, clinical outcomes after the intervention were typically positive, and clinical processes, such as participation and compliance, continued uninterrupted. In addition, it was observed that the consultation period was longer, but the satisfaction remained high and was also cost-effective.

Physical, neurogenic, or cognitive disorders, such as motor weakness, spasticity, ataxia, fatigue, and amnesia, are common in MS patients. Long-term multidisciplinary management is recommended for MS patients due to the cumulative effects of these symptoms (11,12). Patients often lack access to MS management advances due to limited mobility, fatigue, and high travel costs. TR is viewed as a potential tool for improving health services by reducing care costs (13). This study aims to evaluate the effects of a structured rehabilitation application that has been shown to affect a specific population in the MS clinic (14) when used remotely on cognitive functions. The study also evaluated the potential protective effect of TR at the end of the non-intervention (silent) period.

Materials and Methods

University of Health Sciences Turkey, Hamidiye Clinical Research Ethics Committee approved the study protocol (approval number: 20-60, date: 28.09.2020). All participants provided their written consent after being fully informed.

Participants

The study included 61 patients with MS according to McDonald's criteria (15). The ages of these participants were between 23 and 65 years, the disease duration ranged from 2 to 38 years, and their EDSS score ranged from 1 to 5.5. In addition, the age of onset of the disease varies between 10 and 55. The study included participants who were at least primary school graduates, actively using mobile devices, had no relapse in the last 3 months, or had not received corticosteroid treatment in the previous 1 month. Symbol Digit Modalities Test (SDMT) (<37.25±12.98) and PASAT (<34.51±12.47) scores were used to identify MS patients with cognitive impairment (16).

Neuropsychological Assessment

Rao's Brief Repeatable Battery of neuropsychological tests (BRB-N) (17) was used to evaluate the changes in the cognitive profiles of the participants at the beginning of the TR application and at the sixth and 12th months. The BRB-N consists of five subtests: the Selective Reminding Test (SRT), which measures immediate (SRT-IML) and total learning (SRT-TL), delayed recall (SRT-DR), long-term storage (SRT-LTS), and controlled retrieval (SRT-CLTR) skills. 10/36 Spatial Recall Test measures immediate (SPART-IML) and total learning (SPART-TL), delayed recall (SPART-DR), and confabulations (SPART-TL/Con and SPART-DR/Con). The SDMT, which measures the speed of information processing, and the Paced Auditory Serial Addition Test (PASAT 3"), which measures attention and multitasking abilities. Finally, the Controlled Oral Word Association Test (COWAT) assesses verbal fluency categorically (COWAT-Animal) and lexically (COWAT-KAS). In addition to this battery, the Stroop test was used to evaluate participants' interference abilities (STROOP D), and the Beck Depression Inventory (BDI) was used to evaluate their mood.

Telerehabilitation Application and Intervention Protocols

In the study, the participants were divided into two groups - telerehabilitation intervention group (TR) and unstructured intervention group (nTR) - and two periods - intervention period and silent period. During the intervention period, 32 patients were given NOROSOFT, and 29 patients were given a home-based task. The NOROSOFT program was used for the TR application. The protocol has been described in a previous study (14). In addition to the protocol, the weekly usage times of the participants in the current study were determined using the interface of the NOROSOFT application. Moreover, the control group received no TR and was required to solve SUDOKU for at least 1 h a day for 6 months. However, the exercise frequency of the control group was not included in the research data because it was based only on their verbal statements.

Statistical Analysis

The SPSS program (Version 24.0, IBM Corp., Armonk, New York) was used to analyze the obtained data. Kolmogorov-Smirnov test was used to evaluate whether the data fit the normal distribution. Parametric tests were used because the data were normally distributed (p>0.05). The data are presented as percentage, mean, and standard deviation. The study used the repeated measures analysis of variance (ANOVA) method to understand the change in cognitive performance in intervention and the silent period. Repeated measures ANCOVA test was used to understand the effect of numerical variables on cognitive performances that changed during the intervention and silent periods. P-values of less than 0.05 were considered as significant.

Results

Demographic Features

The nominal and ordinal demographic characteristics of 61 participants with TR and without TR (nTR) are shown in Table 1. Although the independent sample t-test results were insignificant (p>0.05), the mean age of the TR group was 41.21±11.57, and the mean age of the nTR group was 37.62±6.95. The duration of disease in the TR group was 11.46±8.28, the age at onset of disease was 29.71±10.11, and the mean total relapse number was 6.96±4.41, whereas the

duration of disease in the nTR group was 9.68±5.06, the age of onset was 27.93±6.67, and the mean total number of relapses was 5.20±2.48. The weekly duration of the patients participating in the TR application ranges from 0.3 to 7 days. On average, the weekly attendance was 1.88±2.44 days.

In the present study, the distribution of factors, such as education level, disease progression, and depression level, which are known to affect cognitive performance, was evaluated between the TR and nTR groups. However, neither education level, disease progression, nor depression levels were shown to be significantly different across the groups (p>0.05).

The Effects of The Intervention Period on Cognitive Performance: Possible Benefits

Changes in neuropsychological tests administered to the patients before and 6 months after the application were evaluated with repeated measures ANOVA. Accordingly, there was no significant change in verbal and visual immediate learning (SRT-IML and SPART-IML), total learning (SRT-TL and SPART-TL), delayed recall (SRT-DR and SPART-DR), verbal long-term storage (SRT-LTS) and retrieval (SRT-CLTR) abilities (Table 2). In addition, when the errors made in total visual learning (SPART-TL/Con) were evaluated, a significant improvement was found within 6 months [F(1, 59)=4,713, p=0.034]. There was a decrease in errors made during visual learning in both groups. Table 2 shows that this significant change was at the trend level between the groups [F(1, 59)=3,660, p=0.061; Figure 1].

When the effect of the exercises performed for 6 months was evaluated on working memory and ability to maintain attention (PASAT 3"), a significant improvement was observed [F(1, 59)=21,202, p=0.000). However, as seen in Table 2, this

Table 1. Demographic features of patients

n		TR		nTR	
		%	n	%	
Sex	Female	23	71.9	20	69.0
	Male	9	28.1	9	31.0
Education	Primary	8	25.0	8	27.6
	Secondary	0	0.0	2	6.9
	High	7	21.9	9	31.0
	Undergraduate	16	50.0	8	27.6
	Graduate	1	3.1	2	6.9
MS type	RRMS	26	81.3	24	82.8
	SPMS	5	15.6	4	13.8
	CIS	1	3.1	1	3.4
Duration of TR usage (hr/weekly)	<4	19	59.4		
	≥4	13	40.6		

TR: Telerehabilitation intervention, nTR: No telerehabilitation intervention, RRMS: Relapsing-remitting multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, CIS: Clinically isolated syndrome

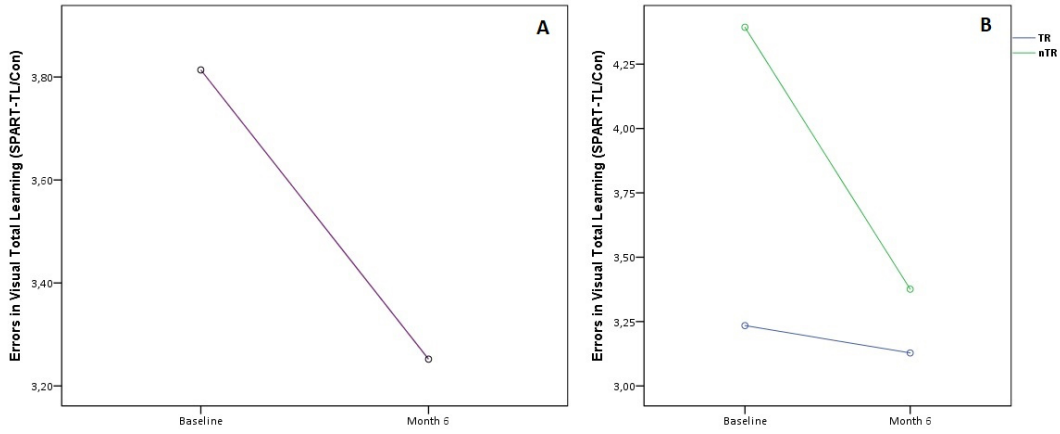

Figure 1. Change in 10/36 SPART-TL confabulation scores after the intervention period. (a) Within-subject effect: repeated measures ANOVA results of score change before splitting in the telerehabilitation (TR) and unstructured exercise (nTR) groups. (b) Between-subject effect: repeated measures ANOVA results of previous score change dividing those in the telerehabilitation (TR) and unstructured exercise (nTR) groups

significant change was not observed between the groups [F(1, 59)=1,078, p=0.303; Figure 2].

In addition, it was observed that information processing speed, categorical and lexical verbal fluency, or interference skills did not change significantly within the 6 months or between the groups (p>0.05, Table 2).

Factors Affecting Cognitive Improvement After the Intervention Period

SPART-TL/Con and PASAT 3" scores were evaluated with repeated measures of the ANCOVA test. According to these results, it can be said that the total number of relapses of the patients [F(1, 55)=6.257, p=0.015) is effective on the errors made in total

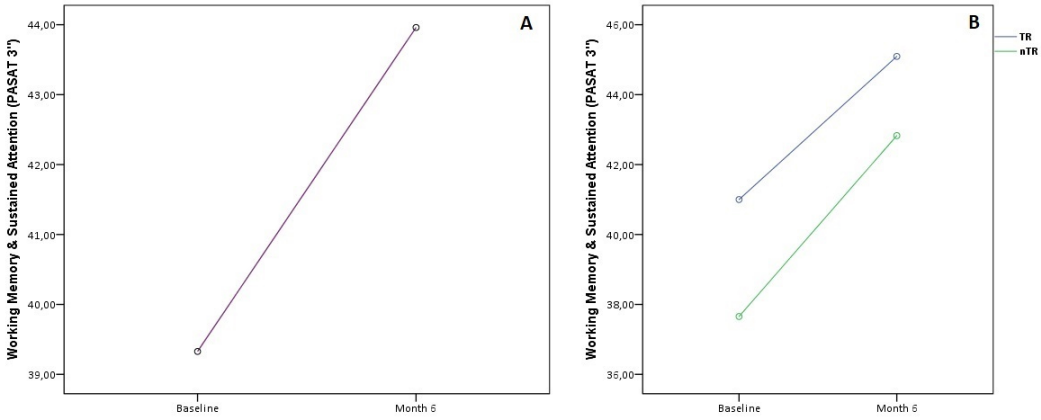

Figure 2. Change in PASAT 3" scores after the intervention period. (a) Within-subject effect: repeated measures ANOVA results of score change before splitting in the telerehabilitation (TR) and unstructured exercise (nTR) groups. (b) Between-subject effect: repeated measures ANOVA results of previous score change dividing those in the telerehabilitation (TR) and unstructured exercise (nTR) groups

Table 2. The effects of the ıntervention period (baseline to month 6)

	TR (n=32)		nTR (n=29)		p**	F***	p***
	Baseline*	Month 6	Baseline	Month 6			
SRT-IML	4.75±1.29	5.34±1.51	5.72±1.50	4.96±1.20	0.660	0.963	0.330
SRT-TL	7.73±1.46	7.92±1.47	7.95±1.20	7.83±1.18	0.848	0.055	0.816
SRT-LTS	38.21±12.84	38.90±14.18	36.44±11.66	39.37±11.29	0.329	0.060	0.808
SRT-CLTR	28.93±12.94	29.00±16.22	25.82±10.35	28.44±12.99	0.454	0.391	0.534
SRT-Int	0.43±1.01	0.43±0.80	0.17±0.46	0.31±0.84	0.636	1,710	0.196
SRT-DR	7.56±2.72	7.46±2.79	6.75±2.42	7.34±2.36	0.360	0.580	0.449
SPART-IML	3.75±1.60	3.71±1.59	4.27±1.99	3.72±2.15	0.327	0.519	0.474
SPART-TL	4.54±1.44	4.80±1.53	5.20±1.55	4.67±1.58	0.567	0.712	0.402
SPART-TL/Con	3.23±1.93	3.12±1.61	4.39±1.36	3.37±2.01	0.034	3,660	0.061
SPART-DR	4.43±1.72	4.93±1.88	5.17±2.61	4.17±2.31	0.483	0.001	0.972
SPART-DR/Con	4.03±2.68	3.59±2.06	4.31±2.31	4.48±3.08	0.720	1,159	0.286
PASAT 3"	41.00±10.57	45.09±10.33	37.65±12.27	42.82±11.84	0.000	1,078	0.303
SDMT	35.65±14.02	37.62±14.78	37.62±13.02	34.75±12.15	0.578	0.018	0.895
COWAT-Animal	20.81±4.66	22.46±5.17	22.31±4.01	20.37±5.22	0.840	0.083	0.775
COWAT-KAS	31.96±14.35	37.43±15.22	32.72±14.44	31.86±13.19	0.055	0.478	0.492
COWAT-Total	53.09±16.86	59.28±18.49	54.34±18.00	52.93±17.14	0.090	0.351	0.556
STROOP D	45.55±30.48	41.86±25.43	47.20±28.30	56.74±38.22	0.327	1,269	0.264
BDI	11.25±9.72	10.62±9.24	12.68±6.86	11.13±6.25	0.254	0.268	0.607

TR: Telerehabilitation intervention, nTR: No telerehabilitation intervention, *mean ± standart deviation, **p-value of within-subjects effect, ***F and p-value of between subject effect, SRT-IML: Selective reminding test-immediate learning, SRT-TL: Selective reminding test-total learning, SRT-LTS: Selective reminding test-long term storage, SRT-CLTR: Selective reminding test-controlled long term retrieval, SRT-Int: Selective reminding test-intrusion, SRT-DR: Selective reminding test-delayed recall, SPART-IML: Spatial recall test-immediate learning, SPART-TL: Spatial recall test-total learning, SPART-TL/Con: Spatial Recall test-total learning confabulations, SPART-DR: Spatial recall test-delayed recall, SPART-DR/Con: Spatial Recall test-delayed recall confabulations, PASAT: Paced auditory serial addition test, SDMT: Symbol digit modalities test, COWAT: Controlled oral word association test, BDI: Beck depression inventory

visual learning (SPART-TL/Con). Age, duration of disease, and age of onset of disease did not have any effect on this change. None of these covariates affected the improvement in working memory and ability to maintain attention (PASAT 3", p>0.05).

Effects of the Silent Period on Cognitive Performance: Possible Protective Effect

Positive or negative cognitive differences after TR or exercise were evaluated with repeated measures ANOVA. Accordingly, no changes were observed in visual immediate learning (SPART-IML), total learning (SPART-TL), delayed recall (SPART-DR), errors in total learning and delayed recall (SPART-TL/Con and SPART-DR/Con), maintaining attention (PASAT 3"), information processing (SDMT), verbal fluency (COWAT), interference (STROOP D), or mood (BDI) (p>0.05). However, when verbal total learning (SRT-TL; F(1, 59)=4,860, p=0.031), long-term storage [SRT-LTS; F(1, 59)=9.37, p=0.003], retrieval [SRT-CLTR; F(1, 59)=8,576, p=0.005], and delayed recall [F(1, 59)=3,947, p=0.052] skills were evaluated, significant deterioration were observed in both groups. As shown in Table 3, it can be said that the verbal learning and recording capacities of both the TR group and the nTR group were not preserved after the 6-month exercise period.

Factors Affecting Cognitive Deterioration After a Silent Period

The factors affecting the performance decline of the patients at the end of the silent period were evaluated with the repeated measures ANCOVA test. Accordingly, it was observed that patients' age [F(1, 55)=3,943, p=0.052] and a total number of relapses [F(1, 55)=5.269, p=0.026) affected the decrease in long-term verbal storage. In addition, disease duration [F(1, 55)=3,943, p=0.052), age of disease onset [F(1, 55)=4,079, p=0.048), and patient's age [F(1, 55)=4,145, p=0.047) were found to be effective on delayed recall of verbal information (Figure 3).

Discussion

The present study showed that TR and unstructured mental exercises had no differential effect on cognitive performance at the end of the 6-month intervention period. At the end of this period, it was observed that the patient's capacity to maintain attention (PASAT 3") increased and the errors made while scanning visual information (SPART-TL/Con) decreased. However, these developments did not differ between groups. In addition, a decrease in verbal memory performance was observed at the end of the 6-month silent period after the intervention. In particular, learning verbal information (SRT-TL), long-term storage (SRT-LTS), and recall (SRT-DR) skills have decreased. However, the decline in these skills did not differ between the intervention groups. In addition, it was observed that the improvement after the intervention period varied according to the number of relapses of the patients. It was found that factors, such as current age, disease duration, or disease onset age, did not affect this development. Contrary to these findings, the problems experienced in restoring verbal information at the end of the silent period are related to the duration of the disease and the age of onset of the disease.

There are few studies in which home-based cognitive TR practices have been applied to MS patients (18,19). These studies include fatigue, balance control, and strengthening exercises (20,21). In a randomized and double-blind study by Charvet et al. (19), the information processing (SDMT) and visual memory (BVMT-R) skills of the intervention group (adaptive cognitive remediation) improved. The reason for the difference in our results may be that the control group of this study was also semistructured. According to a TR meta-analysis by Di Tella et al. (18), the integrated TR approach mainly reduces physical problems and has little effect on cognitive impairments. It is noteworthy that most of the studies were conducted with populations other than MS, such as Alzheimer's disease, mild

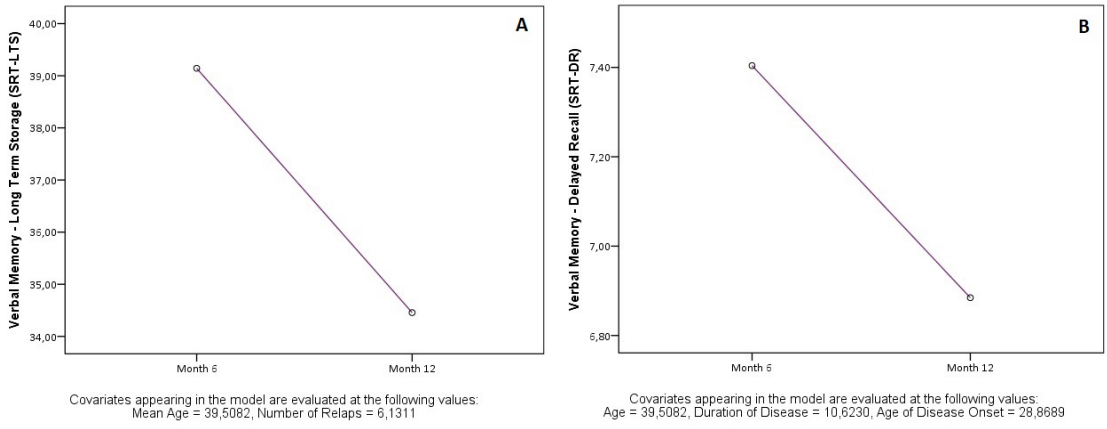

Figure 3. Change in SRT-LTS and SRT-DR scores after a silent period. (a) Repeated measures ANCOVA results of the factors affecting the long-term storage of information in verbal memory after the silent period. (b) Repeated measures ANCOVA results of the factors affecting the delayed recall score change of stored data after the silent period

Table 3. Effects of silent period (month 6 to month 12)

	TR (n=32)		nTR (n=29)		p**	F***	p***
	Month 6*	Month 12	Month 6	Month 12			
SRT-IML	5.34±1.51	5.65±1.57	4.96±1.20	5.00±1.36	0.369	2.737	0.103
SRT-TL	7.92±1.47	7.66±1.62	7.83±1.81	7.36±1.55	0.031	0.444	0.508
SRT-LTS	38.90±14.18	34.25±15.91	39.37±11.29	34.72±13.73	0.003	0.021	0.885
SRT-CLTR	29.00±16.22	24.96±14.89	28.44±12.99	24.31±14.04	0.005	0.030	0.863
SRT-Int	0.43±0.80	0.34±0.70	0.31±0.84	1.10±1.44	0.060	3.310	0.074
SRT-DR	7.46±2.79	6.87±2.88	7.34±2.36	6.89±2.25	0.052	0.007	0.934
SPART-IML	3.71±1.59	4.28±1.98	3.72±2.15	4.13±1.80	0.091	0.031	0.861
SPART-TL	4.80±1.53	4.67±1.58	5.25±1.82	5.00±1.84	0.098	0.256	0.615
SPART-TL/Con	3.12±1.61	3.09±1.90	3.37±2.10	3.22±2.22	0.678	0.175	0.677
SPART-DR	4.93±1.88	5.25±2.06	4.17±2.31	5.02±2.17	0.105	1.465	0.231
SPART-DR/Con	3.59±2.06	3.62±2.25	4.48±3.08	3.72±2.96	0.278	0.725	0.398
PASAT 3"	45.09±10.33	43.87±11.16	42.82±11.84	43.34±11.34	0.758	0.283	0.597
SDMT	37.62±14.78	36.71±12.09	34.75±12.15	35.34±12.95	0.901	0.468	0.496
COWAT-Animal	22.46±5.17	21.65±4.81	20.37±5.22	20.44±4.93	0.571	2.187	0.144
COWAT-KAS	37.43±15.22	35.93±14.32	31.86±13.19	29.44±11.88	0.131	3.360	0.072
COWAT-Total	59.28±18.49	57.90±17.76	52.93±17.14	49.55±15.50	0.118	3.099	0.084
STROOP D	41.86±25.43	41.19±27.85	56.74±38.22	55.27±36.75	0.691	3.424	0.069
BDI	10.62±9.24	10.75±7.70	11.13±6.25	9.96±6.85	0.626	0.007	0.934

TR: Telerehabilitation intervention, nTR: No telerehabilitation ınterventıon, *mean ± standart deviation, **p-value of within-subjects effect, ***F and p-value of between subject effect, SRT-IML: Selective reminding test-immediate learning, SRT-TL: Selective reminding test-total learning, SRT-LTS: Selective reminding test-long term storage, SRT-CLTR: Selective reminding test-controlled long term retrieval, SRT-Int: Selective reminding test-intrusion, SRT-DR: Selective reminding test-delayed recall, SPART-IML: Spatial recall test-immediate learning, SPART-TL: Spatial recall test-total learning, SPART-TL/Con: Spatial recall test-total learning confabulations, SPART-DR: Spatial recall test-delayed recall, SPART-DR/Con: Spatial recall test-delayed recall confabulations, PASAT: Paced auditory serial addition test, SDMT: Symbol digit modalities test, COWAT: Controlled Oral Word Association Test, BDI: Beck depression inventory

cognitive impairment, and primary progressive aphasia. According to a meta-analysis by Cotelli et al. (22), the effects of cognitive rehabilitation are relatively limited, and the quality of the method needs to be improved. In addition, unlike our results, cognitive TR applied in neurodegenerative diseases is more effective than traditional face-to-face methods, but these results do not appear to be valid for MS disease for now.

Our study also evaluated in terms of mood levels. One study (23) has stated that depression affects cognitive performance, but no study has been found to evaluate its effect on TR. Unlike our study, most studies evaluated fatigue and quality of life (24).

Study Limitations

Some points should be evaluated in further research. The information obtained on the nTR group depended only on the verbal statement of the participant, and the absence of weekly follow-up interviews over the phone is an important shortcoming of this study. In addition, there are studies in which the intervention and silent period are kept shorter because assessing the rehabilitation effect is difficult (25,26). The follow-up of the intervals between neuropsychological assessments may be determined differently in further studies. One of the data not included in the study is the drugs used by the participants and the duration of use of these drugs. Although studies are showing that interferon and natalizumab treatments did not provide a significant improvement in sustained attention, delayed recall, or information processing skills in both the treatment group and placebo group, it would be useful to include data on the drugs used in the study (27,28).

Conclusion

The present study found that the long-term effects of home-based TR are not discriminating between groups. In addition, the errors made during visual learning decreased and the attention span increased in all groups. However, this development was not observed in the silent period; conversely, regression was shown in the verbal learning processes independently of the groups. In our study, there was a difference between benign MS patients and RRMS patients, which used face-to-face rehabilitation software, although there was a need for improvements in remote application. Furthermore, the difference between these results is due to the evaluation intervals, the adequacy of the practitioner interface, and the lack of structuring of the control exercises.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Hamidiye Clinical Research Ethics Committee approved the study protocol (approval number: 20-60, date: 28.09.2020).

Informed Consent: All participants provided their written consent after being fully informed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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CASE REPORT

Seeing is Deceiving: Optic Neuritis Parading as Glioma

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Abstract

Optic neuritis and optic glioma are diseases that affect the optic nerve and cause visual disturbances. Although they can have different clinical presentations, they can also mimic each other. Optic glioma is a slow-growing tumor that causes gradual vision loss, whereas optic neuritis is an acute inflammatory disease that causes sudden onset vision loss and pain with eye movements. Due to the limitations of magnetic resonance imaging, distinguishing between the two conditions is not always possible. Herein, we have reported the case of a patient who was diagnosed with optic neuritis after extensive investigations and who recovered completely with medical treatment.

Keywords: Optic neuritis, optic glioma, vision loss

Introduction

Optic neuritis (ON) and optic glioma (OG) are conditions that can affect the optic nerve and cause visual problems. ON is an acute inflammatory disorder that primarily affects young individuals and presents as pain with eye movements and sudden vision loss (1). In ON, the myelin sheath is considered to be the target of an autoimmune response, which results in demyelination and inflammation (2). In contrast, OG is a slow-growing tumor that constitutes 5% of all juvenile brain tumors and is the most common primary optic nerve tumor (3,4). It can cause progressive vision loss, proptosis, and ocular misalignment, and is reportedly associated with neurofibromatosis type-1 (4). OG and ON can be mistaken for each other due to the similarities in presentation and imaging.

Herein, we have discussed the case of a patient in whom, despite the initial findings suggesting OG, a diagnosis of ON was ultimately made based on subsequent testing. We have described the patient's clinical progress and radiographic findings as well as emphasized the value of a complete clinical assessment with the right diagnostic workup.

Case Report

A 37-year-old right-handed woman presented to us with progressive vision loss in the right eye for 10 days, which eventually progressed to complete vision loss. The patient first visited an ophthalmologist when her symptoms began. The ophthalmic examination revealed a relative afferent pupillary defect and partial loss of visual field in the right eye. The patient had no complaints regarding the left eye, no pain associated with the eye movements, and no papilledema. Optical coherence tomography, color fundus photography, and fundus fluorescein angiography findings were normal. The patient was referred to a neurosurgeon for further evaluation.

A cranio-orbital magnetic resonance imaging (MRI) (Figure 1) was obtained, which revealed a lesion in the right optic nerve close to the chiasm with marked enhancement and nerve thickening. The lesion was considered to be an OG. A positron emission tomography/computed tomography was ordered, which revealed uptake in the area of the lesion. This also suggested that the lesion was an OG. Although surgery was recommended, the patient sought a second opinion.

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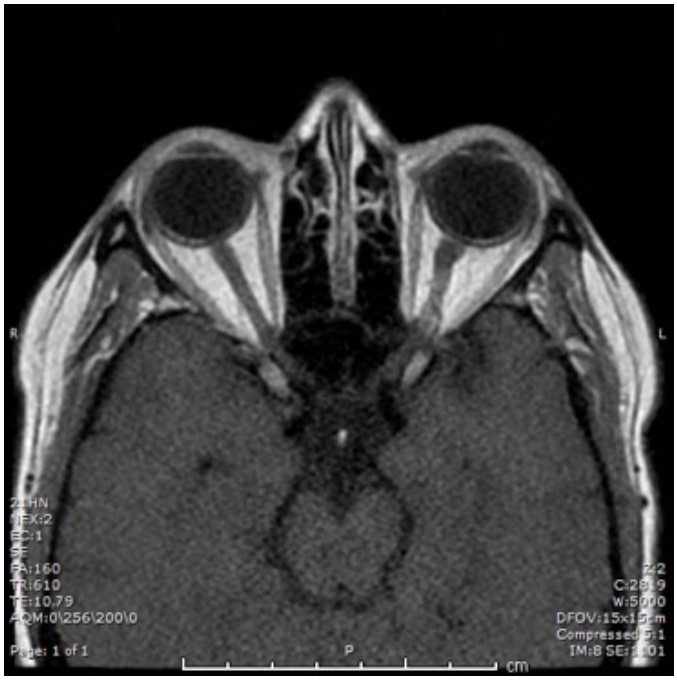

Figure 1. Cranio-orbital MRI stills before treatment

MRI: Magnetic resonance imaging

A visual evoked potential (VEP) test was performed, which could not record any response in the right eye. Thus, the patient was referred to the neurology department.

A comprehensive set of blood tests was performed to identify vasculitis markers [ANA, ENA, RF, anti-cardiolipin immunoglobulin G (IgG), and ACE], C3, C4, homocysteine, thrombophilia, anti-Borrelia and anti-Brucella IgG and IgM, herpes simplex virus-1 (HSV) and HSV-2 IgG and IgM, HLA-B27, and HLA-B5. All the tests yielded negative results. A lumbar puncture revealed increased protein content and type-2 oligoclonal bands. Additionally, serum IgG for neuromyelitis optica (NMO) and anti-MOG were negative. Considering these results, the patient was diagnosed to have ON and was treated with intravenous corticosteroids for 10 days. The patient recovered completely, and no lesions were detected on the MRI following the treatment (Figure 2). The patient was followed up for ON and the possibility of progression to multiple sclerosis without any additional treatments. Informed consent was obtained from patients.

Discussion

In this case report, we have highlighted the challenges associated with diagnosing ON and the importance of comprehensive testing via the case discussion of a 37-year-old woman with progressive vision loss in her right eye. An MRI revealed a lesion, and it was assumed to be an OG. However, a second opinion was sought. A VEP was performed, and the patient was diagnosed to have ON after extensive testing. The patient recovered completely after being treated with intravenous corticosteroids.

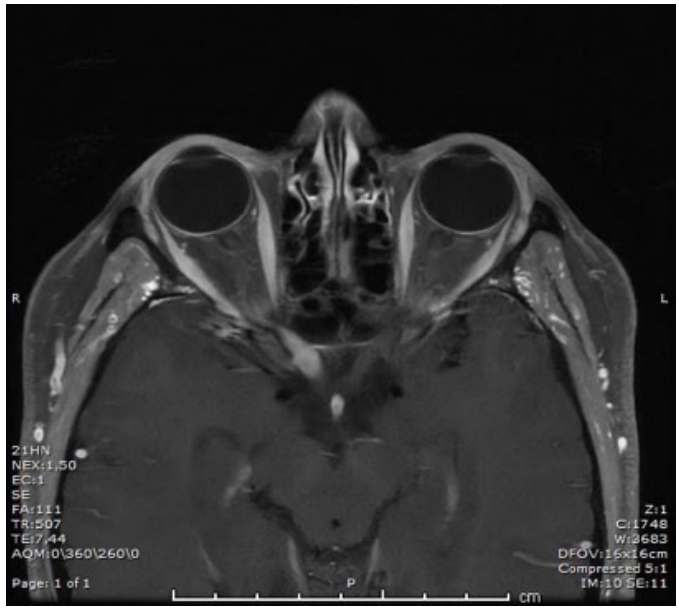

Figure 2. Cranio-orbital MRI stills after treatment

MRI: Magnetic resonance imaging

Our study findings are in accordance with those of previous studies that emphasize the challenges of differentiating between conditions that affect the optic nerve. Tumialán et al. (5) reported a case in which OG and ON mimicked each other and the diagnostic process was similar to that utilized in our patient. Even though the MRI suggested OG, the comprehensive testing led to a diagnosis of ON. Similarly, Bergmann et al. (6) reported a case that was initially thought to be OG based on the MRI findings. However, a biopsy that was subsequently performed confirmed ON.

In some cases, ON can mimic other diseases. Chacko et al. (7) reported a case of multicentric malignant glioma that was initially misdiagnosed as ON. Furthermore, Ramakrishnan et al. (8) and Kalnins et al. (9) described cases of ON that were later determined to be malignant OG.

VEP can be abnormal in conditions that affect the retina, visual pathways, or visual cortex. Hence, we considered several differential diagnoses, including NMO; ischemic and hereditary optic neuropathies; infectious ON (due to Lyme disease, syphilis, tuberculosis, or brucellosis); retinal artery occlusion; HSV; and autoimmune diseases (sarcoidosis, systemic lupus erythematosus, Sjögren's syndrome, and Behcet's disease) (10). Having an extensive differential diagnoses list is essential, especially for unusual conditions that may not be immediately diagnosed. Roy et al. (11) reported a case of ON, which was diagnosed late because his only symptom was neurosyphilis. Furthermore, Kataoka et al. (12) and Shima et al. (13) reported cases of ON that were caused by sarcoidosis and HSV type-2 infection, respectively. These reports highlight the importance of an extensive differential diagnoses list and their careful evaluation.

Other diseases that should be considered when ON is suspected are NMO and myelin oligodendrocyte glycoprotein antibody disease (MOGAD). In NMO, patients can present with ON and inflammation of the spinal cord and brain, causing more severe and longer-lasting visual issues (14). In MOGAD, ON may be the first symptom, along with disc edema (15). Although both conditions can occur bilaterally with extensive longitudinal lesions, MOGAD usually affects the intraorbital optic nerve and sheet, while NMO affects the intracranial optic nerve, chiasm, and tracts (15).

Conclusion

In summary, thorough assessment of the patient, an extensive differential diagnoses list, and appropriate diagnostic test are essential for diagnosing optic nerve diseases. The presentation of the diseases can be very similar, and thus, they can get mistaken for each other. Previous studies have demonstrated diagnostic pitfalls that are comparable to those in our case. Collectively, these reports highlight the value of a thorough clinical examination and imaging tests in distinguishing between optic nerve diseases.

Ethics

Informed Consent: Informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.A.U., Design: S.B., H.A.U., Data Collection or Processing: H.G., Analysis or Interpretation: O.Y.K., Literature Search: S.B., H.A.U., Writing: S.B.

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

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