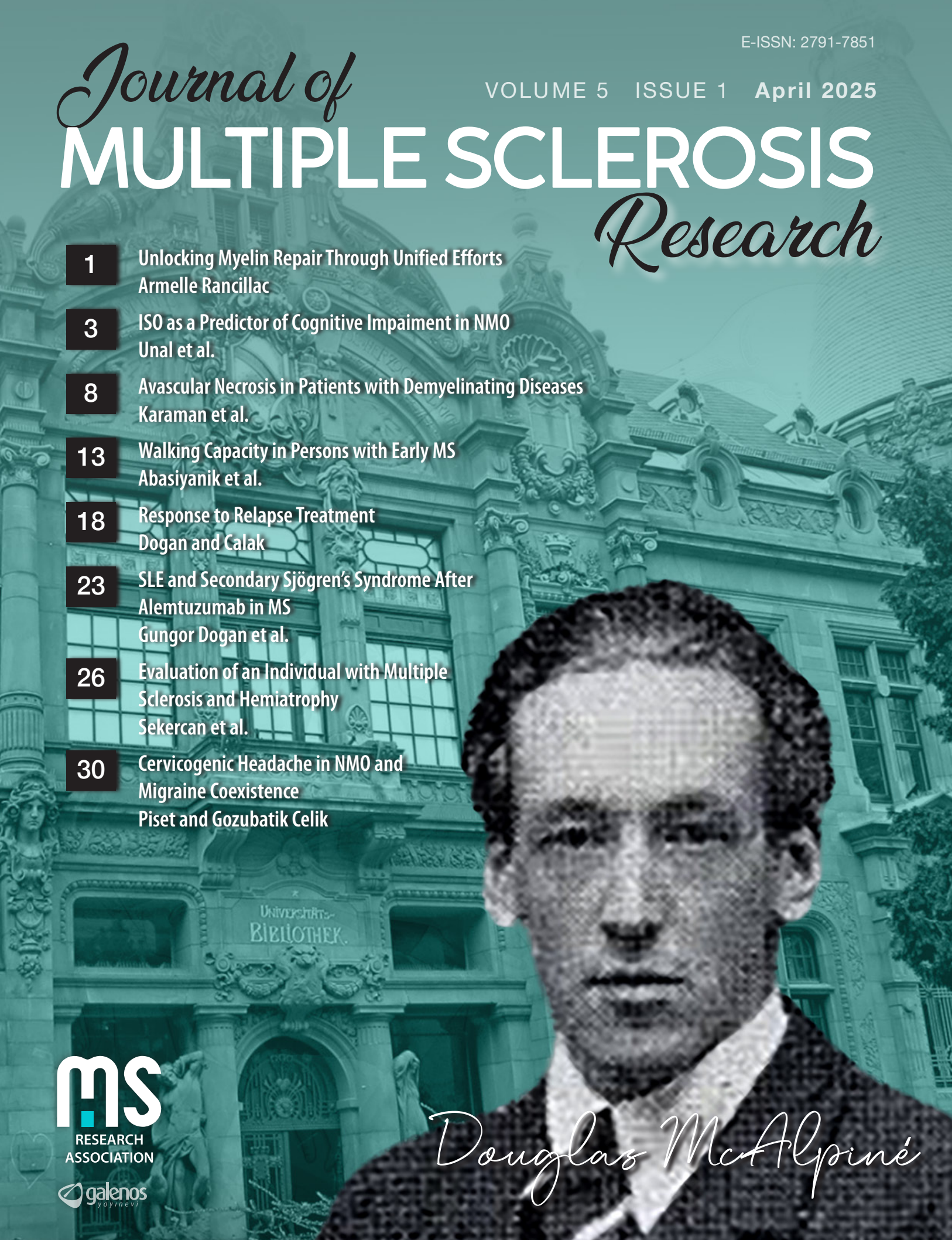
E-ISSN: 2791-7851

VOLUME 5 ISSUE 1 April 2025

Journal of MULTIPLE SCLEROSIS Research



Douglas McAlpine

MS RESEARCH ASSOCIATION

galenos yayinevi

Journal of
MULTIPLE SCLEROSIS
Research

MS ARAŞTIRMALARI DERNEĞİ

Please refer to the journal's webpage **(https://jmsres.com/)** *for "Ethical Policy" and "Instructions to Authors".*

The editorial and publication process of the Journal of Multiple Sclerosis Research are shaped in accordance with the guidelines of the ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing. Journal of Multiple Sclerosis Research is indexed in **J-Gate, Embase, Türk Medline, EBSCO Host** *and* **Gale***.*

The journal is published online.

Owner: *Multiple Sclerosis Research Association*

Responsible Manager: *Serkan Ozakbas*

galenos yayınevi

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkiye
Phone: +90 (530) 177 30 97 / +90 (539) 307 32 03
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publication Date: May 2025

E-ISSN: 2791-7851

International scientific journal published triannual.

Journal of MULTIPLE SCLEROSIS Research

MS ARAŞTIRMALARI DERNEĞİ

CONTENTS

DOI: 10.4274/jmsr.galenos.2025.2025.1-1

J Mult Scler Res 2025;5(1):1-2

LETTER to the EDITOR

The Future of Multiple Sclerosis Research: Unlocking Myelin Repair Through Unified Efforts

Armelle Rancillac

Center for Interdisciplinary Research in Biology, Collège de France, CNRS, INSERM, Université PSL, Paris, France

Dear Editor,

A new French foundation for research and patient support, France Sclérose en Plaques, was established on May 15, 2024, by merging the following three major organizations the "Association pour la Recherche sur la Sclérose En Plaques", the "Ligue Française contre la Sclérose en Plaques", and the "Union pour la lutte contre la sclérose en plaques". This new foundation unites the efforts to fund research, support patients, and raise awareness regarding multiple sclerosis (MS), marking a pivotal step in combating the disease.

For the 26th edition of Brain Awareness Week, the France Sclérose en Plaques and French Glial Cells Club organized a conference on MS at the Collège de France to raise public awareness regarding MS. Professor Céline Louapre and Dr. Brahim Nait Oumesmar from Sorbonne University presented the current advancements in MS research and the therapeutic prospects (1). The event also featured information booths and discussions regarding MS, providing a forum for debate between patients and the scientific community.

During this event, the speakers presented actual MS treatment modalities that primarily focused on immunomodulators and immunosuppressants that reduce inflammation and relapses. However, these drugs cannot entirely halt disease progression (Figure 1). Persistent inflammation in older lesions on high-resolution magnetic resonance imaging highlight the need for therapies targeting the underlying disease activity. Although 15 immune-modulating drugs are currently available, no therapy addresses the central nervous system's repair processes (2).

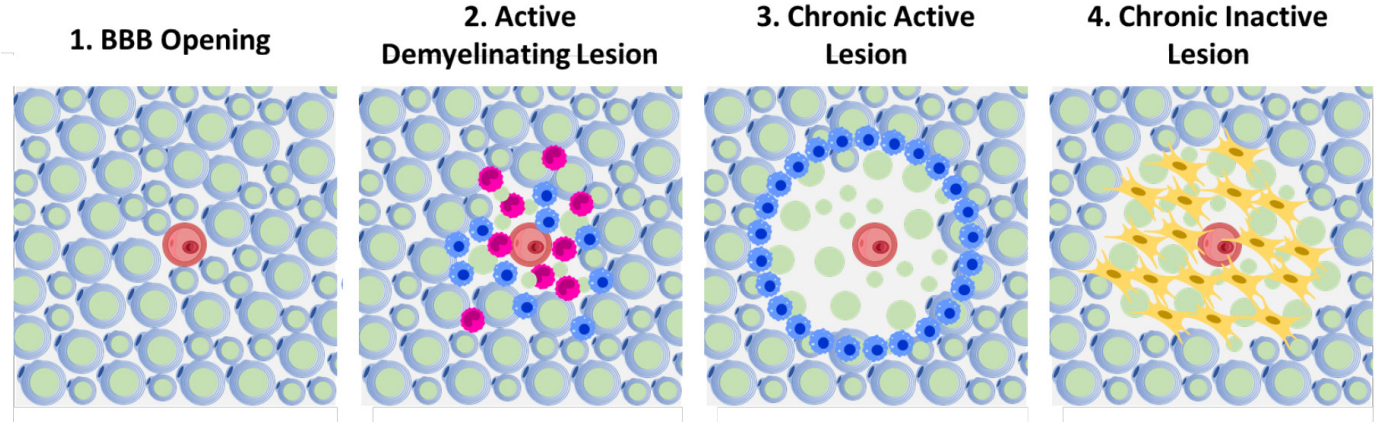


Figure 1. Formation of a chronic inactive lesion. **(1)** Opening of the Blood-Brain Barrier (BBB). **(2)** Immune cell attack. **(3)** Clearance by macrophages. **(4)** Astrocytes proliferate and form a glial scar

Address for Correspondence: Armelle Rancillac, Center for Interdisciplinary Research in Biology, Collège de France, CNRS, INSERM, Université PSL, Paris, France
E-mail: armelle.rancillac@college-de-france.fr **ORCID-ID:** orcid.org/0000-0003-1085-5929
Received: 04.01.2025 **Accepted:** 24.01.2025 **Epub:** 11.03.2025 **Publication Date:** 09.05.2025

Cite this article as: Rancillac A. The future of multiple sclerosis research: unlocking myelin repair through unified efforts. J Mult Scler Res. 2025;5(1):1-2

Emerging Insights Into Remyelination Studies

Research is progressively moving toward remyelination strategies by examining how oligodendrocyte precursor cells (OPCs) mature and contribute to the regeneration of myelin. Advanced imaging technologies such as positron emission tomography are being used to monitor remyelination dynamics in real-time, offering critical insights into therapeutic efficacy, drug discovery, and stimulating neuronal activity to accelerate repair.

The discovery of promyelinating molecules, via molecular screening, in cultures of OPCs has paved the way for trials using preclinical models of myelin lesions. These molecules, primarily derived by the repositioning of existing compounds, have been selected from among 1,500 candidates using bioinformatics analyses that were designed to predict their effects on myelination and neuroprotection. After being tested in culture, these molecules have been evaluated *in vivo* in mice, which have leading to the identification of promising candidates for promoting remyelination and neuroprotection. Several of these molecules could undergo clinical trials in the near future.

Ortiz et al. (3) demonstrated that neuronal activity *in vivo* following lesion formation enhances functional myelin repair, highlighting the potential of neural stimulation techniques to promote remyelination. A clinical trial is currently underway to explore this avenue. Researchers have also aimed to overcome remyelination decline with age by exploring transcription factors (e.g., Olig2, Sox10, RXR-γ), neurotransmitters, receptors, and external influences such as microbiota and genetics (4).

Future Prospects

Future studies must focus on combining these approaches to create comprehensive strategies for remyelination. Additionally, personalized medicine that leverages patient-specific genetic and microbiome profiles may optimize treatment outcomes. These initiatives highlight the growing understanding of MS and the critical need for innovative approaches to improve patient outcomes.

References

1. Rancillac A, Louapre C, Nait Oumesmar B, Plassart-Schiess E, Boulay AC. Sclérose en plaques, les espoirs de la recherche. In: Medecine Sciences. 2024;10:770-773.
2. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis-success from bench to bedside. Nat Rev Neurol. 2019;15:53-58.
3. Ortiz FC, Habermacher C, Graciarena M, Houry PY, Nishiyama A, Nait Oumesmar B, Angulo MC. Neuronal activity in vivo enhances functional myelin repair. JCI Insight. 2019;5:e123434.
4. Graves JS, Krysko KM, Hua LH, Absinta M, Franklin RJM, Segal BM. Ageing and multiple sclerosis. Lancet Neurol. 2023;22:66-77.

DOI: 10.4274/jmsr.galenos.2025.2024-12-4

J Mult Scler Res 2025;5(1):3-7

RESEARCH ARTICLE

Can the Age of the First Symptom of Neuromyelitis Optica be Used to Predict Cognitive Impairment?

Gozde Deniz Unal[1], Said Alizada[2], Irem Kara[3], Can Calıskan[3], Ulvi Samadzade[3], Ela Simay Zengin[3]

[1]Dokuz Eylul University Institute of Health Sciences, Department of Physical Therapy and Rehabilitation, Izmir, Turkiye
[2]Dokuz Eylul University Faculty of Medicine, Department of Neurology, Izmir, Turkiye
[3]Izmir University of Economics, Medical Point Hospital, Department of Neurology, Izmir, Turkiye

Abstract

Objective: Cognitive functions, including working memory, attention, word fluency, and information processing speed, are known to be impaired in persons with multiple sclerosis (pwMS). Despite the clinical similarity of cognitive symptoms between persons with neuromyelitis optica (pwNMO) and pwMS, there is a dearth of research addressing cognitive impairment (CI) in NMO-related literature. This study aimed to examine the potential link between the age of initial symptom onset (ISO) and the presence of CI in pwNMO.

Materials and Methods: This study comprised two groups of pwNMO: eleven patients with age at ISO between 18 and 29, and 15 with age at ISO between 30 and 50. To mitigate the confounding effects on CI, pwNMO with matched education levels and ages were included in the study. A cohort of 467 healthy controls was assessed using the Brief International Cognitive Assessment for Multiple Sclerosis battery with a predefined cut-off value for CI set at 1.5 standard deviations below the mean. Participants with scores below this threshold value were classified as exhibiting CI in the respective domains. The severity of CI was stratified based on the number of impacted domains: participants exhibiting impairment in one domain were classified as experiencing moderate-to-severe impairment, those with impairment in two domains as severe, and those with impairment across all three domains as very severe.

Results: None of the pwNMO who developed ISO between the ages of 18-29 exhibited CI. However, among those with ISO between the ages of 30 and 50, three demonstrated moderate-to-severe CI, one experienced severe CI, and one showed very severe CI.

Conclusion: The study results indicate a potential link between the age at ISO and the development of CI in pwNMO. Specifically, none of the pwNMO who experienced ISO between the ages of 18 and 29 exhibited signs of CI, whereas a significant percentage of those who experienced ISO between the ages of 30 and 50 showed signs of CI to varying degrees. These findings indicated that the onset of NMO symptoms at a later age may raise the risk of developing CI. Therefore, an early initiation of treatment could be vital in preventing and managing CI in pwNMO. Additional research is warranted to validate these findings and clarify the underlying mechanisms causing this connection.

Keywords: NMOSD, cognitive impairment, age, first symptom

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune, inflammatory disease of the central nervous system affecting the optic nerve and spinal cord (1). The prevalence of NMOSD ranges from 0.07 to 10 per 100,000, while its incidence varies from 0.029 to 0.880 per 100,000. Compared to other demyelinating illnesses, it is less frequently observed (2). Although the disease mainly affects the optic nerve and spinal cord, it may also involve the brain parenchyma, third ventricle, and periaqueductal areas (3,4). Autoantibodies against astrocytes have been identified in most NMOSD patients (5). Two different definitions of seropositive and seronegative NMOSD are employed based on the presence of antibodies against the aquaporin four channels (6,7). These

Address for Correspondence: PhD Gozde Deniz Unal, Dokuz Eylul University Institute of Health Sciences, Department of Physical Therapy and Rehabilitation, Izmir, Turkiye
E-mail: gozdedenizu@gmail.com **ORCID-ID:** orcid.org/0009-0004-2434-7241
Received: 11.12.2024 **Accepted:** 21.02.2025 **Publication Date:** 09.05.2025

Cite this article as: Unal GD, Alizada S, Kara I, Calıskan C, Samadzade U, Zengin ES. Can the age of the first symptom of neuromyelitis optica be used to predict cognitive impairment? J Mult Scler Res. 2025;5(1):3-7

autoantibodies are present throughout the central nervous system, particularly in the optic nerves and spinal cord (8). They are especially evident in the periventricular regions (9). Despite the widespread belief that the cerebrum is preserved in NMO, recent research has revealed that 60% of NMO patients develop cerebral lesions (8,10). While the relationship between multiple sclerosis (MS) and cognitive functions has been well established and demonstrated in numerous studies, research on the effects of NMO on cognitive functions appears to be significantly scarce. According to recent research, NMO patients have a 30% to 70% prevalence of cognitive impairment (CI) (11). Studies involving patients with NMO and MS have demonstrated that both groups have similar cognitive profiles and that there are alterations in attention, memory, information processing speed, and verbal fluency (12-15). There is no standardized test for assessing cognitive functions in NMOSD patients. Most studies employed batteries applied for evaluating cognitive function in MS patients (9,12-21). Not every cognitive domain was assessed in these studies. Although visual and verbal memory, attention, verbal fluency, and executive functions were measured in most studies (11,14,16-20), some studies assessed only a single domain, such as attention or executive functions, to evaluate cognition (21,22). Studies on NMO have focused on serological variables, education level, depression and anxiety, brain atrophy, and lesions in gray and white matter (11-15,17,19-21). Cognitive functions such as working memory, attention, word fluency and information processing speed have been shown to be impaired in MS patients. Few studies in the NMO literature have addressed CI, despite the clinical similarities in cognitive symptoms between patients with neuromyelitis optica and MS. Due to a paucity of studies examining the effect of age at first symptom on cognition in NMO patients, we focused on this aspect across all cognitive domains.

Materials and Methods

Participants

This retrospective study included twenty-six persons with NMO (PwNMO) and 467 healthy controls (HCs). The HCs were selected from the relatives of patients presenting to our clinic and comprised individuals without a diagnosis of MS or NMO. Conversely, in the 26 NMO patients, the inclusion criteria required them to have a definite diagnosis of NMOSD between the ages of 18-50 years and to have completed the Brief International Cognitive Assessment for MS (BICAMS) battery. The exclusion criteria included having experienced an attack in the previous three months, having other neurological diseases, and being unable to follow the instructions for BICAMS. Individuals with NMO were categorized according to the age at the first symptom. Two groups were formed: 11 NMOs with first symptoms appearing between 18 and 29 years of age and 15 NMOs who experienced their first symptoms between 30 and 50 years of age. To remove potential effects on CI, the study included PwNMOs with matched educational levels and no significant age difference between the two groups. The current study protocol, compared with previous data, was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (approval no.: 3, date: 02.02.2015), and all participants provided written informed consent.

Assessment

The cognitive status was determined using the BICAMS battery, which includes the Symbol Digit Modalities Test to evaluate information processing speed, the California Verbal Learning Test-II to assess verbal memory and learning, and the Brief Visuospatial Memory Test Revised to examine visual memory and learning. Since CI in MS patients is observed in auditory, visual, and information processing speed, BICAMS is accepted as the gold standard for testing cognition in MS patients (23). This battery has been validated for the Turkish population.

The 467 HCs completed the BICAMS battery, and the cut-off value for CI was established as 1.5 standard deviation (SD) below (Table 1). Participants with performance scores for a cognitive domain below the cut-off value were deemed to exhibit CI in that domain. Those with impairment in one domain were assessed as experiencing moderate-to-severe CI, those with impairment in two domains were classified as having severe CI, and those with impairment in all three domains were deemed to have very severe CI.

The Brief Repeatable Battery of Neuropsychological Tests is frequently employed in studies to identify CI in NMO patients.

Table 1. Study population and criteria

Group	Number of participants	Include criteria	Exclusion criteria
PwNMO (18-29)	11	Definite diagnosis of NMOSD	Attack in the last three months, other neurological diseases, non-compliance with BICAMS.
PwNMO (30-50)	15	Definite diagnosis of NMOSD	Attack inthe last three months, other neurological diseases, non-compliance with BICAMS.
HC	467	Healthy, age 18-50, completed BICAMS	Not applicable

PwNMO: Persons with neuromyelitis optica, HC: Healthy control, BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis, NMOSD: Neuromyelitis optica spectrum disorder

In the available research, NMO patients with CI comparable to MS patients have not been evaluated using the BICAMS battery. In this context, to facilitate the comparison of MS and NMO patients in terms of CI, the NMO patients in this study were assessed using BICAMS.

Statistical Analysis

The data analysis was conducted using IBM SPSS statistics software for Windows (ver. 24.0: IBM Corp., Armonk, NY, USA). The normality assumption for the data was examined employing the Shapiro-Wilk test and the histograms. The gained scores (posttest-pretest) were analyzed using the independent samples t-test. Additionally, the 95% confidence intervals were examined. A p-value <0.05 was considered to be statistically significant.

Results

In this study, 11 pwNMO with initial symptom onset (ISO) aged 18-29 years and 15 pwNMO with ISO aged 30-50 years were included. In the sporadic group, 467 individuals underwent cognitive assessment. The BICAMS (24) battery was used to conduct the cognitive evaluation. The value used for diagnosing CI was determined as 1.5 SD below the mean, and individuals with scores below this threshold were classified as exhibiting CI (Table 2).

On the BICAMS assessment, no CI was detected in the 11 pwNMO who had experienced ISO at ages 18-29. Five of the 15 pwNMO who developed ISO between the ages of 30 and 50 exhibited various levels of CI. Three of these individuals experienced moderate-severe CI, one exhibited severe CI, and one had very severe CI (Table 3).

The findings demonstrated a statistically significant relationship between the age of ISO and CI ($p<0.05$). Notably, no CI was detected in pwNMO with ISO in the 18-29 age group, whereas significant CI was observed in pwNMO with ISO at ages 30-50 years (Table 4).

Discussion

According to the literature, between 30% and 70% of NMOSD patients experience CI (11). Patients may exhibit deficits, especially in attention, language, memory, and information processing. A meta-analysis reported that NMOSD patients demonstrated significantly more impaired cognitive functions than healthy individuals, especially in the areas of attention, language, short-term memory, information processing speed, and executive functions (25). Cognitive function in these several domains may exhibit age-related variations, with varying consequences for different age groups. Studies have revealed that older adults with NMOSD experienced more significant impairments in attention and verbal memory compared to younger individuals (19,21). Similarly, some studies have (13) examined the prevalence of CI in NMOSD patients and reported that these impairments were related to aging and disease progression.

The age at ISO should be considered when assessing cognitive functions in NMOSD patients (18). Showed that CIs in NMOSD were linked to white matter atrophy and cortical degeneration. This indicates that the development of CI, especially in the 30-50 age group, may be influenced by the neurodegenerative processes associated with aging. This study examined in detail the potential relationship between CI and age at ISO in NMOSD patients. Our results suggested a statistically significant association between the age at ISO and the development of CI. More specifically, although we did not detect any CI in the cognitive tests administered to patients with ISO between 18 and 29 years of age, significant CI was documented in patients with ISO between 30 and 50 years of age. Our data suggests that NMOSD symptoms that present at an older age may impact cognitive functions. Our results imply that CIs, which are more common in older age, may be due to the increasing disease burden of NMOSD with age.

The link between NMOSD and cognitive functions has not been extensively studied, so our study is important in this regard. Specifically, the impact of age at ISO on CI demonstrates

Table 2. Cut-off values for classifying cognitive impairment using the BICAMS* battery

Symbol Digit Modalities Test (SDMT)	25.2
California Verbal Learning Test-II (CVLT-II)	34.26
Brief Visuospatial Memory Test Revised (BVMT-R)	17.04

*BICAMS data from 467 healthy controls below 1.5 standard deviation (SD), BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis

Table 3. Cognitive impairment severity levels

Number of domains affected	Severity classification	Cut-off threshold
One domain	Moderate-to-severe	1.5 (SD) below mean
Two domains	Severe	1.5 (SD) below mean
Three domains	Very severe	1.5 (SD) below mean

SD: Standard deviation

Table 4. Severity of cognitive impairment

Severity levels	PwNMO (18-29)	PwNMO (30-50)
Number of patients with ISO	11	15
Number with CI	0	5
Severe CI	0	3
Moderate-severe CI	0	1
Very severe CI	0	1

ISO: Initial symptom onset, CI: Cognitive impairment, PwNMO: Persons with neuromyelitis optica

the significance of evaluating cognitive findings in NMOSD patients. In addition, the lack of standardized cognitive assessment methods in NMOSD patients is a limitation. The BICAMS battery, which is commonly used in MS patients, was used in our investigation; however, it should be noted that these tests may not be able to fully capture abnormalities specific to NMOSD (19). Nevertheless, utilizing the standardized BICAMS battery for MS in the study enhanced the comparability of the results.

However, the study also has certain limitations. Patients with NMOSD frequently experience depression, a known condition linked to cognitive decline. Depression rates in these patients have been reported to be between 42.8% and 58.3% (14,25). Gathering information regarding psychiatric comorbidities (depression, anxiety) and including neurological imaging findings in the study may contribute to the elucidation of the mechanisms underlying cognitive disorders.

More precisely, one of the shortcomings is the limited sample size; future research could improve the findings' generalizability by including more patients. This study was conducted retrospectively, and the long-term effects of ISO age on CI may be better explored in future research that takes a prospective approach.

Conclusion

This study demonstrates that there is a significant relationship between the age at ISO and the development of CI in NMOSD patients. The findings imply that an older age at ISO may exacerbate the risk of developing CI, highlighting the significance of early diagnosis and intervention. Although the study provides valuable insights into the cognitive alterations associated with NMOSD, prospective research with larger, diverse groups is required to corroborate these findings and clarify the underlying mechanisms. Furthermore, considering the other parameters that may influence the cognitive findings in this patient group, participation in the analysis will make future studies more qualitative.

Ethics

Ethics Committee Approval: Was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (approval no.: 3, date: 02.02.2015)

Informed Consent: All participants provided written informed consent

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., U.S., E.S.Z., Concept: G.D.U., I.K., C.C., U.S., E.S.Z., Design: G.D.U., S.A., I.K., C.C., U.S., E.S.Z., Data Collection or Processing: G.D.U., I.K., C.C., U.S., E.S.Z., Analysis or Interpretation: G.D.U., S.A., C.C., U.S., E.S.Z., Literature Search: G.D.U., S.A., I.K., C.C., U.S., E.S.Z., Writing: G.D.U., S.A., C.C., U.S., E.S.Z.

Conflict of Interest: No potential conflict of interest relevant to this article was reported.

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

References

1. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, De Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE, Weinshenker BG. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177-189.
2. Bagherieh S, Afshari-Safavi A, Vaheb S, Kiani M, Ghaffary EM, Barzegar M, Shaygannejad V, Zabeti A, Mirmosayyeb O. Worldwide prevalence of neuromyelitis optica spectrum disorder (NMOSD) and neuromyelitis optica (NMO): a systematic review and meta-analysis. Neurol Sci. 2023;44:1905-1915.
3. Sen S, Tuncer A, Terzi M, Bunul SD, Ozen-Acar P, Altunrende B, Ozakbas S, Tutuncu M, Uygunoglu U, Akman-Demir G, Karabudak R, Efendi H, Siva A. Severe disease reactivation in seropositive neuromyelitis optica spectrum disorders patients after stopping eculizumab treatment. Mult Scler Relat Disord. 2023;79:104949. Erratum in: Mult Scler Relat Disord. 2024;92:105917.
4. Roemer SF, Parisi JE, Lennon VA, Benarroch EE, Lassmann H, Bruck W, Mandler RN, Weinshenker BG, Pittock SJ, Wingerchuk DM, Lucchinetti CF. Pattern-specific loss of aquaporin-4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. Brain. 2007;130:1194-1205.
5. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med. 2005;202:473-477.
6. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004;364:2106-2112.
7. Uzunköprü C, Tütüncü M, Gündüz T, Gümüş H, Şen S, Demir S, Çınar BP, Türe HS, Uygunoğlu U, Toğrol RE, Terzi M, Kürtüncü M, Özakbaş S, Tütüncü M, Beckmann Y, Siva A. The efficacy of rituximab in patients with neuromyelitis optica spectrum disorder: a real-world study from Turkey. Int J Clin Pract. 2021;75:e14158.
8. Pittock SJ, Weinshenker BG, Lucchinetti CF, Wingerchuk DM, Corboy JR, Lennon VA. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol. 2006;63:964.
9. Venero JL, Vizuete ML, Ilundáin AA, Machado A, Echevarria M, Cano J. Detailed localization of aquaporin-4 messenger RNA in the CNS: preferential expression in periventricular organs. Neuroscience. 1999;94:239-250.
10. Barnett Y, Sutton IJ, Ghadiri M, Masters L, Zivadinov R, Barnett MH. Conventional and advanced imaging in neuromyelitis optica. AJNR Am J Neuroradiol. 2014;35:1458-1466.
11. He D, Chen X, Zhao D, Zhou H. Cognitive function, depression, fatigue, and activities of daily living in patients with neuromyelitis optica after acute relapse. Int J Neurosci. 2011;121:677-683.
12. Blanc F, Zéphir H, Lebrun C, Labauge P, Castelnovo G, Fleury M, Sellal F, Tranchant C, Dujardin K, Vermersch P, De Seze J. Cognitive functions in neuromyelitis optica. Arch Neurol. 2008;65:84-88.
13. Zhang N, Li Y, Fu Y, Shao J, Luo L, Yang L, Shi F, Liu Y. Cognitive impairment in Chinese neuromyelitis optica. Mult Scler. 2015;21:1839-1846.
14. Moore P, Methley A, Pollard C, Mutch K, Hamid S, Elsone L, Jacob A. Cognitive and psychiatric comorbidities in neuromyelitis optica. J Neurol Sci. 2015;360:4-9.
15. Salama S, Marouf H, Reda MI, Mansour AR, ELKholy O, Levy M. Cognitive functions in Egyptian neuromyelitis optica spectrum disorder. Clin Neurol Neurosurg. 2019;189:105621.

16. Blanc F, Noblet V, Jung B, Rousseau F, Renard F, Bourre B, Longato N, Cremel N, Di Bitonto L, Kleitz C, Collongues N, Foucher J, Kremer S, Armspach JP, De Seze J. White matter atrophy and cognitive dysfunctions in neuromyelitis optica. PLoS One. 2012;7:e33878.
17. Kim SH, Park EY, Park B, Hyun JW, Park NY, Joung A, Lee SH, Kim HJ. Multimodal magnetic resonance imaging in relation to cognitive impairment in neuromyelitis optica spectrum disorder. Sci Rep. 2017;7:9180.
18. Kim SH, Kwak K, Jeong IH, Hyun JW, Jo HJ, Joung A, Yu ES, Kim JH, Lee SH, Yun S, Joo J, Lee DK, Lee JM, Kim HJ. Cognitive impairment differs between neuromyelitis optica spectrum disorder and multiple sclerosis. Mult Scler. 2016;22:1850-1858.
19. Liu Y, Fu Y, Schoonheim MM, Zhang N, Fan M, Su L, Shen Y, Yan Y, Yang L, Wang Q, Zhang N, Yu C, Barkhof F, Shi FD. Structural MRI substrates of cognitive impairment in neuromyelitis optica. Neurology. 2015;85:1491-1499.
20. Vanotti S, Cores EV, Eizaguirre B, Melamud L, Rey R, Villa A. Cognitive performance of neuromyelitis optica patients: comparison with multiple sclerosis. Arq Neuropsiquiatr. 2013;71:357-361.
21. Saji E, Arakawa M, Yanagawa K, Toyoshima Y, Yokoseki A, Okamoto K, Otsuki M, Akazawa K, Kakita A, Takahashi H, Nishizawa M, Kawachi I. Cognitive impairment and cortical degeneration in neuromyelitis optica. Ann Neurol. 2012;73:65-76.
22. Kawahara Y, Ikeda M, Deguchi K, Hishikawa N, Kono S, Omote Y, Matsuzono K, Yamashita T, Ikeda Y, Abe K. Cognitive and affective assessments of multiple sclerosis (MS) and neuromyelitis optica (NMO) patients utilizing computerized touch panel-type screening tests. Intern Me. 2014;53:2281-2290.
23. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, Hämäläinen P, Hartung HP, Krupp L, Penner IK, Reder AT, Benedict RH. Recommendations for a brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012;18:891-898.
24. Benedict, R.H., Amato, M.P., Boringa, J. et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC Neurol 12, 55 (2012).
25. Meng H, Xu J, Pan C, Cheng J, Hu Y, Hong Y, Shen Y, Dai H. Cognitive dysfunction in adult patients with neuromyelitis optica: a systematic review and meta-analysis. J Neurol. 2016;264:1549-1558.

DOI: 10.4274/jmsr.galenos.2025.2025-3-1

J Mult Scler Res 2025;5(1):8-12

RESEARCH ARTICLE

Steroid-induced Avascular Necrosis in Patients with Demyelinating Diseases: A Single-center Experience

Bedriye Karaman[1], Gulcan Nesem Baskan[2], Ozgul Ekmekci[1], Nur Yuceyar[1]

[1]Ege University Faculty of Medicine, Department of Neurology, Izmir, Turkiye

[2]University of Health Science Turkiye, Izmir Bozyaka Training and Reserach Hospital, Clinic of Neurology, Izmir, Turkiye

Abstract

Objective: Steroids used especially during relapses of demyelinating diseases such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are a well-known risk factor for the development of avascular necrosis. The aim of this study was to evaluate the frequency of steroid-induced avascular necrosis (SIAVN) in our patients with demyelinating disease and the demographic, clinical and radiological features of these cases.

Materials and Methods: Patients with regular follow-up were screened from electronic patient records for the development of avascular necrosis retrospectively. Descriptive features of patients with avascular necrosis were evaluated.

Results: SIAVN necrosis was detected in 7 (0.06%) of 1204 patients (6 with MS and 1 with NMOSD) who were regularly followed up in the demyelinating diseases outpatient clinic. Two of the patients had osteopenia before avascular necrosis. The mean cumulative steroid dose was 19.57±13.53 [minimum (min.) 7, maximum (max.) 44] grams. The mean time between the symptoms of avascular necrosis and diagnosis was 6±3.37 (min. 3-max. 12) months. Avascular necrosis was diagnosed in all patients by magnetic resonance imaging. Core decompression surgery was performed in 5 of the cases.

Conclusion: Avascular necrosis is a rare but important complication that can cause disability and should be recognized and treated early in the course of demyelinating diseases. It can develop independently of steroid dose and duration and is unpredictable, so it should be kept in mind especially in patients who develop hip or leg pain.

Keywords: Avascular necrosis, steroid treatment, multiple sclerosis, neuromyelitis optica spectrum diseases

Introduction

Steroid-induced avascular necrosis (SIAVN) is a notable complication in patients with demyelinating diseases, particularly multiple sclerosis (MS), who receive corticosteroids during acute relapse treatment. Intravenous methylprednisolone (IVMP) at a dose of 1000 mg/day is typically administered for 3-10 days, and this is often followed by oral corticosteroids, especially in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (1,2). SIAVN is a serious condition resulting from reduced blood supply to the trabecular bone, leading to ischemia, most commonly affecting the femoral head (3). Corticosteroids can contribute to SIAVN through several mechanisms, including fat accumulation within the bone marrow, osteocyte necrosis, and fat embolism formation, which can obstruct blood vessels and impair capillary formation and repair (4,5). Steroids also suppress osteoblast differentiation and function while promoting osteocyte apoptosis, resulting in impaired bone regeneration and increased necrosis (6,7). Additionally, corticosteroids activate inflammatory and oxidative stress pathways, which enhance apoptosis and reduce autophagy. Mitochondria-dependent apoptosis may also be triggered, involving the

Address for Correspondence: Bedriye Karaman MD, Ege University Faculty of Medicine, Department of Neurology, Izmir, Turkiye
E-mail: drbedriyekaraman@gmail.com **ORCID-ID:** orcid.org/0000-0001-6364-1911
Received: 27.03.2025 **Accepted:** 18.04.2025 **Publication Date:** 09.05.2025

Cite this article as: Karaman B, Baskan GN, Ekmekci O, Yuceyar N. Steroid-induced avascular necrosis in patients with demyelinating diseases: a single-center experience. J Mult Scler Res. 2025;5(1):8-12

release of cytochrome c and the activation of caspases-key enzymes in programmed cell death (6). These mechanisms have been demonstrated in animal studies (8). The risk of SIAVN appears to be linked to the cumulative steroid dose, although some studies have reported no significant association between the two (9). SIAVN is commonly observed following high-dose steroid use but has also been reported after the use of topical or inhaled steroids (10,11), intra-articular injections (12), and even short-term, low-dose oral corticosteroids (13). Some research indicates that patients with MS may have an elevated risk of osteoporosis, fractures, and AVN due to the autoimmune and inflammatory nature of the disease (14,15). In a study by Ce et al. (16) 15.5% of MS patients who received pulse steroid therapy developed AVN, whereas no cases were found in the control group. Patients with SIAVN often experience severe pain and limited joint mobility, but these symptoms may be misattributed to MS itself, potentially delaying diagnosis. Such delays can lead to further disability as bone necrosis progresses (17). Magnetic resonance imaging (MRI) plays a key role in diagnosing AVN, detecting necrotic areas, joint effusion, and varying levels of bone collapse and secondary degenerative changes (18,19). This study aimed to explore factors contributing to SIAVN by analyzing the clinical features of seven patients diagnosed with the condition-six with MS and one with NMOSD.

Materials and Methods

This study included 1204 patients with long-term, regular follow-up and current data from the MS and Demyelinating Diseases outpatient Department at Ege University Hospital. These patients were retrospectively reviewed for the occurrence of SIAVN. Demographic and clinical data for patients diagnosed with SIAVN were obtained from electronic medical records. The clinical and radiological assessment of AVN was conducted using the Ficat-Arlet classification system (20):

- Grade 0: No clinical symptoms or X-ray findings; MRI shows a double-line sign.
- Grade 1: Normal joint appearance; femoral head remains spherical. X-ray may reveal slight osteoporosis. MRI shows a single line on T1 and a double-line sign on T2 indicating necrotic bone.
- Grade 2: Double-line sign present; reactive bone borders the infarcted area. The joint remains normal, and the femoral head is still spherical.
- Grade 3: Loss of the femoral head's spherical shape with subchondral bone fracture; X-ray reveals a crescent sign.
- Grade 4: Further collapse of the femoral head with articular cartilage and joint space narrowing.

This study received approval from the Ege University Faculty of Medicine Ethics Committee (decision no.: 25-3.1T/68, date: 20.03.2025). Written informed consent was obtained from all patients.

Statistical Analysis

Descriptive statistical analysis (mean, standard deviation, minimum, and maximum) was performed using SPSS version 26.0.

Results

SIAVN was identified in seven patients (0.6%) patients, including one with NMOSD and six with MS. Of these, five were female and two were male. The median Expanded Disability Status Scale score was 2.0 (range, 0-3.0), the mean age was 33.29±6.69 years (range, 28-44), and the mean disease duration was 6.57±6.72 years (range, 3-22). Four patients had never smoked, two were former smokers, and one was an active smoker. None reported chronic alcohol use. The mean body mass index (BMI) was 23.9 (range, 19.4-33.2), with only one patient classified as obese (BMI >30). Detailed case information is presented in Table 1. None of the patients had any comorbid conditions. Two patients (cases 1 and 5) were diagnosed with osteopenia. The mean cumulative corticosteroid dose prior to the development of AVN was 19.57±13.53 grams (range, 7-44 grams). The average interval between the last IVMP treatment and the onset of AVN symptoms (hip or leg pain) was 6±3.37 months (range, 3-12 months). AVN was diagnosed in all patients by MRI, as initial hip X-rays taken after symptom onset were unremarkable (Figure 1 displays the MRI findings of case 2). The mean duration from the onset of AVN symptoms to diagnosis was 4.86±3.56 months (range, 1-12 months). Non-steroidal anti-inflammatory drugs were sufficient for symptom management in two cases. Core decompression surgery was performed in five patients; one of these had received hyperbaric oxygen therapy prior to surgery.

Discussion

In demyelinating neurological disorders, immune dysregulation and inflammatory activity may lead to vascular alterations that potentially compromise the blood supply to bone tissue, contributing to the development of AVN (14). Most cases of non-traumatic AVN are associated with corticosteroid therapy (16). The incidence of AVN in patients receiving high-dose steroids has been reported to range from 3% to 20% (21). In our study, the incidence was 0.6%, which is lower than previously reported rates. This discrepancy may be attributed to differences in steroid dosage, treatment duration, patient populations, and study methodologies. For instance, another study conducted in our country found a 15.5% incidence of AVN in MS patients treated with steroids, compared to none in those who were not.

Table 1. Demographic and clinical characteristics of the cases

Cases	Gender (F/M)	Age (years)	Disease	Disease duration (years)	EDSS	BMI (kg/m^2)	IMTs before AVN (months)	Cumulative CST dose (gram)	Duration between the last CST and AVN (months)	Duration between the first symptom and diagnosis (months)	Ficat-Arlet classification of the AVN	Treatment of AVN
Case 1	F	44	SPMS	21	3.0	21.6	IFN beta-1a (15), teriflunomide (33)	37	3	2	Grade 3	Core decompression operation
Case 2	M	38	RRMS	2	2.5	22.5	IFN beta-1b (5), teriflunomide (15), ocrelizumab (3ay)	13	9	6	Grade 3	Core decompression operation
Case 3	F	24	RRMS	2	0.0	20.3	IFN beta-1a (5), fingolimod (8)	12	4	2	Grade 2	Conservative treatment (NSAID)
Case 4	F	32	RRMS	1	0.0	33.2	Glatiramer acetate (12)	7	12	12	Grade 1	Conservative treatment (NSAID)
Case 5	M	28	NMOSD	2	2.0	26.2	Azathioprine (12), oral CS (18), rituximab (12)	44	5	4	Grade 2	Hyperbaric oxygen, core decompression operation
Case 6	F	39	RRMS	10	0.0	24.1	IFN beta-1a (114), fingolimod (16)	14	3	1	Grade 3	Core decompression operation
Case 7	F	28	RRMS	8	3.0	19.4	IFN beta-1a (39), fingolimod (15), natalizumab (26), ocrelizumab (8)	10	6	7	Grade 2	Core decompression operation

F: Female, M: Male, EDSS: Expanded Disability Status Scale, BMI: Body mass index, IMT: Immunomodulatory treatment, AVN: Avascular necrosis, CST: Corticosteroid therapy, SPMS: Secondary progressive multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis, NMOSD: Neuromyelitis optica spectrum disorder, IFN: Interferon, NSAID: Non-steroidal anti-inflammatory drug

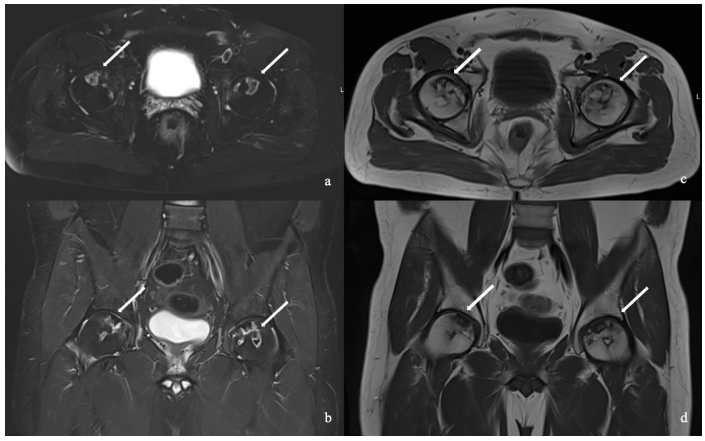


Figure 1. T2-weighted axial (a), coronal (b), T1-weighted axial (c), and coronal (d), images of the case 2 with steroid-induced osteonecrosis showing areas of necrosis in the bilateral femoral head

In that study, AVN was identified using MRI screening, and most of the detected cases were asymptomatic (16). In contrast, in our study, AVN was diagnosed based on the investigation of symptomatic patients. Various risk factors have been identified across different conditions, with high-dose corticosteroid therapy being the most recognized in inflammatory diseases, particularly systemic lupus erythematosus. In our cohort, the mean cumulative intravenous corticosteroid dose was 19.57±13.53 grams. Although the cumulative dose may appear high, one patient developed AVN after receiving only 7 grams of IVMP, suggesting that additional factors also contribute to AVN development. Known risk factors include younger age, smoking, chronic alcohol use, obesity, increased disease activity, comorbidities, and immunosuppressive treatments (22-24). In our series, patients were relatively young, with a mean age of 33.29±6.69 years. One patient (case 7) was an active smoker, while none reported chronic alcohol consumption. Obesity was present in only one case (case 4). Aside from two patients with osteopenia, no comorbidities were identified. The interval between steroid administration and symptom onset has been reported to range from a few months to nearly 3 years (25). In our cohort, the mean duration between the last IVMP treatment and the appearance of AVN symptoms was 6±3.37 months (range, 3-12 months). However, prospective studies using MRI to detect early AVN suggest that this interval may be shorter (26). Five patients had been treated with interferon (IFN)-beta during their disease course. IFN-alpha, used in chronic myeloid leukemia, has associated with AVN due to its inhibition of new blood vessels formation through increased plasminogen activator inhibitor synthesis (27). However, there is currently no evidence linking IFN-beta to AVN development. Delayed diagnosis of AVN can occur when pain is misinterpreted as a symptom of the underlying inflammatory disease. In our cases, the average time from the onset of hip or leg pain to the diagnosis of AVN was 4.5±3.73 months (range, 1-12 months). Relying solely on X-rays, which may appear normal in early stages, instead of using MRI the gold standard for AVN diagnosis can also contribute to diagnostic delays. In all of our patients, AVN was confirmed by MRI despite normal X-ray findings. Treatment options for AVN range from conservative approaches to surgical interventions, depending on the extent of bone damage. Therefore, early diagnosis and management are crucial to prevent progression and reduce disability.

Study Limitations

As this was a retrospective study, the assessment of AVN relied solely on existing electronic patient records, and patients were not re-evaluated specifically for AVN. Consequently, the reported incidence may underestimate the true rate due to incomplete data.

Conclusion

AVN is an uncommon but potentially disabling complication associated with corticosteroid use in demyelinating diseases. It may develop regardless of steroid dose or duration and is not always predictable. Clinicians should consider AVN in patients presenting with hip or leg pain. X-rays may be insufficient for diagnosis, so MRI should be used as the gold standard. Early identification is essential to minimize tissue damage and improve clinical outcomes.

Ethics

Ethics Committee Approval: This study received approval from the Ege University Faculty of Medicine Ethics Committee (decision no.: 25-3.1T/68, date: 20.03.2025).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., O.E., N.Y., Concept: O.E., N.Y., Design: B.K., N.Y., Data Collection or Processing: B.K., G.N.B., Analysis or Interpretation: B.K., G.N.B., Literature Search: B.K., Writing: B.K., G.N.B.

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

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

References

1. Barnes D, Hughes RA, Morris RW, Wade-Jones O, Brown P, Britton T, Francis DA, Perkin GD, Rudge P, Swash M, Katifi H, Farmer S, Frankel J. Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. Lancet.1997;349:902-906.
2. Myhr KM, Mellgren SI. Corticosteroids in the treatment of multiple sclerosis. Acta Neurol Scand Suppl. 2009:73-80.

3. Lu C, Qi H, Xu H, Hao Y, Yang Z, Yu W, Xu P. Global research trends of steroid-induced osteonecrosis of the femoral head: A 30-year bibliometric analysis. Front Endocrinol (Lausanne). 2022;13:1027603.
4. Wang KZ, Mao LZ, Hu CG. [Experimental study on mechanism of steroid-induced avascular necrosis of femoral head]. Zhonghua Wai Ke Za Zhi. 1994;32:515-517.
5. Cruess RL, Ross D, Crawshaw E. The etiology of steroid-induced avascular necrosis of bone. A laboratory and clinical study. Clin Orthop Relat Res. 1975:178-183.
6. Feng Z, Zheng W, Tang Q, Cheng L, Li H, Ni W, Pan X. Fludarabine inhibits STAT1-mediated up-regulation of caspase-3 expression in dexamethasone-induced osteoblasts apoptosis and slows the progression of steroid-induced avascular necrosis of the femoral head in rats. Apoptosis. 2017;22:1001-1012.
7. Lv W, Yu M, Yang Q, Kong P, Yan B. Total flavonoids of Rhizoma drynariae ameliorate steroid-induced avascular necrosis of the femoral head via the PI3K/AKT pathway. Mol Med Rep. 2021;23:345.
8. Zhang Y, Ma L, Lu E, Huang W. Atorvastatin upregulates microRNA-186 and inhibits the TLR4-mediated MAPKs/NF-kappaB pathway to relieve steroid-induced avascular necrosis of the femoral head. Front Pharmacol. 2021;12:583975.
9. Kale N, Agaoglu J, Tanik O. Correlation of cumulative corticosteroid treatment with magnetic resonance imaging assessment of avascular femoral head necrosis in patients with multiple sclerosis. Neurol Int. 2010;2:e17.
10. el Maghraoui A, Tabache F, Bezza A, Ghafir D, Ohayon V, Archane MI. Femoral head osteonecrosis after topical corticosteroid therapy. Clin Exp Rheumatol. 2001;19:233.
11. Egger AC, Ballock RT. Osteonecrosis of the femoral head in an adolescent on long-term inhalational corticosteroids. Case Rep Pediatr. 2017;2017:6969787.
12. Al-Omari AA, Aleshawi AJ, Marei OA, Younes HMB, Alawneh KZ, ALQuran E, Mohaidat ZM. Avascular necrosis of the femoral head after single steroid intra-articular injection. Eur J Orthop Surg Traumatol. 2020;30:193-197.
13. Dilisio MF. Osteonecrosis following short-term, low-dose oral corticosteroids: a population-based study of 24 million patients. Orthopedics. 2014;37:e631-e636.
14. Bazelier MT, van Staa TP, Uitdehaag BM, Cooper C, Leufkens HG, Vestergaard P, Herings RM, de Vries F. Risk of fractures in patients with multiple sclerosis: A population-based cohort study. Neurology. 2012;78:1967-1973.
15. Zikan V. Bone health in patients with multiple sclerosis. J Osteoporos. 2011;2011:596294.
16. Ce P, Gedizlioglu M, Gelal F, Coban P, Ozbek G. Avascular necrosis of the bones: An overlooked complication of pulse steroid treatment of multiple sclerosis. Eur J Neurol. 2006;13:857-861.
17. Sahraian MA, Yadegari S, Azarpajouh R, Forughipour M. Avascular necrosis of the femoral head in multiple sclerosis: Report of five patients. Neurol Sci. 2012;33:1443-1446.
18. Clinkscales A, Cleary JD. Steroid-induced avascular necrosis. Ann Pharmacother. 2002;36:1105.
19. Chen S, Kavanagh A, Zarick C. Steroid-induced avascular necrosis in the foot and ankle-pathophysiology, surgical, and nonsurgical therapies: Case study and literature review. Foot Ankle Spec. 2024;17:168-176.
20. Stoller DW. Magnetic resonance imaging in orthopaedics and sports medicine, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2007.
21. Pritchett JW. Statin therapy decreases the risk of osteonecrosis in patients receiving steroids. Clin Orthop Relat Res. 2001:173-178.
22. Nevskaya T, Gamble MP, Pope JE. A meta-analysis of avascular necrosis in systemic lupus erythematosus: Prevalence and risk factors. Clin Exp Rheumatol. 2017;35:700-710.
23. Xu W, Wang L, Shi P, Liu L, Zhang W. Risk factors and prediction model for osteonecrosis of the femoral head in female systemic lupus erythematosus. Front Immunol. 2024;15:1381035.
24. Tsai HL, Chang JW, Lu JH, Liu CS. Epidemiology and risk factors associated with avascular necrosis in patients with autoimmune diseases: A nationwide study. Korean J Intern Med. 2022;37:864-876.
25. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum. 2002;32:94-124.
26. Ramos-Casals M, García-Carrasco M, Cervera R, Filella X, Trejo O, de la Red G, Gil V, Sánchez-Tapias JM, Font J, Ingelmo M. Th1/Th2 cytokine imbalance in patients with Sjögren syndrome secondary to hepatitis C virus infection. Semin Arthritis Rheum. 2002;32:56-63.
27. Yassin M, Al-Mashdali AF, Al-Dubai HN. Avascular necrosis in patients with chronic myeloid leukemia: A systematic review. Acta Biomed. 2022;93:e2022017.

DOI: 10.4274/jmsr.galenos.2025.2025-3-3

J Mult Scler Res 2025;5(1):13-17

RESEARCH ARTICLE

Tracking Walking Capacity in People with Multiple Sclerosis Without Disability: 3-year Follow-up of Objective and Subjective Gait Measures

Zuhal Abasiyanik[1], Cavid Baba[2], Pinar Yigit[2], Ulvi Samadzade[3], Turhan Kahraman[1]

[1]Izmir Katip Celebi University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkiye
[2]Dokuz Eylul University Institute of Health Sciences, Department of Neurosciences, Izmir, Turkiye
[3]Izmir University of Economic Medical Point Izmir Hospital, Department of Neurology, Izmir, Turkiye

Abstract

Objective: This study aimed to examine changes in walking performance over a 3-year period in persons with multiple sclerosis (pwMS) with no or mild disability.

Materials and Methods: A total of 321 pwMS (mean age 32.3± 9.8 years, 75% female, median Expanded Disability Status Scale 1.0) were followed for 3 years. Walking performance was assessed using the Timed 25-Foot Walk Test (T25FW), Six-Spot Step Test (SSST), 2-Minute Walk Test (2MWT), Timed Up and Go (TUG) test, and the Multiple Sclerosis Walking Scale-12 (MSWS-12). Leisure-time exercise habits were assessed with the Godin Leisure-Time Exercise Questionnaire.

Results: Walking performance remained stable over the 3-year period. The median T25FW time showed no significant change (4.8 s to 4.7 s, p=0.3), nor did the SSST time (7.7 s to 7.2 s, p=0.517). Similarly, there were no significant changes in the 2MWT distance (171 m to 174 m, p=0.178) or TUG time (6.8 s to 6.9 s, p=0.831). Self-reported walking disability MSWS-12 and leisure-time physical activity levels also remained consistent (p=0.692 and p=0.394, respectively).

Conclusion: The findings indicate that pwMS with no or mild disability maintained stable walking performance over a 3-year span. This stability may be attributed to functional reserve and lifestyle factors that support mobility preservation despite disease progression. Future studies should incorporate more detailed gait analyses and further explore the role of lifestyle factors.

Keywords: Multiple sclerosis, walking, gait, capacity, performance

Introduction

Walking impairment is a major concern for persons with multiple sclerosis (pwMS) and can appear early in the disease course, even in those with minimal or no visible disability (1,2). Subtle declines in gait function may go unnoticed by patients but can have significant long-term effects on mobility, physical activity, and overall quality of life. Early detection of these gait changes is essential for implementing timely interventions and treatments aimed at maintaining mobility in MS (3,4).

In pwMS with low Expanded Disability Status Scale (EDSS) scores, minor impairments such as slower walking speed, shorter step length, and longer double support time can already be identified through instrumented or sensitive gait assessments, even in the absence of clear clinical symptoms. As EDSS score increase, more evident gait abnormalities often develop, including asymmetrical stepping, foot drop, balance issues, reduced gait regularity, greater variability, and altered gait kinematics and kinetics (5,6). Recognizing these

Address for Correspondence: Zuhal Abasıyanık PhD, Izmir Katip Celebi University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkiye
E-mail: zuhalabasiyanik@gmail.com **ORCID-ID:** orcid.org/0000-0003-3086-8102
Received: 10.04.2025 **Accepted:** 24.04.2025 **Publication Date:** 09.05.2025

Cite this article as: Abasiyanik Z, Baba C, Yigit P, Samadzade U, Kahraman T. Tracking walking capacity in people with multiple sclerosis without disability: 3-year follow-up of objective and subjective gait measures. J Mult Scler Res. 2025;5(1):13-17

progressive gait changes in relation to EDSS stages is important for designing targeted rehabilitation strategies.

In clinical settings without access to instrumental assessments, standardized tools are commonly used to measure walking ability in MS, including the Timed 25-Foot Walk Test (T25FW), 6-Minute Walk Test (6MWT), 2-Minute Walk Test (2MWT), MS Walking Scale (MSWS-12), Timed Up and Go (TUG) test, and Six-Spot Step Test (SSST) (7). Some studies have identified abnormal results in clinical walking tests even among pwMS with low levels of disability (4,8). While these assessments are commonly used in clinical practice and research, there are still few longitudinal studies that track changes over longer periods, especially in individuals with no or minimal disability (e.g., EDSS scores between 0 and 1.5). Understanding how walking performance evolves in this population is important for detecting early signs of disease progression and shaping therapeutic interventions (9).

This study aimed to investigate longitudinal changes in walking performance over a 3-year period in pwMS with no or minimal disability. By monitoring both functional walking tests and patient-reported outcomes, we sought to identify whether early gait changes could be detected and to assess the degree of walking decline. The findings may offer valuable insights into the early development of mobility impairment in MS and help guide targeted rehabilitation strategies to preserve walking function.

Materials and Methods

This study is part of an ongoing longitudinal project, approved by the Dokuz Eylul University Ethics Board (approval no.: 2021/17-05, date: 02.06.2021). All participants provided written informed consent after receiving a full explanation of the study.

Inclusion criteria were a confirmed diagnosis of MS (10), age between 18 and 60 years, and an EDSS score between 0 and 1.5. Participants were excluded if they had any condition affecting walking ability or any other neurological disorder.

Outcomes

Timed 25-Foot Walk Test (T25FW)

Participants were instructed to walk a marked 25-foot (7.62 m) course as quickly as possible while ensuring their safety. The test was performed twice, and the average of the two times was used as the final score. Longer times indicated slower walking speed (11). The T25FW has demonstrated good to excellent test-retest reliability, with intraclass correlation coefficients (ICC) ranging from 0.71 to 0.99 (12).

Six-Spot Step Test (SSST)

The SSST is a timed functional mobility test that evaluates speed, balance, coordination, and lower limb function. Participants were required to move as quickly as possible to specified targets and kick five cylindrical blocks out of marked circles on the floor. Each participant completed four trials (twice for each leg), and the average time across all trials was used as the final score (13,14). The SSST has demonstrated excellent test-retest reliability (ICC:0.99) (12,15).

Timed Up and Go Test (TUG)

The TUG assessed functional mobility by measuring the time taken for participants to rise from a seated position, walk 3 m, turn around, walk back, and sit down (16). The TUG test has shown excellent test-retest reliability (ICC:0.90) in pwMS with mild disability (17).

2-Minute Walk Test (2MWT)

The 2MWT assessed walking endurance. Participants were instructed to walk as far as possible within 2 min without taking a rest. The total distance covered was recorded (18). The 2MWT has demonstrated excellent test-retest reliability (ICC:0.95) in pwMS with mild disability (17).

MS Walking Scale-12 (MSWS-12)

The MSWS-12 consists of 12 items that assess perceived walking difficulties in daily life. Each item is scored from 1 (not at all) to 5 (extremely), with higher scores reflecting greater walking impairment. The total score was converted to a scale ranging from 0 to 100 (19). The MSWS-12 has shown excellent test-retest reliability, with ICC values between 0.89 and 0.98 (12).

Godin Leisure-time Exercise Questionnaire (GLTEQ)

Leisure-time physical activity was assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ), which consists of three items evaluating the frequency of strenuous, moderate, and mild exercise. Higher scores reflect greater levels of physical activity (20). The GLTEQ is a valid and reliable self-reported measure of physical activity in pwMS, with an ICC of 0.74 (21).

Statistical Analysis

Normality was assessed by examining histograms and plots. Descriptive statistics are presented as mean and standard deviation or median and interquartile range (IQR), as appropriate. Since the walking assessments were not normally distributed, the Wilcoxon signed-rank test (a non-parametric test) was used to compare results between visits 1 and 2. Additionally, exploratory analysis was conducted to examine the relationship between changes in EDSS scores and changes in clinical walking outcomes using Spearman correlation analysis. Data were analyzed using IBM SPSS version 28.0 (Armonk, NY, IBM Corp). A p-value of 0.05 or less was considered statistically significant result.

Results

A total of 321 pwMS (mean age 32.3±9.8 years, 75% female) were followed over a 3-year period. The median EDSS score at baseline was 1.0. Clinical and demographic characteristics are presented in Table 1.

Across the 3-year follow-up, changes in walking performance were evaluated using various measures (Table 2). The median T25FW time remained stable, decreasing slightly from 4.8 s at baseline to 4.7 s at visit 2 (p=0.3). Similarly, performance on the SSST showed a minor improvement from 7.7 s (IQR: 6.8-8.7) to 7.2 s (IQR: 6.4-8.6), which was not statistically significant (p=0.517). The 2MWT demonstrated a small median increase in distance from 171 m (IQR: 157.3-187) to 174 m (IQR: 154.3-189.8) (p=0.178). TUG test results showed minimal change, with times increasing slightly from 6.8 s (IQR: 6.2-7.6) to 6.9 s (IQR: 6.3-7.9) (p=0.831). Self-reported walking disability, assessed through the MSWS-12, and leisure-time physical activity levels both remained stable over the 3 years (p=0.692 and p=0.394, respectively). Overall, no statistically significant changes were observed in walking performance over the 3-year period. Additionally, there were no significant correlations between changes in EDSS scores and changes in any of the clinical walking tests (p>0.05).

Discussion

This study examined longitudinal changes in walking performance over a 3-year period in pwMS with no or mild disability. The results showed no significant decline across objective walking performance measures, including the T25FW, SSST, 2MWT, and TUG, nor in perceived walking ability assessed by the MSWS-12.

The stable T25FW times over 3-years suggest that short-distance walking speed is preserved in pwMS at this disability level. This finding aligns with a previous study that reported no decline over 2-years in a group with a median EDSS of 2 and a median T25FW of 3.94, although worsening was noted in participants with greater disability and a higher risk of progression (22). Similarly, the absence of significant change in SSST performance indicates that dynamic stability and coordination are maintained, likely reflecting functional reserve that supports mobility even during more demanding tasks. The stable TUG results further reinforce the notion that functional mobility remains intact in this cohort. While walking performance often declines in individuals with greater disability, our findings suggest that pwMS with mild impairments can maintain walking function over time. This preservation may be explained by functional reserve, which enables compensation for disease effects at an early stage, or by factors such as medication adherence and lifestyle habits. Although we assessed leisure-time physical activity using the self-reported GLTEQ, we did not include objective measurements of physical activity or a detailed assessment of lifestyle behaviors. Future research should address these factors more thoroughly, as doing so may offer valuable insights into disease management.

The lack of significant change in self-reported walking ability indicates that participants did not perceive notable changes in their mobility over the 3-year period, consistent with the objective walking assessments. This finding suggests that pwMS with no or minimal disability may maintain a stable perception of their walking ability, possibly due to effective compensatory mechanisms or stable disease activity.

Monitoring and following subtle deficits during the early or low-disability stages of MS is critical for implementing early and targeted interventions. The validated tests used to assess Progression Independent of Relapse Activity primarily rely on clinical measures, which may not be sensitive enough to detect subtle changes (23,24). As suggested by the findings of this study, the lack of deterioration in clinical tests may be considered a positive result for disease management. However, it is essential to recognize the potential limitations of these tests in identifying subtle progression. While a key strength of our study is the 3-year follow-up of walking function in a large sample, it

Table 1. Demographic and clinical characteristics of participants

	Total (n=321)
Age (years), mean (SD)	32.3 (9.8)
Gender, n (%)	
Female	239 (74.5%)
Male	82 (25.5%)
EDSS, median (interquartile range)	1.0 (0-1.5)

EDSS: Expanded disability status scale, SD: Standard deviation

Table 2. Changes in walking measures over 3 years

	Visit 1	Visit 2	Change	p-value
T25FW, seconds	4.8 (4.3-5.3)	4.7 (4.3-5.2)	-0.06 (-0.53-0.44)	0.3
SSST, seconds	7.7 (6.8-8.7)	7.2 (6.4-8.6)	-0.32 (-1.3-0.68)	0.517
2MWT, meters	171 (157.3-187)	174 (154.3-189.8)	0 (-11-15)	0.178
TUG, seconds	6.8 (6.2-7.6)	6.9 (6.3-7.9)	0.28 (-0.63-1.15)	0.831
MSWS-12 (%)	25.9 (22.2-35.2)	25.9 (22.2-37.4)	0 (-5.6-3.7)	0.692
GLTEQ	0 (0-15)	1 (0-17.25)	0 (-7-10)	0.394

Values are presented as median (interquartile range)

T25FW: Timed 25-Foot Walk Test, SSST: Six-Spot Step Test, 2MWT: 2-Minute Walk Test, TUG: Timed Up and Go Test, MSWS-12: 12-item MS Walking Scale, GLTEQ: Godin Leisure-Time Exercise Questionnaire

is important to note that our assessments were based solely on clinical tests measuring time and distance. More detailed gait parameters related to neural control, such as stability, variability, and smoothness, which may not be captured by these tests, could be important for long-term monitoring and identifying progression risk (25-28). Additionally, our assessments were limited to relatively short-duration tests and did not include extended walking tasks that could reveal fatigue. Previous research has shown that speed trajectories during the 6MWT can help detect progression over 2-years (22).

Study Limitations

The study sample consisted of individuals with no or mild disability, which may limit the generalizability of the findings to those with more severe disability. The absence of a healthy control group also restricts the ability to make comparisons. Furthermore, although our participants had low disability levels, we were unable to identify those at higher risk of progression. As such, separate analyses for individuals at higher risk should be conducted to better assess potential deterioration. Additionally, factors such as fatigue, cognitive function, lifestyle behaviors, and environmental influences were not considered, but these may impact long-term walking performance. This study also did not include detailed clinical information, such as immunomodulating treatment status or magnetic resonance imaging lesion load, which could limit our ability to explore potential predictors of walking performance. Future research should include these variables to offer a more comprehensive understanding of mobility changes in MS. Lastly, the clinical walking tests used in this study may lack the sensitivity to detect subtle gait changes in pwMS with minimal disability, potentially overlooking early functional decline. Ceiling effects may also limit their ability to capture meaningful longitudinal changes.

Conclusion

This study indicates that pwMS with no or mild MS-related disability maintain stable walking performance over a 3-year period, with no significant decline in objective measures or self-reported walking ability. These results suggest that the functional reserve may help preserve mobility at this early stage of the disease. However, the limited sensitivity of clinical measures to detect subtle changes underscores the need for more comprehensive assessments, including complex gait parameters and long-duration tests, to better identify progression and guide early interventions.

Ethics

Ethics Committee Approval: The non-invasive Research Ethics Board of Dokuz Eylul University approved the study protocol (approval no.: 2021/17-05, date: 02.06.2021).

Informed Consent: Each participant provided written informed consent.

Footnotes

Authorship Contributions

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

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

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

References

1. Krieger SC, Antoine A, Sumowski JF. EDSS 0 is not normal: Multiple sclerosis disease burden below the clinical threshold. Multiple Sclerosis Journal. 2022;28:2299-303.
2. Heesen C, Böhm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. Mult Scler. 2008;14:988-991.
3. Riemenschneider M, Hvid LG, Ringgaard S, Nygaard MKE, Eskildsen SF, Gaemelke T, Magyari M, Jensen HB, Nielsen HH, Kant M, Falah M, Petersen T, Stenager E, Dalgas U. Investigating the potential disease-modifying and neuroprotective efficacy of exercise therapy early in the disease course of multiple sclerosis: The Early Multiple Sclerosis Exercise Study (EMSES). Mult Scler. 2022;28:1620-1629.
4. Cattaneo D, Gervasoni E, Anastasi D, Di Giovanni R, Brichetto G, Carpinella I, Cavalla P, Confalonieri P, Groppo E, Prosperini L, Tacchino A, Rovaris M, Solaro C. Prevalence and patterns of subclinical motor and cognitive impairments in non-disabled individuals with early multiple sclerosis: A multicenter cross-sectional study. Ann Phys Rehabil Med. 2022;65:101491.
5. Karatsidis A, Angelini L, Scaramozza M, Bartholome E, Clinch SP, Shen C, Lindemann M, Mazzà C, Scotland A, van Beek J, Belachew S, Craveiro L. Characterizing gait in people with multiple sclerosis using digital data from smartphone sensors: A proposed framework. Mult Scler. 2025;31:512-528.
6. Chee JN, Ye B, Gregor S, Berbrayer D, Mihailidis A, Patterson KK. Influence of multiple sclerosis on spatiotemporal gait parameters: a systematic review and meta-regression. Arch Phys Med Rehabil. 2021;102:1801-1815.
7. Soler B, Ramari C, Valet M, Dalgas U, Feys P. Clinical assessment, management, and rehabilitation of walking impairment in MS: an expert review. Expert Rev Neurother. 2020;20:875-886.
8. Thrue C, Hvid LG, Diechmann M, Gaemelke T, Stenager E, Dalgas U, Riemenschneider M. Early phase multiple sclerosis patients present substantial deficits in physical-, cognitive-, and patient-reported outcomes compared to matched healthy controls. Neurorehabil Neural Repair. 2025:15459683251318246.
9. Gervasoni E, Anastasi D, Di Giovanni R, Solaro C, Rovaris M, Brichetto G, Confalonieri P, Tacchino A, Carpinella I, Cattaneo D. Uncovering subtle gait deterioration in people with early-stage multiple sclerosis using inertial sensors: a 2-year multicenter longitudinal study. Sensors (Basel). 2023;23:9249.
10. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162-173.
11. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome

assessment. National MS Society Clinical Outcomes Assessment Task Force. Task Force. Mult Scler. 1999;5:244-250.

12. Skjerbæk AG, Hvid LG, Boesen F, Taul-Madsen L, Stenager E, Dalgas U. Psychometric measurement properties and reference values of the six-spot step test, the six-minute walk test, the 25-foot walk test, and the 12-item multiple sclerosis walking scale in people with multiple sclerosis. Mult Scler Relat Disord. 2025;94:106242.
13. Sandroff BM, Motl RW, Sosnoff JJ, Pula JH. Further validation of the Six-Spot Step Test as a measure of ambulation in multiple sclerosis. Gait Posture. 2015;41:222-227.
14. Fritz NE, Jiang A, Keller J, Zackowski KM. Utility of the six-spot step test as a measure of walking performance in ambulatory individuals with multiple sclerosis. Arch Phys Med Rehabil. 2016;97:507-512.
15. Callesen J, Richter C, Kristensen C, Sunesen I, Næsby M, Dalgas U, Skjerbæk AG. Test-retest agreement and reliability of the Six Spot Step Test in persons with multiple sclerosis. Mult Scler. 2019;25:286-294.
16. Sebastião E, Sandroff BM, Learmonth YC, Motl RW. Validity of the Timed Up and Go Test as a measure of functional mobility in persons with multiple sclerosis. Arch Phys Med Rehabil. 2016;97:1072-1077.
17. Valet M, Lejeune T, Devis M, van Pesch V, El Sankari S, Stoquart G. Timed Up-and-Go and 2-Minute Walk Test in patients with multiple sclerosis with mild disability: reliability, responsiveness and link with perceived fatigue. Eur J Phys Rehabil Med. 2019;55:450-455.
18. Scalzitti DA, Harwood KJ, Maring JR, Leach SJ, Ruckert EA, Costello E. Validation of the 2-Minute Walk Test with the 6-Minute Walk Test and other functional measures in persons with multiple sclerosis. Int J MS Care. 2018;20:158-163.
19. Dib H, Tamam Y, Terzi M, Hobart J. Testing patient-reported outcome measurement equivalence in multinational clinical trials: An exemplar using the 12-item Multiple Sclerosis Walking Scale. Mult Scler J Exp Transl Clin. 2017;3:2055217317728740.
20. Gosney JL, Scott JA, Snook EM, Motl RW. Physical activity and multiple sclerosis: validity of self-report and objective measures. Fam Community Health. 2007;30:144-150.
21. Sikes EM, Richardson EV, Cederberg KJ, Sasaki JE, Sandroff BM, Motl RW. Use of the Godin leisure-time exercise questionnaire in multiple sclerosis research: a comprehensive narrative review. Disabil Rehabil. 2019;41:1243-1267.
22. Goldman MD, Chen S, Motl R, Pearsall R, Oh U, Brenton JN. Progression risk stratification with six-minute walk gait speed trajectory in multiple sclerosis. Front Neurol. 2023;14:1259413.
23. Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, Model F, Koendgen H, Manfrini M, Belachew S, Hauser SL. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. JAMA Neurol. 2020;77:1132-1140.
24. Giovannoni G, Hawkes CH, Lechner-Scott J, Levy M, Yeh EA. Smouldering-associated worsening or SAW: the next therapeutic challenge in managing multiple sclerosis. Mult Scler Relat Disord. 2024;92:106194.
25. Müller R, Hamacher D, Hansen S, Oschmann P, Keune PM. Wearable inertial sensors are highly sensitive in the detection of gait disturbances and fatigue at early stages of multiple sclerosis. BMC Neurol. 2021;21:337.
26. Carpinella I, Gervasoni E, Anastasi D, Di Giovanni R, Tacchino A, Brichetto G, Confalonieri P, Rovaris M, Solaro C, Ferrarin M, Cattaneo D. Instrumentally assessed gait quality is more relevant than gait endurance and velocity to explain patient-reported walking ability in early-stage multiple sclerosis. Eur J Neurol. 2021;28:2259-2268.
27. Cofré Lizama LE, Strik M, Van der Walt A, Kilpatrick TJ, Kolbe SC, Galea MP. Gait stability reflects motor tracts damage at early stages of multiple sclerosis. Mult Scler. 2022;28:1773-1782.
28. Pau M, Mandaresu S, Pilloni G, Porta M, Coghe G, Marrosu MG, Cocco E. Smoothness of gait detects early alterations of walking in persons with multiple sclerosis without disability. Gait Posture. 2017;58:307-309.

DOI: 10.4274/jmsr.galenos.2025.2025-4-2

J Mult Scler Res 2025;5(1):18-22

RESEARCH ARTICLE

Evaluation of Response to Relapse Treatment in Multiple Sclerosis According to Relapse Characteristics

Hasan Dogan, Suheda Calak

Samsun University Faculty of Medicine, Department of Neurology, Samsun, Turkiye

Abstract

Objective: Relapses in patients with multiple sclerosis (MS) were evaluated based on symptom characteristics, treatment response, and recovery rates. These factors were evaluated before and after relapse treatment, as well as at the first- and sixth-months following treatment.

Materials and Methods: Patient's physical status was evaluated using the Expanded Disability Status scale (EDSS). Based on the characteristics of their relapses, patients were categorized as either monosymptomatic or polysymptomatic. Treatment response was then analyzed according to these groupings.

Results: The study included 59 MS patients, with a mean age of 33.69±8.28 years (46 females, 13 males). Based on relapse symptom characteristics, 27.1% of patients had polysymptomatic relapses, while 72.9% were monosymptomatic. A total of 23 patients experienced monosymptomatic relapses. Regarding specific relapse symptoms, 66.1% presented with sensory symptoms, 47.5% with motor symptoms, 32.2% with optic neuritis (ON), 6.8% with cerebellar signs, 35.6% with brainstem involvement, and 13.6% with sphincter symptoms. Significant improvement following treatment was observed in patients with brainstem involvement and in the ON group (p=0.04 and p=0.039, respectively). However, no significant difference in EDSS scores was noted at 1 and 6 months posttreatment (p=0.068 and p=0.194, respectively). In the sensory involvement group, the mean EDSS score was 2.65±1.24 before treatment, 2.05±0.76 after treatment, 1.85±0.81 at 1 month, and 1.55±0.98 at 6 months, indicating significant improvement (p=0.04 and p=0.041, respectively).

Conclusion: Both ON and sensory involvement were associated with favorable prognosis. While significant improvement n EDSS was noted in the ON group before and after treatment, this improvement was not sustained at the first and sixth months. In contrast, patients with sensory involvement demonstrated continuous and significant improvement across all time points-before treatment, after treatment, and at 1 and 6 months. These findings highlight the importance of addressing sensory relapses and their potential for sustained recovery.

Keywords: Expanded disability status scale (EDSS), multiple sclerosis, relapses

Introduction

Multiple sclerosis (MS) is a demyelinating and neurodegenerative disorder that impacts various functional systems within the central nervous system. Common symptoms include blurred vision, double vision, limb weakness, sensory loss, imbalance, and disturbances in bowel and bladder function (1,2). A neurological symptom lasting more than 24 hours in the absence of fever, infection, or stress is defined as a relapse, with at least 30 days required between separate relapse episodes. Relapses are linked to functional decline and reduced quality of life. If symptoms persist following a relapse, this may contribute to cumulative disability, referred to as relapse-associated worsening (RAW) (3,4). Proper management of relapses is important to prevent long-term disability (1,2). In cases of moderate to severe relapse, intravenous methylprednisolone at 1 g/day is typically administered for 5-10 days. If the response to corticosteroids is inadequate, plasmapheresis may be considered. Early detection of even mild neurological deterioration is critical for prompt and effective treatment (5).

Address for Correspondence: Suheda Calak, Samsun University Faculty of Medicine, Department of Neurology, Samsun, Turkiye
E-mail: suheda369@hotmail.com **ORCID-ID:** orcid.org/0009-0009-5342-2438
Received: 18.04.2025 **Accepted:** 27.04.2025 **Publication Date:** 09.05.2025

Cite this article as: Dogan H, Calak S. Evaluation of response to relapse treatment in multiple sclerosis according to relapse characteristics. J Mult Scler Res. 2025;5(1):18-22

Poor prognostic indicators in MS include male sex, smoking, obesity, low vitamin D levels, African descent, early age at disease onset, and rapid disease progression. Moreover, factors such as brain volume loss, relapse frequency, presence of new T2 lesions, and contrast-enhancing lesions are important predictors of disability within 5 years. Clinically, sphincter dysfunction, pyramidal and cerebellar involvement, early cognitive impairment, brainstem symptoms, and a high Expanded Disability Status scale (EDSS) score at the first relapse are associated with worse outcomes (5).

Studies have shown that relapse recovery tends to be more favorable in younger patients, those receiving disease-modifying therapies, individuals with longer disease duration, and those without bowel or bladder involvement. The EDSS is a commonly used tool to assess disease progression in MS by evaluating central nervous system functions, including pyramidal, cerebellar, brainstem, sensory, sphincter, visual, and cerebral domains. The EDSS uses a scale from 0 to 10: scores from 0 to 4 reflect neurological deficits, scores from 4 to 6 primarily assess walking ability, and scores from 6 to 10 focus on ambulatory function. During relapses, EDSS scores typically increase depending on the symptoms and areas affected in the central nervous system. Following appropriate treatment, partial, complete, or near-complete improvements in EDSS scores may occur in treatment-responsive relapses. The initial and predominant pathophysiological mechanism in MS involves disruption of the blood-brain barrier, leading to immune-mediated damage to myelin and axons in both white and gray matter. In addition, intrathecal immune activation involving various glial and immune cells has recently been recognized as a complex and significant contributor to disease progression. Therefore, initiating effective treatment at the earliest possible stage is considered important for long-term outcomes (1).

This study aimed to evaluate the response to relapse treatment based on symptom characteristics and to compare EDSS changes before and after treatment, as well as at the first and sixth months following treatment.

Materials and Methods

Study Population

This study included patients diagnosed with MS who were followed at the Neurology Clinic of Samsun University and received treatment for MS relapses between January 2023 and June 2024. Demographic data of the patients were recorded. Relapse characteristics and severity were evaluated using the EDSS. Based on relapse presentation, patients were categorized as either monosymptomatic or polysymptomatic.

Data Collection

EDSS scores prior to treatment, immediately after treatment, and at the first- and sixth-months posttreatment were retrieved from patient records and the hospital database. Relapses were classified into sensory, motor, brainstem involvement, and optic neuritis (ON) groups based on presenting symptoms. EDSS scores for each group were compared across the pretreatment, posttreatment, first month, and sixth month time points.

Ethics Approval

The study received approval from the Samsun University Non-interventional Clinical Research Ethics Committee (decision no.: 2025/6/20, date: 19.03.2025). Written informed consent was obtained from all patients who agreed to participate.

Statistical Analysis

The collected data were coded and analyzed using the SPSS software package (Version 22.0, SPSS Inc., Chicago, IL, USA). Continuous variables with a normal distribution were presented as mean ± standard deviation, while non-normally distributed continuous variables were expressed as median (minimum-maximum). Categorical variables were reported as number and percentage. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. A p-value of <0.05 was considered significant in all analyses.

Results

A total of 59 patients diagnosed with MS were included in the study, with a mean age of 33.69±8.28 years and an average disease duration of 3.16±4.48. The study population consisted of 46 females and 13 males. Based on relapse symptom characteristics, 27.1% of the patients were classified as polysymptomatic and 72.9% as monosymptomatic. The distribution of relapse symptoms was as follows: sensory symptoms in 66.1%, motor involvement in 47.5%, ON in 32.2%, cerebellar signs in 6.8%, brainstem involvement in 35.6%, and sphincter dysfunction in 13.6% (Figure 1). In addition, 66.1% of patients demonstrated poor prognostic indicators, including sphincter involvement, motor symptoms at onset, and brainstem or cerebellar findings. In patients with sensory involvement, the mean EDSS score was 2.65±1.24 before

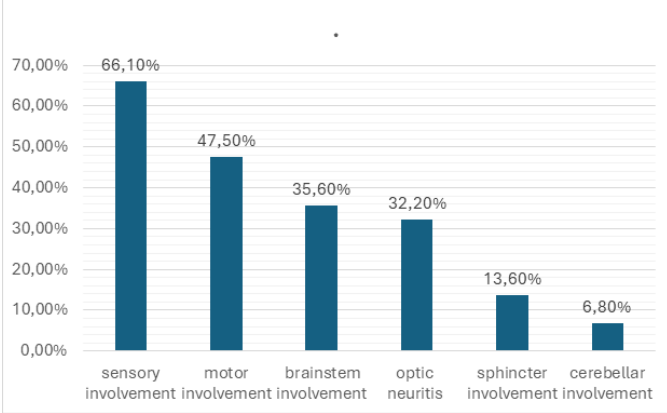


Figure 1. Distribution of relapse symptoms in the study group

treatment, 2.05±0.76 after treatment, 1.85±0.81 at the first month, and 1.55±0.98 at the sixth month, showing significant improvement over time (p=0.04 and p=0.041, respectively). This improvement persisted across both follow-up periods. In contrast, among patients without sensory involvement, the mean EDSS was 1.34±0.58 after treatment, 1.42±0.53 at 1 month, and 1.76±0.43 at 6 months, with a continued increase in EDSS at the sixth month, indicating ongoing deterioration (p=0.04 and p=0.045, respectively) (Table 1). In the ON group, the mean EDSS was 2.21±0.56 before treatment, 1.28±0.75 after treatment, 1.42±0.34 at the first month, and 1.92±0.44 in the sixth month (p=0.589 and p=0.068, respectively). These results indicate that although some improvement was noted immediately after treatment, no statistically significant change was observed at the first- or sixth-month. In patients without ON, the mean EDSS was 2.46±1.10 before treatment, 1.81±0.70 after treatment, 1.68±0.79 at the first month, and 1.56±0.79 at the sixth month, showing continued improvement over time (p=0.398 and p=0.49, respectively) (Table 2). Among patients with brainstem involvement, the mean EDSS was 2.35±0.89 before treatment, 1.50±0.40 after treatment, and 1.42±0.67 at the first month. Although there was a reduction in EDSS from posttreatment to the first month, the change was not statistically significant. By the sixth month, the mean EDSS had increased to 1.71±0.48, indicating no sustained improvement (p=0.854 and p=0.194, respectively). In the group without brainstem findings, the mean EDSS was 2.40±1.02 before treatment, 1.71±0.85,1 after treatment, 1.68±0.70 at the first month, and 1.65±0.81 at the sixth month. Although the EDSS score showed a slight decrease over time, no statistically significant improvement was observed (p=0.776 and p=0.80, respectively) (Table 3).

Discussion

Corticosteroids are commonly used to manage MS relapses. Evaluating relapse severity using EDSS is critical, and if the EDSS score increases by 1 point or more, treatment is strongly advised. However, mild relapses-particularly sensory relapses-with less than 1 point increase in EDSS may not require immediate treatment; these patients should be re-evaluated within 2 weeks. If an increase in EDSS is observed during this period, treatment should then be initiated (6). According to a study on managing severe relapses in MS, not all relapses necessitate treatment. Instead, therapy should be prioritized for relapses that result in functional impairment or disability, in order to

Table 1. EDSS scores of patients with and without sensory involvement (excluding poor prognostic factors)

	Sensory relapses		Relapses without sensory involvement	
EDSS before treatment	2.65±1.24	p=0.041	2.19±0.66	p=0.005
EDSS after treatment	2.05±0.76		1.34±0.59	
EDSS in 1st month of treatment	1.85±0.81	p=0.04	1.42±0.53	p=0.04
EDSS in 6th months of treatment	1.55±0.98	p=0.23	1.76±0.43	p=0.045

EDSS: Expanded Disability Status scale

Table 2. EDSS scores of patients with and without optic neuritis (excluding poor prognostic factors)

	Optic neuritis relapses		Relapses without optic neuritis	
EDSS before treatment	2.21±0.56	p=0.039	2.46±1.10	p=0.006
EDSS after treatment	1.28±0.75		1.81±0.70	
EDSS in 1st month of treatment	1.42±0.34	p=0.589	1.68±0.79	p=0.398
EDSS in 6th months of treatment	1.92±0.44	p=0.068	1.56±0.79	p=0.49

EDSS: Expanded Disability Status scale

Table 3. EDSS scores of patients with and without brainstem involvement (excluding poor prognostic factors)

	Relapses without brainstem involvement		Relapses without brainstem involvement	
EDSS before treatment	2.35±0.89	p=0.04	2.46±1.10	p=0.005
EDSS after treatment	1.50±0.40		1.81±0.70	
EDSS in 1st month of treatment	1.42±0.67	p=0.854	1.68±0.79	p=0.776
EDSS in 6th months of treatment	1.71±0.48	p=0.194	1.56±0.79	p=0.09

EDSS: Expanded Disability Status scale

restore function and limit lasting disability (7). In contrast to this approach, there is an argument that every relapse should be treated promptly, emphasizing the importance of early and effective inflammation control. RAW has been shown to occur from the early stages of the disease and contributes to permanent disability and transition to the progressive phase (3,8). Additionally, RAW has been linked to the number of relapses experienced early in the course of relapsing-remitting MS (3,4). Failure to effectively manage a relapse is directly associated with RAW and is is a primary factor in the accumulation of disability. In our study, patients with sensory symptoms showed continued improvement after treatment, as well as at the first and sixth months. This highlights the importance of treating sensory relapses and supporting sustained recovery. However, one limitation of our study is the lack of untreated patients for comparison. Nonetheless, it is noteworthy that these patients showed benefits from relapse treatment. While RAW is a key contributor to disability in pediatric MS, progressive, irreversible disability (PIRA) is a major factor in adult-onset MS, a finding supported by several studies (9-13). In addition, while a significant improvement in EDSS was observed in the ON group before and after treatment, no significant difference was found at the first and sixth months.

A study found that patients who experienced RAW and PIRA reached a significant disability milestone simultaneously. However, the progression was faster in the PIRA group. The more rapid disability development in the PIRA group suggests that these patients require more urgent treatment interventions. Additionally, there is evidence that relapses contribute to long-term disability in the early stages of MS (14). It has been confirmed that relapses contribute to long-term disability early in the disease, although PIRA remains the primary factor in cumulative disability (2). While PIRA is recognized as the leading cause of cumulative disability, it is crucial to emphasize the importance of treating relapses. Timely management of relapses is essential to prevent long-term disability and enhance quality of life. Untreated relapses can lead to permanent nervous systems damage, resulting in irreversible disability beyond temporary flare-ups (15). Effective relapse treatment helps reduce disability and slows disease progression (16). Consequently, early diagnosis and treatment strategies are vital for improving the quality of life in MS patients.

Study Limitations

The limitations of this study its retrospective design, single-center setting, and small sample size. A multicenter prospective study with a larger patient population could provide more robust insights.

Conclusion

In conclusion, this study emphasizes the importance of actively treating all MS relapses, regardless of their initial symptoms. Our results show that patients with sensory relapses, in particular, benefit from timely and appropriate treatment, with lasting improvements in EDSS scores observed up to 6 months after the relapse. Despite being limited by its retrospective and single-center nature, this study adds to the growing body of evidence suggesting that early intervention during relapses can positively impact long-term neurological outcomes and help reduce RAW.

Ethics

Ethics Committee Approval: The study received approval from the Samsun University Non-interventional Clinical Research Ethics Committee (decision no.: 2025/6/20, date: 19.03.2025).

Informed Consent: Written informed consent was obtained from all patients who agreed to participate.

Footnotes

Authorship Contributions

Design: H.D., S.C., Data Collection or Processing: H.D., S.C., Analysis or Interpretation: H.D., S.C., Literature Search: H.D., S.C., Writing: H.D., S.C.

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

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

References

1. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol. 2014;14:58.
2. Lublin FD, Häring DA, Ganjgahi H, Ocampo A, Hatami F, Čuklina J, Aarden P, Dahlke F, Arnold DL, Wiendl H, Chitnis T, Nichols TE, Kieseier BC, Bermel RA. How patients with multiple sclerosis acquire disability. Brain. 2022;145:3147-3161.
3. Portaccio E, Bellinvia A, Fonderico M, Pastò L, Razzolini L, Totaro R, Spitaleri D, Lugaresi A, Cocco E, Onofrj M, Di Palma F, Patti F, Maimone D, Valentino P, Confalonieri P, Protti A, Sola P, Lus G, Maniscalco GT, Brescia Morra V, Salemi G, Granella F, Pesci I, Bergamaschi R, Aguglia U, Vianello M, Simone M, Lepore V, Iaffaldano P, Filippi M, Trojano M, Amato MP. Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study. Brain. 2022;145:2796-2805.
4. Toscano S, Spelman T, Ozakbas S, Alroughani R, Chisari CG, Lo Fermo S, Prat A, Girard M, Duquette P, Izquierdo G, Eichau S, Grammond P, Boz C, Kalincik T, Blanco Y, Buzzard K, Skibina O, Sa MJ, van der Walt A, Butzkueven H, Terzi M, Gerlach O, Grand'Maison F, Foschi M, Surcinelli A, Barnett M, Lugaresi A, Onofrj M, Yamout B, Khoury SJ, Prevost J, Lechner-Scott J, Maimone D, Amato MP, Spitaleri D, Van Pesch V, Macdonell R, Cartechini E, de Gans K, Slee M, Castillo-Triviño T, Soysal A, Sanchez-Menoyo JL, Laureys G, Van Hijfte L, McCombe P, Altintas A, Weinstock-Guttman B, Aguera-Morales E, Etemadifar M, Ramo-Tello C, John N, Turkoglu R, Hodgkinson S, Besora S, Van Wijmeersch B, Fernandez-Bolaños R, Patti F; MSBase Study Group. First-year treatment response predicts the following 5-year disease course in patients with relapsing-remitting multiple sclerosis. Neurotherapeutics. 2025;22:e00552.
5. Berkovich R. Treatment of acute relapses in multiple sclerosis. Neurotherapeutics. 2013;10:97-105.

6. Ramo-Tello C, Blanco Y, Brieva L, Casanova B, Martínez-Cáceres E, Ontaneda D, Ramió-Torrentá L, Rovira À. Recommendations for the diagnosis and treatment of multiple sclerosis relapses. J Pers Med. 2021;12:6.
7. Bevan C, Gelfand JM. Therapeutic management of severe relapses in multiple sclerosis. Curr Treat Options Neurol. 2015;17:345.
8. Matza LS, Kim K, Phillips G, Zorn K, Chan KS, Smith KC, Mowry EM. Multiple sclerosis relapse: Qualitative findings from clinician and patient interviews. Mult Scler Relat Disord. 2019;27:139-146.
9. Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, Model F, Koendgen H, Manfrini M, Belachew S, Hauser SL. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. JAMA Neurol. 2020;77:1132-1140.
10. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology. 2003;61:1528-1532.
11. Novotna M, Paz Soldán MM, Abou Zeid N, Kale N, Tutuncu M, Crusan DJ, Atkinson EJ, Siva A, Keegan BM, Pirko I, Pittock SJ, Lucchinetti CF, Noseworthy JH, Weinshenker BG, Rodriguez M, Kantarci OH. Poor early relapse recovery affects onset of progressive disease course in multiple sclerosis. Neurology. 2015;85:722-729.
12. Scott TF, Diehl D, Elmalik W, Gettings EJ, Hackett C, Schramke CJ. Multiple sclerosis relapses contribute to long-term disability. Acta Neurol Scand. 2019;140:336-341.
13. Koch-Henriksen N, Thygesen LC, Sørensen PS, Magyari M. Worsening of disability caused by relapses in multiple sclerosis: a different approach. Mult Scler Relat Disord. 2019;32:1-8.
14. Chen B, Ji SQ, Shen F, Tian DS, Bu BT. Contribution of relapse-associated worsening to overall disability accrual in patients with relapsing-onset multiple sclerosis: A mediation analysis. Mult Scler Relat Disord. 2022;59:103555.
15. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) advisory committee on clinical trials of new agents in multiple sclerosis. Neurology. 1996;46:907-911.
16. Eriksson M, Andersen O, Runmarker B. Long-term follow up of patients with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis. Mult Scler. 2003;9:260-274.

DOI: 10.4274/jmsr.galenos.2025.2024-11-2

J Mult Scler Res 2025;5(1):23-25

CASE REPORT

Systemic Lupus Erythematosus and Secondary Sjögren's Syndrome Following Treatment with Alemtuzumab for Multiple Sclerosis: Case Report

Ipek Gungor Dogan[1], Seda Kutlug Agackiran[2], Beril Tasdelen[1], Damla Cetinkaya Tezer[1], Serkan Demir[1]

[1]University of Health Sciences Turkiye, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Clinic of Neurology, Istanbul, Turkiye
[2] University of Health Sciences Turkiye, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Clinic of Rheumatology, Istanbul, Turkiye

Abstract

Alemtuzumab, a humanized monoclonal antibody that targets CD52, is a potent treatment for relapsing-remitting multiple sclerosis (RRMS). Despite its efficacy, alemtuzumab can trigger secondary autoimmune disorders, which most commonly involve the thyroid and hematologic systems. Herein, we have presented the case of a 36-year-old woman with highly active RRMS who developed a rare presentation of systemic lupus erythematosus (SLE) and secondary Sjögren's syndrome (sSS) 42 months after her last alemtuzumab infusion. While cases of SLE following alemtuzumab administration are extremely rare, the development of Sjögren's syndrome (SS) in this context is previously unreported. The patient exhibited pancytopenia, proteinuria, autoimmune marker positivity (anti-nuclear, anti-double stranded DNA, anti-Sjögren's syndrome type A), and low complement levels. leading to the SLE and sSS diagnoses and treated with corticosteroids, hydroxychloroquine, mycophenolate mofetil, and tacrolimus. This case underscores the importance of monitoring alemtuzumab-treated patients for delayed autoimmune complications and highlights the potential role of B and T cell dysregulation in secondary autoimmunity. Further research is necessary to elucidate the mechanisms underlying these rare adverse events.

Keywords: Alemtuzumab, anti-CD52 therapy, systemic lupus erythematosus, Sjögren's syndrome, secondary autoimmunity, adverse events

Introduction

Alemtuzumab is a highly effective humanized monoclonal antibody that targets the cell surface protein CD52. It is widely recognized and utilized as a powerful disease-modifying treatment in patients with active relapsing-remitting multiple sclerosis (RRMS) (1). Patients with RRMS undergoing treated with alemtuzumab may experience some side effects such as infusion-associated reactions, infections, and secondary autoimmune disorders involving the thyroid gland and hematologic system. Besides thyroid and hematological disorders, other secondary autoimmune disorders are rare (2,3).

Herein, we have presented a rare case of systemic lupus erythematosus (SLE) and secondary Sjögren's syndrome (sSS) that developed 42 months after a patient with highly active RRMS was treated with alemtuzumab. Only one other case of post-alemtuzumab infusion SLE has been reported in the literature (4). However Sjögren's syndrome (SS), alone or in conjunction with other autoimmune diseases, has not been reported. This case report highlights the potential for further understanding and managing the adverse effects of alemtuzumab treatment.

Case Report

A 36-year-old female was diagnosed with RRMS in 2013, at the age of 25, after she had complained of imbalance. Disease-modifying therapy was initiated with glatiramer acetate (GA) (20 mg/daily). In 2014, GA was escalated to fingolimod because of persistent clinical and radiological

Address for Correspondence: MD Serkan Demir, University of Health Sciences Turkiye, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Clinic of Neurology, Istanbul, Turkiye
E-mail: drsrkndemir@gmail.com **ORCID-ID:** orcid.org/0000-0003-4395-5141
Received: 19.12.2024 **Accepted:** 20.01.2025 **Epub:** 18.03.2025 **Publication Date:** 09.05.2025

Cite this article as: Demir S, Gungor Dogan I, Kutlug Agackiran S, Tasdelen B, Cetinkaya Tezer D. Systemic lupus erythematosus and secondary sjogren syndrome following treatment with alemtuzumab for multiple sclerosis: case report. J Mult Scler Res. 2025;5(1):23-25

disease activity. In 2019, a severe multisymptomatic attack was treated with intravenous high-dose methylprednisolone and a series of plasma exchanges. After fingolimod therapy failed, alemtuzumab was administered in December 2019. A second cycle of alemtuzumab therapy was initiated in December 2020. After initiation of alemtuzumab therapy, no further clinical or radiological disease activity was observed.

Forty-two months after the last alemtuzumab infusion, the patient presented to our neuroimmunology clinic with complaints of widespread body pain and swelling of the hand and foot that had gradually worsened over the past 4 weeks. Although the patient's neurological condition appeared both clinically and radiologically stable, she was diagnosed with pancytopenia (white blood cell count, $2.92x10^3$/uL; hemoglobin level, 7.4 g/dL; and platelet count, 50×10^3/uL) and proteinuria (1.025 g/24h). The nutritional parameters were within the normal range, and the peripheral blood smear did not reveal any abnormality. Further tests yielded the following results: positive anti-nuclear antibody titer of +3, anti-double stranded DNA antibodies level of 718.23 IU/mL (reference value <100 IU/mL), anti-Sjögren's syndrome type A positivity, low complement levels (C3: 0.32 g/L, reference value 0.9-1.80; C4: 0.03 g/L, reference value 0.1-0.4), and direct and indirect Coombs positivity without overt hemolysis. Creatinine values ranged from 0.9 to 1.23 mg/dL (reference value: 0.5-0.9) during follow-up, and no casts or dysmorphic erythrocytes were observed in the urinary sediment. The Schirmer test yielded a positive result, with 2 mm of wetting in each eye. Furthermore, imaging revealed the presence of pericardial and pleural effusion.

Based on the available data, the patient was diagnosed with SLE with sSS. The patient was promptly treated with intravenous methylprednisolone (250 mg for three consecutive days), followed by oral corticosteroids, hydroxychloroquine (5 mg/kg), and mycophenolate mofetil (2*500 mg/daily) for remission induction. Because the patient was underweight, lower doses of the drugs were preferred. Due to the presence of thrombocytopenia, a renal biopsy was not feasible. In the first month of the treatment, the proteinuria level reached the nephrotic range while the corticosteroid doses were tapered. As a result of the insufficient renal response, tacrolimus (1 mg/daily) was added to the treatment regimen.

Discussion

Alemtuzumab targets CD52, a protein found in abundance on the surface of T- and B-lymphocytes and in lower concentration on the surface of natural killer cells and other cell. It causes a rapid and significant decrease in the number of peripheral lymphocytes via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytolysis, and apoptosis (5). Subsequently, T- and B-lymphocytes repopulate in the periphery at distinctive speeds across different subsets, significantly rebalancing the immune system (6). The cause for the emergence of secondary autoimmunity after treatment with alemtuzumab remains unclear. However, it has been attributed to unexpected off-target effects as a result of imbalances among the different cell subsets during immune cell repopulation. In particular, the recovery of B-cells in the context of a delayed recovery of regulatory T-cells may account for the secondary B-cell autoimmunity (7,8). Furthermore, incomplete T-cell repertoire renewal and homeostatic clonal T-cell expansion can contribute to an autoimmune state (9,10). In this context, both antibody-mediated and T-cell-mediated autoimmune diseases have been described in the literature following treatment with alemtuzumab (4,11).

Understanding the immune system's response to treatments is crucial. Our patient, who had an 11-year duration of highly active RRMS, was sequentially administered GA, fingolimod, and alemtuzumab. She developed a rare case of secondary autoimmunity (SLE and sSS) 42 months after the last alemtuzumab infusion. Because they are closely related to chronic inflammatory clinical conditions of autoimmune nature, the incidence of sSS in patients with SLE can reach up to 19.5% (12,13). This case report not only sheds light on secondary autoimmune disorders caused by alemtuzumab but also provides evidence of the strong immune connection between SLE and SS, particularly in terms of B cell immunity, and an abnormal T cell response even appeared as secondary immunity.

Conclusion

In conclusion, thorough research is crucial to enhance our knowledge of B-cell colonization and T-cell repertoire in relation to secondary immunity. Furthermore, patients being administered alemtuzumab should be closely monitored for the development of various autoimmune conditions. This responsibility is crucial to minimize the risk of delayed diagnosis and treatment.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

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

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

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

References

1. Willis MD, Robertson NP. Alemtuzumab for multiple sclerosis. Curr Neurol Neurosci Rep. 2016;16:84.
2. Berger T, Elovaara I, Fredrikson S, McGuigan C, Moiola L, Myhr KM, Oreja-Guevara C, Stoliarov I, Zettl UK. Alemtuzumab use in clinical practice: recommendations from european multiple sclerosis experts. CNS Drugs. 2017;31:33-50.
3. Yang J, Sun Y, Zhou X, Zhang D, Xu Z, Cao J, Fan B. Risk of secondary autoimmune diseases with alemtuzumab treatment for multiple sclerosis: a systematic review and meta-analysis. Front Immunol. 2024;15:1343971.
4. Adamec I, Mayer M, Ćorić M, Ruška B, Habek M. Systemic erythematous lupus after treatment of multiple sclerosis with alemtuzumab. Mult Scler Relat Disord. 2020;46:102589.
5. Stanglmaier M, Reis S, Hallek M. Rituximab and alemtuzumab induce a nonclassic, caspase-independent apoptotic pathway in B-lymphoid cell lines and in chronic lymphocytic leukemia cells. Ann Hematol. 2004;83:634-645.
6. Zhang X, Tao Y, Chopra M, Ahn M, Marcus KL, Choudhary N, Zhu H, Markovic-Plese S. Differential reconstitution of T cell subsets following immunodepleting treatment with alemtuzumab (anti-CD52 monoclonal antibody) in patients with relapsing-remitting multiple sclerosis. J Immunol. 2013;191:5867-5874.
7. Baker D, Herrod SS, Alvarez-Gonzalez C, Giovannoni G, Schmierer K. Interpreting lymphocyte reconstitution data from the pivotal phase 3 trials of alemtuzumab. JAMA Neurol. 2017;74:961-969.
8. von Kutzleben S, Pryce G, Giovannoni G, Baker D. Depletion of CD52-positive cells inhibits the development of central nervous system autoimmune disease, but deletes an immune-tolerance promoting CD8 T-cell population. Implications for secondary autoimmunity of alemtuzumab in multiple sclerosis. Immunology. 2017;150:444-455.
9. Ruck T, Barman S, Schulte-Mecklenbeck A, Pfeuffer S, Steffen F, Nelke C, Schroeter CB, Willison A, Heming M, Müntefering T, Melzer N, Krämer J, Lindner M, Riepenhausen M, Gross CC, Klotz L, Bittner S, Muraro PA, Schneider-Hohendorf T, Schwab N, Meyer Zu Hörste G, Goebels N, Meuth SG, Wiendl H. Alemtuzumab-induced immune phenotype and repertoire changes: implications for secondary autoimmunity. Brain. 2022 ;145:1711-1725.
10. von Essen MR, Chow HH, Holm Hansen R, Buhelt S, Sellebjerg F. Immune reconstitution following alemtuzumab therapy is characterized by exhausted T cells, increased regulatory control of proinflammatory T cells and reduced B cell control. Front Immunol. 2023;14:1249201.
11. Ruck T, Pfeuffer S, Schulte-Mecklenbeck A, Gross CC, Lindner M, Metze D, Ehrchen J, Sondermann W, Pul R, Kleinschnitz C, Wiendl H, Meuth SG, Klotz L. Vitiligo after alemtuzumab treatment: secondary autoimmunity is not all about B cells. Neurology. 2018;91:2233-2237.
12. Alani H, Henty JR, Thompson NL, Jury E, Ciurtin C. Systematic review and meta-analysis of the epidemiology of polyautoimmunity in Sjögren's syndrome (secondary Sjögren's syndrome) focusing on autoimmune rheumatic diseases. Scand J Rheumatol. 2018;47:141-154.
13. Pasoto SG, Adriano de Oliveira Martins V, Bonfa E. Sjögren's syndrome and systemic lupus erythematosus: links and risks. Open Access Rheumatol. 2019;11:33-45.

DOI: 10.4274/jmsr.galenos.2025.2024-11-1

J Mult Scler Res 2025;5(1):26-29

CASE REPORT

Evaluation of an Individual with Multiple Sclerosis and Hemiatrophy in Terms of Muscle Strength, Balance, and Quality of Life: A Case Report

Gizem Sekercan[1], Hanife Abakay[2], Mehmet Fatih Yetkin[3]

[1]Kocaeli Health and Technology University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Kocaeli, Turkiye
[2]Kayseri University Incesu Ayse ve Saffet Arslan Vocational School of Health Services, Department of Therapy and Rehabilitation, Kayseri, Turkiye
[3]Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Turkiye

Abstract

This report presents the case of a 35-year-old male patient with hemiatrophy, a rare condition accompanying the diagnosis of multiple sclerosis (MS), in terms of muscle strength, balance, and quality of life. The patient presented with an Expanded Disability Status Scale level of 4 and left hemiatrophy with a diagnosis of MS. According to the muscle strength measurements, the left upper and lower extremity muscles were weaker compared to the right extremity. The present report highlights that hemiatrophy, although uncommon in MS, may impact functional outcomes such as muscle strength, balance, quality of life, and depression. The evaluation of hemiatrophy may contribute to the existing literature.

Keywords: Balance, hemiathrophy, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by axonal loss and demyelination in the central nervous system (1). The involvement of diverse components of the central nervous system can result in motor, sensory, visual, and autonomic symptoms (2). Individuals with MS frequently experience motor impairments, including diminished muscle strength and balance deficits (3,4). These symptoms contribute to a decline in the quality of life (5).

Hemiatrophy may occur in a variety of conditions, including neurodegenerative and autoimmune disorders (6). The common neurological symptoms observed in hemiatrophy syndromes include epilepsy, headache, facial pain, motor deficits, and dizziness (6). Magnetic resonance imaging (MRI) findings under such conditions often reveal structural and signal abnormalities in various brain regions, including the frontal lobe, parietal lobe, subcortical areas, temporal lobe, occipital lobe, and brainstem (6). Although there are similarities in the brain regions affected by hemiatrophy and MS, hemiatrophy is not typically associated with the diagnosis of MS. In this study, we evaluated and shared the relevant care experience with a person with hemiatrophy associated with MS, with a focus on factors such as muscle strength, limb circumference, balance, and quality of life.

Case Report

A 35-year-old right-handed man, diagnosed with secondary progressive MS, with an Expanded Disability Status Scale score of 4. He had no family history of neurodegenerative disease. As a part of the neurological examination, the sensory functions, reflexes, balance, and coordination were assessed. Sensory testing revealed a sensory loss in the face and distal extremities. The assessment of reflexes revealed a reduction in the patellar

Address for Correspondence: Res. Asst. Gizem Sekercan, Kocaeli Health and Technology University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Kocaeli, Turkiye
E-mail: gizemsekercan@gmail.com **ORCID-ID:** orcid.org/0000-0002-0181-6488
Received: 06.11.2024 **Accepted:** 21.03.2025 **Publication Date:** 09.05.2025

Cite this article as: Şekercan G, Abakay H, Yetkin MF. Evaluation of an individual with multiple sclerosis and hemiatrophy in terms of muscle strength, balance, and quality of life: A case report. J Mult Scler Res. 2025;5(1):26-29

tendon reflex. Balance was assessed during unipedal standing, which indicated a weakened balance on the left foot when compared to the right. He was diagnosed with MS in 2015. He had no history of any other disease. The patient has had hemiatrophy in the left extremity for a prolonged period, with significant progression observed in the last 5 years. His initial MS problems, which included walking difficulties and the loss of balance, began in 2004. He was diagnosed with MS in 2015 after experiencing symptoms such as right eye blurriness, loss of balance, and abnormal gait. The symptoms of disorders related to balance and strength loss increased by 2020. The patient has had a neurogenic bladder problem since 2015. The loss of strength and balance increased in 2020 and 2021 following the coronavirus disease (COVID). Throughout the past 2 months, he has also complained of dysphagia. In 2015, interferon beta-1a (44 mcg subcutaneously, thrice a week) was initiated. A change to fingolimod treatment was made effective in 2017 for an increase in the disease activity. Because of the side effects, the treatment plan was modified to include cladribine in 2019. In 2023, he began ocrelizumab and continued the treatment to this day. In 2020 and 2021, the patient suffered from COVID-19. Since 2015, the patient has developed atrophy in the left-lower extremity, left upper extremity and left facial muscles, and left-sided respiratory muscles relative to the other side (Figures 1A-C). The patient's images are shown in Figure 1.

To assess atrophy, a physiotherapist measured the circumferences of the right and left extremities bilaterally using a tape measure at the sites on the quadriceps, gastrocnemius, arm, and forearm, which have the greatest amount of muscle tissues. Muscle strength was assessed by performing a manual muscle test and a back-leg dynamometer (TKK 5402 BACK-D). The quality of life was assessed by using the MS Quality of Life-54 (MSQOL-54) questionnaire, which assessed the effects of MS on cognitive function and fatigue. The MSQOL-54 is a quality of life survey developed by adding 18 items to the Short Form-36, which is specifically aimed at MS (7). The assessment includes two subcategories: the composite mental health score and the physical health score. Each heaading has a number ranging from 0 to 100 (8). Balance was assessed by using the Berg Balance Scale (BBS), which is composed of 14 components, each scored from 0 to 4, with a total possible score of 56 (9). MRI was performed to evaluate the spread of the pathological process in terms of space and time. This imaging technique is essential for ruling out other disorders (10). MRI is also crucial for diagnosing MS, determining a treatment plan, and monitoring changes over time (11). The measurements of muscle atrophy and muscle strength were performed in 2015 and 2023.

The measurements of the extremity circumference showed that the left upper and lower extremities were more atrophic in the

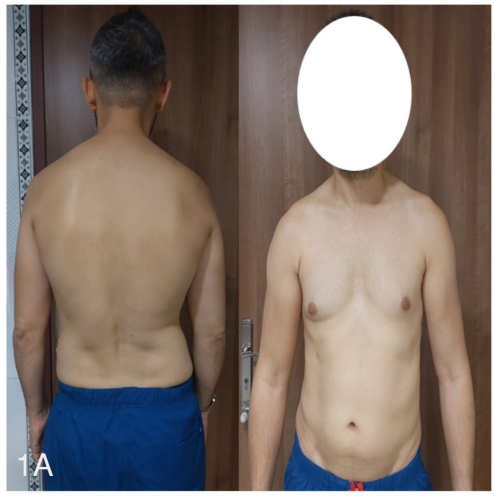


Figure 1A. Pictures of patient

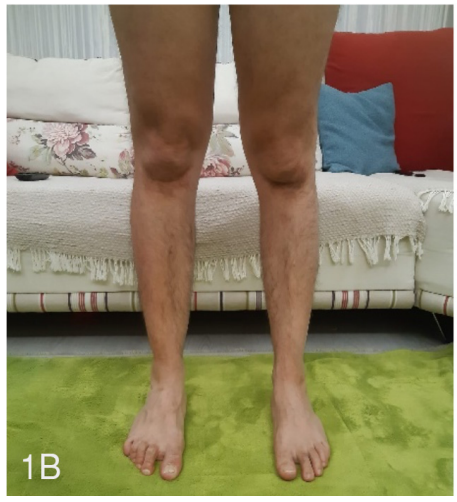


Figure 1B. Pictures of patient

Figure 1C. Pictures of patient

Figure 1. Images of the patient showing **A)** marked weakness in the respiratory and back muscles on the left side, **B)** atrophic appearance in the left leg, particularly in the quadriceps and gastrocnemius muscles, **C)** atrophy in the left facial muscles

Table 1. Results of limb circumference measurement

	2015 (years)			2023 (years)		
Body circumference	**Right side**	**Left side**	**Difference**	**Right side**	**Left side**	**Difference**
Gastrocnemius (cm)	39	38.5	**0.5**	38.5	36	**2.5**
Quadriceps (cm)	48	47.5	**0.5**	47	42	**5**
Biceps (cm)	30	29.6	**0.4**	29.7	28.5	**1.2**
Forearm (cm)	27.5	27	**0.5**	27.3	24.9	**2.4**

Table 2. Upper extremity and lower extremity muscle strength measurement results

Upper extremity muscle strength	Right side	Left side	Lower extremity muscle strength	Right side	Left side
Shoulder flexion	5	4	Hip flexion	4+	3-
Shoulder abduction	5	4	Knee flexion	4	3
Elbow extension	5	4	Knee extension	4	3
Elbow flexion	4+	4	Foot dorsiflexion	5	3-
Wrist flexion	5	4	Foot plantar flexion	5	4
Wrist extension	5	4			
Finger flexors	5	5			
Finger extensors	3+	3+			

year 2015 and 2023 (Table 1). The measurements of muscular strength revealed that the muscles of the left upper and lower extremities were weaker than those of the right in the years 2015 and 2023 (Table 2). The mean of the three measurements with the back-leg dynamometer was 43 kg. The BBS score was 33, theMSQOL-54 composite physical health score was 30.46, and the composite score for mental health was 45.94. MRI findings revealed significant brainstem involvement (Figures 2A, 2B). MRI images are shown in Figures 2A, 2B.

Discussion

Hemiatrophy is characterized by the loss of muscle mass on one side of the body. MS is associated with various neurological and musculoskeletal diseases (6). It is a demyelinating disease of the central nervous system that often leads to asymmetric neurological findings (1). Consequently, the co-occurrence of both conditions is theoretically possible, although there are limited case reports in the literature addressing this specific association.

In the present case, the patient with MS experienced a decline in muscle strength, balance, and quality of life due to hemiatrophy, a condition that is not typically observed in MS patients. The quality of life score indicated a decrease in the patient's overall quality of life. However, as no pre-and post-comparisons were made, it remains unclear whether the outcome is directly associated with hemiatrophy.

MRI findings of the individual revealed brainstem involvement. In cases of hemiatrophy, ipsilateral facial and extremity involvement can occur, which may share similarities with other syndromes such as Parry-Romberg syndrome (PRS). It is also possible to observe additional signs, including cognitive impairment and epilepsy. Although the atrophy of the left side of the face and left extremities in this case presented some similarities to PRS, it is important to note that these features are not exclusive to any one syndrome (6).

Past studies have highlighted the possibility that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection exacerbates spinal and brain demyelination at different illness stages (12). The impact of SARS-CoV-2 on the central nervous system is believed to trigger a post-infection neuroimmune response that initiates the demyelination process (12). In this instance, it is believed that the demyelination process may have been intensified due to the history of COVID-19.

The rare form of MS that exhibits characteristics distinct from other demyelinating diseases is referred to as tumefactive MS. Neurological symptoms may develop in a rapidly progressive manner in such cases. One such manifestation is hemiatrophy, which is characterized by a weakness that is localized to one side of the body (13). However, the ipsilateral limb atrophy recorded in the present case was an uncommon occurrence in MS patients. Therefore, additional diagnosis and long-term follow-up are warranted in the case of left hemiparesis with marked neurological and physical decline in a patient diagnosed with MS in 2015.

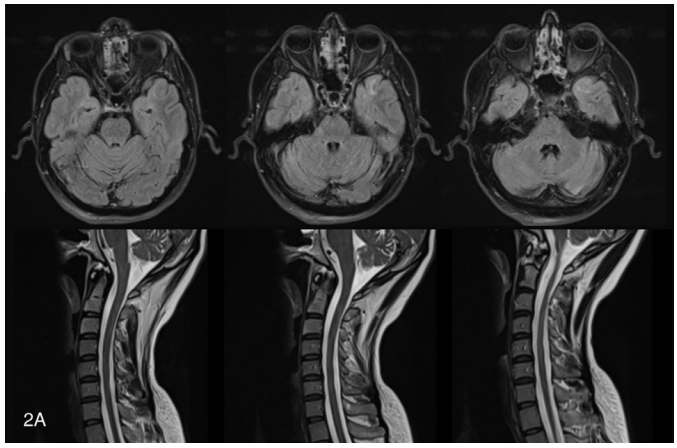


Figure 2A. MRI findings of the patient

MRI: Magnetic resonance imaging

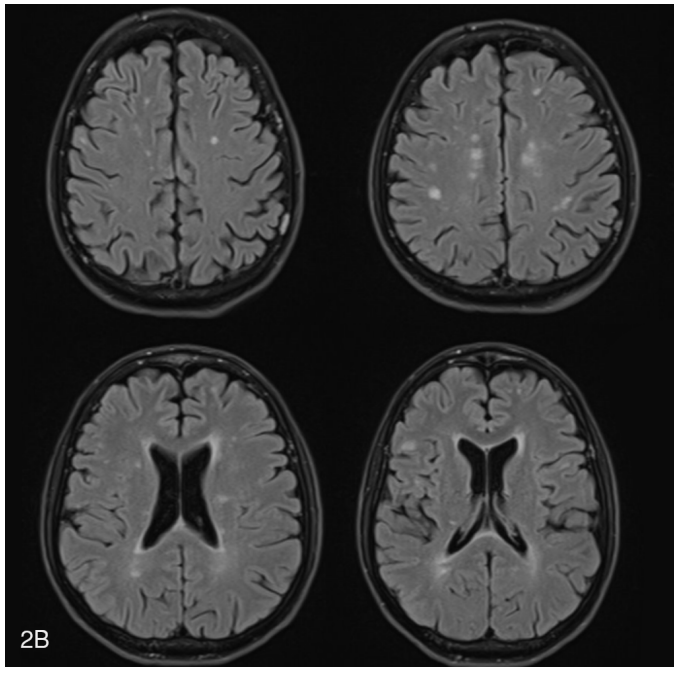


Figure 2B. MRI findings of the patient

Figure 2. A) Axial FLAIR sequence MRI of the brain showing hyperintense lesions in the periventricular white matter, **B)** sagittal T2-weighted MRI of the cervical spinal cord demonstrating hyperintense lesions consistent with multiple sclerosis, the FLAIR sequence MRI of the brain in the upper axial plane revealed hyperintense lesions in the periventricular and subcortical white matter

MRI: Magnetic resonance imaging, FLAIR: Fluid attenuated inversion recovery

Ethics

Informed Consent: Informed consent was obtained from the patient in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

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

Conflict of Interest: All the authors declare no conflicts of interest.

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

References

1. Abakay H, Doğan HA, Yetkin MF, Güç A, Çaliş HT, Caltekin MD. The effects of incontinence on functionality, disability, and quality of life in male and female patients with multiple sclerosis. Mult Scler Relat Disord. 2022;66:104010.
2. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clin Med (Lond). 2017;17(Suppl 6):530-536.
3. Corrini C, Gervasoni E, Perini G, Cosentino C, Putzolu M, Montesano A, Pelosin E, Prosperini L, Cattaneo D. Mobility and balance rehabilitation in multiple sclerosis: A systematic review and dose-response meta-analysis. Mult Scler Relat Disord. 2023;69:104424.
4. Cano-Sánchez J, Aibar-Almazán A, Hita-Contreras F, Afanador-Restrepo DF, Martínez-Amat A, Achalandabaso-Ochoa A, Carcelén-Fraile MDC. Is resistance training an option to improve functionality and muscle strength in middle-aged people with multiple sclerosis? A systematic review and meta-analysis. J Clin Med. 2024;13:1378.
5. Dobson R, Giovannoni G. Multiple sclerosis-a review. Eur J Neurol. 2019;26:27-40.
6. Long L, Kang Z, Chen S, Cui C, Men X, Qiu W. A case report of parry-romberg syndrome misdiagnosed as multiple sclerosis. Front Neurol. 2020;11:797.
7. Fiest KM, Greenfield J, Metz LM, Patten SB, Jetté N, Marrie RA. Discriminative ability of quality of life measures in multiple sclerosis. Health Qual Life Outcomes. 2017;15:246.
8. Martínez-Espejo MD, Limiñana-Gras RM, Patró-Hernández RM, Lallana JEM, Robles EA, Rebollo MCM. Assessment of quality of life in multiple sclerosis through the MSQOL-54 and its relation to the health of the caregiver. Enfermería Global. 2021;20:234-249.
9. Gervasoni E, Jonsdottir J, Montesano A, Cattaneo D. Minimal clinically important difference of Berg balance scale in people with multiple sclerosis. Arch Phys Med Rehabil. 2017;98:337-240. e2.
10. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162-173.
11. Filippi M, Preziosa P, Arnold DL, Barkhof F, Harrison DM, Maggi P, Mainero C, Montalban X, Sechi E, Weinshenker BG, Rocca MA. Present and future of the diagnostic work-up of multiple sclerosis: the imaging perspective. J Neurol. 2023;270:1286-1299.
12. Erdoğan T, Koçer B, Şen S, Balci BP, Terzi M. COVID-19 Enfeksiyonu sonrası yeni tanılı tümefaktif lezyon ve multipl skleroz. Arch Neuropsychiatry. 2023;60:223-230.
13. Benli S. Tümefaktif multipl skleroz: olgu sunumu ve literatürün gözden. Türk Nöroloji Dergisi. 2006;12:391-397.

DOI: 10.4274/jmsr.galenos.2025.2024-11-3

J Mult Scler Res 2025;5(1):30-32

CASE REPORT

Two Rare Coexisting Diseases and an Uncommon Presentation: Migraine, and Neuromyelitis Optica Presented with Cervicogenic Headache - A Case Report

Berkcan Piset, Rabia Gokcen Gozubatik Celik

University of Health Sciences, Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Mental Health and Neurological Disorders, Clinic of Neurology, Istanbul, Turkiye

Abstract

Neuromyelitis optica (NMO) is a rare autoimmune disorder distinguished by optic neuritis, transverse myelitis, and area postrema syndrome. Headaches as an initial manifestation are uncommon and often overlooked. This case describes a 46-year-old female with a 20-year history of migraines. The patient developed cervicogenic headaches three years before presenting with optic neuritis. MRI findings of optic and spinal lesions, together with positive aquaporin-4 immunoglobulin G antibodies, corroborated the diagnosis of NMO. Treatment with intravenous methylprednisolone, azathioprine, and rituximab resulted in substantial improvement in visual acuity and headache intensity. This case emphasizes the significance of investigating secondary causes of cervicogenic headaches and raises awareness about NMO in such patients, highlighting the benefit of early treatment in preventing long-term disability.

Keywords: Headache, neuromyelitis optica, optic neuritis

Introduction

Neuromyelitis optica (NMO), a rare autoimmune disorder that causes inflammation and demyelination of the optic nerves and spinal cord, frequently leads to optic neuritis and transverse myelitis, which may cause significant neurological disability if untreated. The presence of aquaporin-4 (AQP4) immunoglobulin G (IgG) antibodies is a key diagnostic marker. Migraine is a genetically influenced complex neurological disorder typified by episodes of moderate-to-severe headache, usually unilateral and accompanied by nausea and light and sound sensitivity. Headache and other forms of pain have occasionally been identified as NMO symptoms (1,2). Headaches in NMO are less frequently recognized, though cervicogenic headaches and trigeminal autonomic cephalalgias have been reported as atypical manifestations. This case emphasizes the need to consider NMO in patients with unusual headache patterns, especially when accompanied by neurological symptoms. Early diagnosis and investigation are essential for improving outcomes and lowering long-term disability.

Case Report

A 46-year-old female presented with blurred vision in the right eye for five days and a history of worsening chronic headaches. Initially diagnosed with migraine without aura 20 years ago. However, the patient's headache pattern changed three years prior, characterized by left cervical pain radiating to the left side of the head and triggered by forward head positioning. A neurological examination revealed horizontal nystagmus, left upper extremity weakness, hyperreflexia, bilateral Babinski signs, hypoesthesia in left C8-T1 dermatomes,

Address for Correspondence: MD Berkcan Piset, University of Health Sciences, Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Mental Health and Neurological Disorders, Clinic of Neurology, Istanbul, Türkiye

E-mail: berkcanpiset@gmail.com **ORCID-ID:** orcid.org/0009-0000-7268-2416

Received: 24.11.2024 **Accepted:** 18.02.2025 **Publication Date:** 09.05.2025

Cite this article as: Piset B, Gozubatik Celik RG. Two rare coexisting diseases and an uncommon presentation: migraine, and neuromyelitis optica presented with cervicogenic headache - a case report. J Mult Scler Res. 2025;5(1):30-32

and gait instability. No abnormalities were detected on fundus examination. The right eye's visual acuity was 20/160, whereas the left eye's was 20/32. Laboratory test results, including those of autoimmune and infectious panels, were unremarkable except for an elevated cerebrospinal fluid IgG index. Visual evoked potentials demonstrated bilateral latency prolongation. Magnetic resonance imaging (MRI) displayed enhancing lesions in the right optic nerve (Figure 1) and nonenhancing lesions in the cervical spine (C4-C5, C6) (Figure 2). The diagnosis of NMO was verified with a positive AQP4 antibody test result. The newly developed headaches were diagnosed as cervicogenic headaches based on the International Classification of Headache Disorders. The cervical range of motion was found to be restricted, and the headache was significantly aggravated on provocative maneuvers. Furthermore, the headache developed at the same time that the lesion appeared. Imaging data confirmed the presence of a lesion within the cervical spine. The patient was administered intravenous methylprednisolone (IVMP) for 10 days, leading to significant improvement in visual acuity and symptoms. Monthly IVMP pulses and azathioprine were part of the maintenance therapy. Cervicogenic headache pain was managed with weekly greater occipital nerve (GON) blocks, which were then tapered off. A new cervical lesion (C1-C2) (Figure 3) discovered during a routine check-up to evaluate disease activity and progression at three months led to the initial administration of carbamazepine for pain monthsand subsequent rituximab therapy at six months due to the lesion's progression.

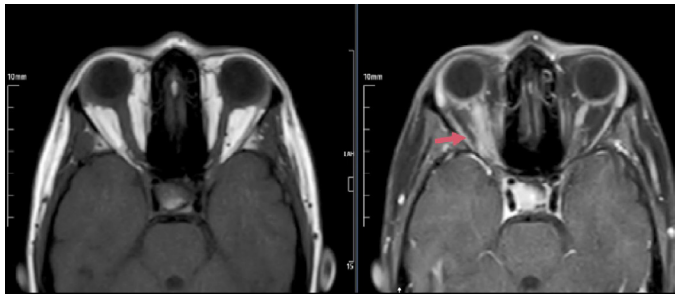


Figure 1. High signal intensity at the right opticnerve. Axial T1-weighted MRI scans of the orbits

MRI: Magnetic resonance imaging

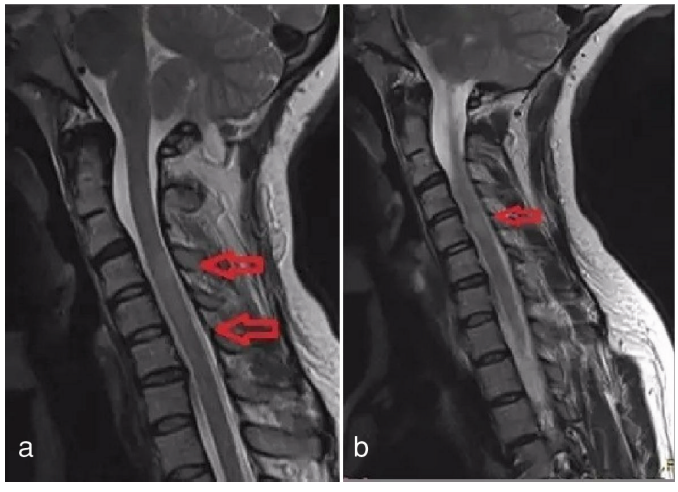


Figure 2. Non-contrast-enhancing lesions are observed involving the C3-C4 and C5 levels. (a) T2-weighted sagittal MRI of the cervical spine, (b) T2-weighted sagittal MRI of the cervical spine

MRI: Magnetic resonance imaging

Discussion

This case highlights the significance of identifying headache, which might occasionally be cervicogenic in origin, as a possible atypical manifestation of NMO. Choi et al. (3) demonstrated that this atypical and extremely uncomon disease presentation can significantly contribute to diagnostic challenges and potential misdiagnosis. It underscores the need to assess secondary etiologies in patients with new or altered headache patterns, particularly in those with a history of migraines. Early identification of NMO can facilitate timely intervention, improving outcomes and mitigating long-term sequelae.

The association of cervicogenic headache with NMO, as suggested by Masters-Israilov and Robbins (4), may be due to spinal cord and optic nerve inflammation and demyelination.

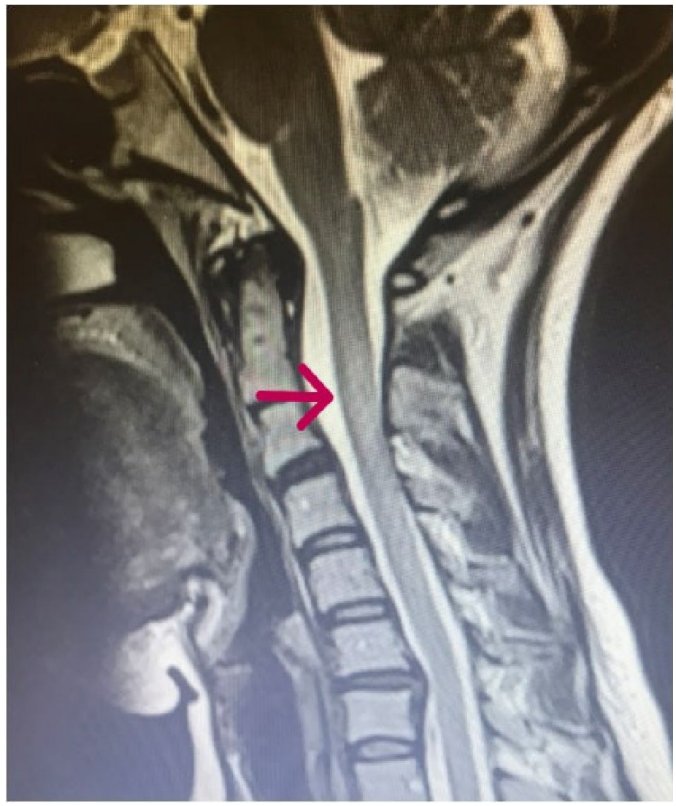


Figure 3A. At the 3 month check up: A new lesion is identified extending to the C1-C2 level, without contrast enhancement. T2-weighted sagittal cervical spine MRI

MRI: Magnetic resonance imaging

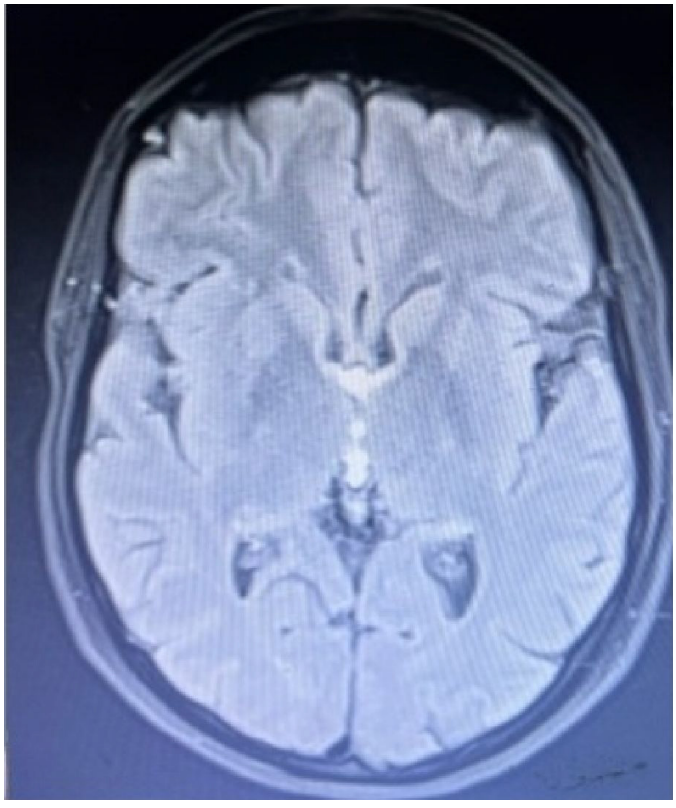


Figure 3B. At the 3 month check up: A normal MRI of the brain. Axial FLAIR of brain MRI

FLAIR: Fluid Attenuated Inversion Recovery, MRI: Magnetic resonance imaging

In this patient, cervical spinal lesions likely induced cervicogenic headache, which is characterized by pain radiating from the neck.

Acute NMO attacks are typically managed with high-dose IVMP, as in this case, resulting in considerable improvement in visual acuity and symptoms. Disease-modifying therapies, such as azathioprine and rituximab, are critical for relapse prevention and disease control.

GON blocks were effectively used to treat cervicogenic headache, lowering pain intensity and frequency. This demonstrates the utility of focused symptom management in addition to standard NMO therapies.

Clinicians should consider NMO in patients with evolving headache patterns and neurological signs. Comprehensive diagnostic evaluation, including MRI and AQP4 antibody testing, is critical. Timely initiation of immunosuppressive therapy and tailored symptom-specific treatments can significantly enhance patient outcomes. As revealed in a case published by Hamami et al. (5), NMO can present atypically with headache in pediatric patients, highlighting the importance of considering this diagnosis in patients with unusual headache presentations.

Conclusion

This case demonstrates that headache can be an early symptom of NMO, preceding conventional features such as optic neuritis or transverse myelitis. Although headaches are often benign, new-onset or atypical patterns warrant thorough evaluation. Recognizing headache as a potential early symptom of NMO allows for timely MRI and AQP4 antibody testing, facilitating prompt diagnosis and treatment. This approach is critical for enhancing long-term outcomes and mitigating the risk of severe neurological impairment.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Concept: R.G.G.C., Design: R.G.G.C., Data Collection or Processing: R.G.G.C., Analysis or Interpretation: R.G.G.C., Literature Search: R.G.G.C., Writing: B.P..

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

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

References

1. Asseyer S, Cooper G, Paul F. Pain in NMOSD and MOGAD: A systematic literature review of pathophysiology, symptoms, and current treatment strategies. Front Neurol. 2020;11:778.
2. Asseyer S, Schmidt F, Chien C, Scheel M, Ruprecht K, Bellmann-Strobl J, Brandt AU, Paul F. Pain in AQP4-IgG-positive and MOG-IgG-positive neuromyelitis optica spectrum disorders. Mult Scler J Exp Transl Clin. 2018;4:1-12.
3. Choi SI, Lee YJ, Kim DW, Yang JY. A case of neuromyelitis optica misdiagnosed as cervicogenic headache. Korean J Pain. 2014;27:77-80.
4. Masters-Israilov A, Robbins MS. Headache in neuromyelitis optica. Curr Pain Headache Rep. 2017;21:1-8.
5. Hamami A, Rkain M, Benhachem M, Ghannam A, Elouali A, Babakhoua A. Neuromyelitis optica revealed by headache in a child: A case report. Open Journal of Pediatrics. 2023;13:432-436.