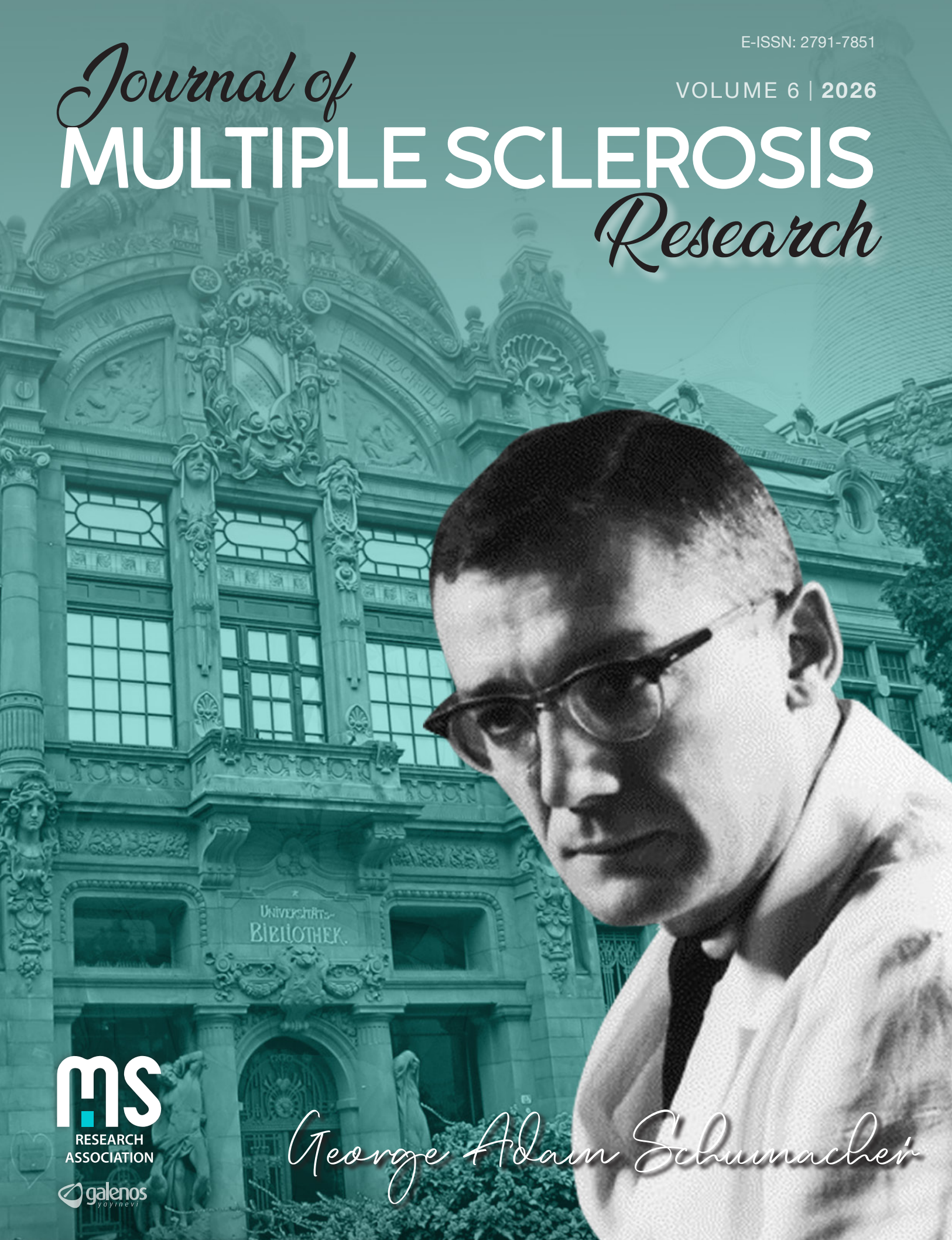
E-ISSN: 2791-7851

VOLUME 6 | 2026

Journal of MULTIPLE SCLEROSIS Research



George Adam Schumacher

MS RESEARCH ASSOCIATION

galenos yayınevi

DOI: 10.4274/jmsr.galenos.2025.2025-3-2

J Mult Scler Res 2026;6:1-8

REVIEW

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Management of Infusion-related Reactions (IRRs) in Patients Receiving Ocrelizumab for Multiple Sclerosis (MS) Treatment: A Systematic Review

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Abstract

Ocrelizumab demonstrates positive outcomes in patients with multiple sclerosis. However, approximately 40% of patients experience infusion-related reactions (IRRs), which can reduce adherence despite premedications. This review examines the safety of shortened infusion protocols in reducing IRRs and improving the patient experience. Additionally, other strategies for minimizing IRRs are discussed. Scopus, PubMed, and the Cochrane Library were searched up to November 30, 2024, for cohort studies, as well as randomized and non-randomized clinical trials. Seven studies were included following two stages of screening. The primary outcome was a documented reduction in the incidence rate of IRRs. The seven included studies comprised a total of 1,834 patients. Overall, shorter infusion protocols were found to be safe as conventional protocols, with only a slight increase in IRR incidence. Patients receiving shorter infusions at-home reported higher satisfaction, comfort, and confidence. Splitting the first dose appears to be safer than administering a full dose at once, although a single full dose is also relatively safe. Shorter infusion rates and a single full dose of ocrelizumab are generally preferred to save time and effort. Premedication has been shown to reduce IRRs, and patients report greater comfort with at-home infusions. Further clinical trials are needed to evaluate all proposed procedures and to establish a comprehensive understanding of the optimal management strategies for ocrelizumab-related IRRs.

Keywords: Systemic review, multiple sclerosis, ocrelizumab, infusion-related reactions, shorter infusion, management

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by inflammation, demyelination, and axonal damage (1). This debilitating disease presents with a wide range of symptoms, including sensory disturbances, motor impairments, and cognitive dysfunction. MS disproportionately affects younger adults aged 20-44 years. Globally, it accounted for over 973,300 disability-adjusted life years and 16,300 deaths in 2021, underscoring its substantial impact on health and productivity (2,3).

The advent of disease-modifying therapies has transformed MS management, providing options to reduce relapse rates, slow disease progression, and enhance quality of life. Among these, ocrelizumab—a humanized monoclonal antibody (mAb) targeting CD20-positive B-cells—has demonstrated efficacy in both relapsing and primary progressive forms of MS (4,5). By modulating immune activity, ocrelizumab targets the inflammatory mechanisms driving the disease. Despite its therapeutic benefits, its use can be complicated by infusion-related reactions (IRRs), ranging from mild symptoms, such as itching and flushing, to severe issues like shortness of breath and hypotension (6).

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Received: 28.03.2025 **Accepted:** 29.09.2025 **Epub:** 15.10.2025 **Publication Date:** 27.01.2026

Cite this article as: Baniamer MN, Matar HI, Baniamer BN, Altaweel AS, Al-Rjoub AA, Aletaywi AN, Alsarayrah AI. Management of infusion-related reactions (IRRs) in patients receiving ocrelizumab for multiple sclerosis (MS) treatment: a systematic review. J Mult Scler Res. 2026;6:1-8

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IRRs, often triggered by cytokine release during infusion, represent a significant barrier to treatment adherence and optimal outcomes. These reactions are commonly observed with mAb treatments and can occur via multiple pathogenic mechanisms, including cytokine release syndrome and hypersensitivity reactions mediated by immunoglobulins E and G (7,8). IRRs may delay therapy, lead to treatment discontinuation, or diminish the therapeutic benefits of ocrelizumab (9). Effective management of IRRs is essential and includes premedication with antihistamines, corticosteroids, and antipyretics, along with close monitoring during and after infusions (10). Despite these premedication strategies, IRRs still occur in 34-40% of patients receiving ocrelizumab, with the highest incidence observed during the first infusion (11). To address these challenges, recent efforts have explored shortening infusion durations as an alternative strategy to reduce IRR incidence and severity while improving overall patient experience.

While existing research has examined IRRs with monoclonal antibodies, there remains a need for more focused investigation of ocrelizumab-specific IRRs. A deeper understanding of their frequency, underlying mechanisms, and risk factors could refine clinical protocols and enhance safety. Clarifying these mechanisms may also improve risk prediction and inform targeted strategies to mitigate adverse reactions.

The absence of well-defined criteria for stratifying patients' IRR risk presents a challenge to personalizing ocrelizumab therapy. In addition, the long-term impact of IRRs on treatment adherence remains understudied; such reactions may lead to therapy discontinuation or hesitation to continue, ultimately compromising effective disease management. By systematically evaluating shortened versus conventional infusion protocols, this review aims to assess whether reduced administration times can lower IRR rates while maintaining treatment efficacy. The findings may inform more patient-centered treatment approaches, optimizing adherence and improving quality of care for individuals with MS.

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (12).

Search Strategy, PICO, and Study Eligibility Criteria

Databases, including PubMed, Cochrane Library, and Scopus, were searched till November 30, 2024. The search strategy used was: ("IRR*" or "Infusion-Related Reaction*" or "Infusion Reaction*" or "Infusion Event*" or "Infusion Syndrome*") and ("Multiple Sclerosis" or "MS" or "Disseminated Sclerosis" or "Cerebrospinal Sclerosis" or "Autoimmune Demyelinating Disorder" or "Encephalomyelitis Disseminata") and ("Ocrelizumab" or "Ocrevus"). Additionally, we made subtle modifications to the search strategy for each database to ensure the most comprehensive results.

The study population included adult patients aged 18-65 years with MS receiving ocrelizumab as the primary treatment. Interventions included any procedures and/or medications used to reduce the incidence or severity of IRRs. As a control, we used data from patients who were not exposed to the interventions described above. The primary outcome of interest was the reduction in IRRs, measured using the Common Terminology Criteria for Adverse Events. Secondary outcomes included treatment satisfaction (Treatment Satisfaction Questionnaire for Medication), sleepiness (Stanford Sleepiness Scale), fatigue (Visual Analog Scale-Fatigue; Modified Fatigue Impact Scale), and disease impact (Multiple Sclerosis Impact Scale) scores.

We included prospective and retrospective studies, randomized and non-randomized trials, and sub-studies that assessed ocrelizumab IRR incidence as a primary outcome. Studies evaluating IRR incidence as a secondary outcome were included only if they reported sufficient data. Case reports and case series were excluded, as none provided detailed data or management procedures. We also excluded studies lacking essential data, animal or *in vitro* studies, book chapters, conference abstracts, and publications presented solely as commentaries.

Study Screening, Quality Assessment, and Data Extraction

Initially, one researcher identified and eliminated duplicate studies based on title, author, publication year, and DOI. Screening was then conducted in two stages: in stage 1, studies were evaluated based on titles and abstracts; in stage 2, full-text screening was performed using the aforementioned eligibility criteria. Both stages were performed by three independent authors, with a fourth author resolving any conflict.

Quality assessment was performed using the Cochrane's risk of bias tool (ROB) for randomized trials. Non-randomized trials were evaluated using the Newcastle-Ottawa Scale (NOS). Assessments were conducted independently by two authors, with a third author resolving any disagreements. Data from eligible studies were extracted using a standardized Excel form, including publication characteristics (authors, national clinical trial numbers, year, study duration) and study design (intervention details, control and treatment groups, total number of participants). Patient demographics (age and gender), as well as study outcomes and conclusions, were also recorded.

Search Results

The literature search identified a total of 745 studies using a pre-formatted search strategy: 59 from PubMed, 645 from Scopus, and 41 from Cochrane. Using EndNote, 76 duplicate studies were removed before the first stage of screening. A total of 699 studies underwent title and abstract screening, of

which 635 were excluded. Following full-text review, seven of the remaining 41 studies met the inclusion criteria and were included in this systematic review.

See PRISMA flow diagram (Figure 1).

Study Characteristics

The seven included studies comprised a total of 1,834 patients. Five studies (9,13-16) were clinical trials: four of which were randomized and one non-randomized. Two (17,18) were cohort studies: one was a single-center cohort (comparative analysis), and the other was an open-label, single-arm, non-randomized study. Study durations ranged from 2 to 252 weeks. All studies reported comparable mean ages, ranging from 34.2 to 48.2 years, and Expanded Disability Status Scale scores ranging from 0 to 6.5. Sample sizes varied from 19 to 745 participants. Regarding gender distribution, 586 patients were male and 1,248 were female, representing 68% female participants. An analysis of 4,495 MS patients found that 3,030 were female (67.4%), confirming that our study population aligns with the gender-based prevalence of MS (19) (Tables 1 and 2).

Four studies (13-15,18) evaluated the safety of rapid ocrelizumab infusion and its effect on IRRs. One study assessed IRRs and

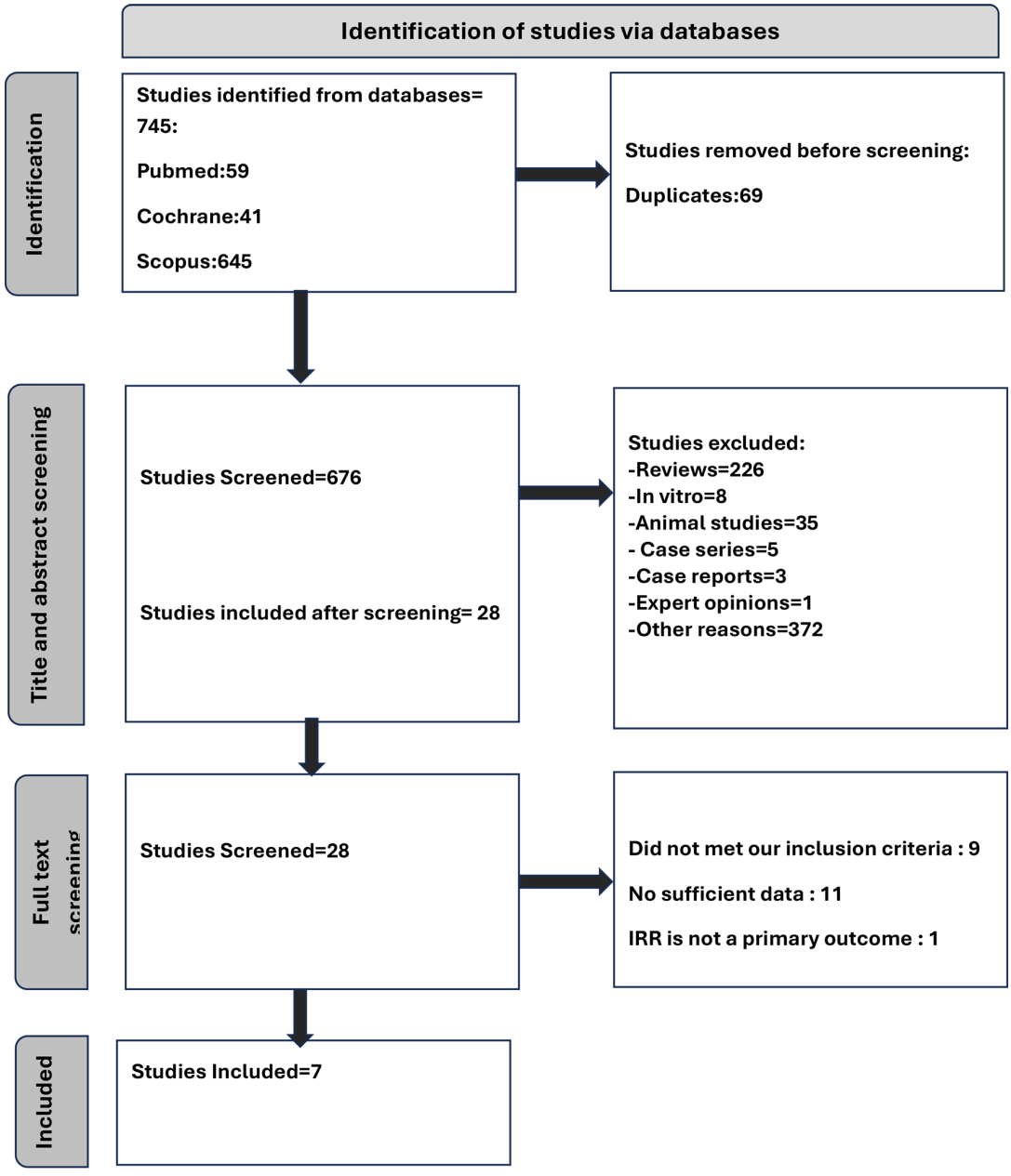


Figure 1. PRISMA flow diagram of study selection. Flow diagram summarizing the identification, screening, eligibility, and inclusion process of studies in the systematic review

PRISMA: Preferred reporting items for systematic reviews and meta-analyses, IRR: Infusion-related reaction

Table 1. Demographic and clinical characteristics of included studies. Overview of patient demographics and clinical characteristics across the included studies, including treatment regimens, age, gender distribution, and MS subtypes

Study	Treatment regime (n)	Gender male/female	Age, year (mean ± SD)	Type of phenotype (n)	EDSS score (mean ± SD)
1. Zanetta et al. (18)	**OCR-RI, OCR-SI**	**154/215**	**39.9 (10.5)**	**PPMS =75 RRMS =274 SPMS =20**	**3 (3.33)**
2. Abbasi Kasbi et al. (16)	**Ocrelizumab**	**82/250**	**38 (9.9)**	**PPMS RRMS Total: 332**	**3 (2.22)**
3. Vollmer et al. (13)	**OCR-SI**	**Cohort 1: 36/59 Cohort 2: 12/34 Total: 48/93**	**Cohort 1: 41.7 (8.8) Cohort 2: 41.1 (8.7) Total: 41.5(8.8)**	**PPMS =12 RMS =129**	**2.64 (1.67)**
4. Smoot et al. (9)	**Ocrelizumab pretreated with cetirizine, ocrelizumab pretreated with diphenhydramine**	**Cetirizine: 1/6 Diphenhydramine: 3/9 Total: 4/15**	**Cetirizine: 48.2 (4) Diphenhydramine: 46.3 (3.1) Total: 47.5 (3.6)**	**PPMS =1 RRMS =16 SPMS =2**	**Not mentioned**
5. Hartung et al. (14)	**OCR-RI, OCR-SI**	**271/474**	**34.2(8.8)**	**PPMS RRMS**	**Not mentioned**
6. Bermel et al. (15) NCT0237856	OCR-SI	**Not mentioned**	**36.7 (8.1)**	**PPMS RMS**	**Not mentioned**
7. Barrera et al. (17) NCT04650321	Home-based ocrelizumab	27/72	42.3 (7.7)	PPMS =13 RMS =178	2 (1.11)

MS: Multiple sclerosis, SD: Standard deviation, EDSS: Expanded Disability Status Scale, OCR-RI: Ocrelizumab rapid infusion, OCR-SI: Ocrelizumab standard infusion, PPMS: Primary progressive multiple sclerosis, RRMS: Relapsing remitting multiple sclerosis, SPMS : Secondary progressive multiple sclerosis, RMS : Relapsing multiple sclerosis

Table 2. Summary of study characteristics. Overview of study designs, participant numbers, treatment arms, and study durations for the seven studies included in the review

Study	Type of ocrelizumab	Treatment group (number of participants)	Total number of participants (n)	Study period (weeks)
1. Zanetta et al. (18)	**OCR-RI OCR-SI**	**OCR-RI: 283 OCR-SI: 86**	**369**	**291**
2. Abbasi Kasbi et al. (16)	**Two 300 mg ocrelizumab doses/ One 600 mg ocrelizumab dose**	**Two 300 mg ocrelizumab doses: 150 One 600 mg ocrelizumab dose: 182**	**332**	**Not mentioned**
3. Vollmer et al. (13)	**OCR-SI**	**Cohort 1: 95 Cohort 2: 46**	**141**	**48**
4. Smoot et al. (9)	**Ocrelizumab pretreated with cetirizine/ Ocrelizumab pretreated with diphenhydramine**	**Ocrelizumab pretreated with cetirizine: 10/ Ocrelizumab pretreated with diphenhydramine: 9**	**19**	**24**
5. Hartung et al. (14)	**OCR-RI OCR-SI**	**OCR-RI: 373 OCR-SI: 372**	**745**	**120**
6. Bermel et al. (15) NCT0237856	**OCR-SI**	**OCR-SI: 129**	**129**	**96**
7. Barrera et al. (17) NCT04650321	**Home-based ocrelizumab**	**Home-based ocrelizumab: 99**	**99**	**2**

OCR-RI: Ocrelizumab rapid infusion, OCR-SI: Ocrelizumab standard infusion

patient satisfaction using patient-reported outcomes during at-home ocrelizumab administration (17). Another study examined the effects of administering 600 mg of ocrelizumab and compared it with the current standard protocol in terms of IRR frequency during the first infusion (16). The final study focused on optimizing treatment safety by investigating diphenhydramine as a premedication and its impact on reaction severity and patient satisfaction (9). All studies included both types of MS, except for two that enrolled only patients with relapsing-remitting MS (14,17).

Risk of Bias

Due to the heterogeneity of study designs, the risk of bias for included studies was assessed using two tools: the NOS (20) for four non-randomized studies (13,15,17,18), and the ROB (21) for three randomized studies (9,14,16). All studies evaluated with NOS scored between 7-8 (Figure 2), indicating a low ROB. Using ROB, one study was assessed (9) as having a high risk of bias due to concerns about outcome measurement and selective reporting. Another study was rated as having some concerns regarding the randomization process and a high ROB for outcome measurement (16). The final study was judged to have a low ROB score (Figure 3) (14).

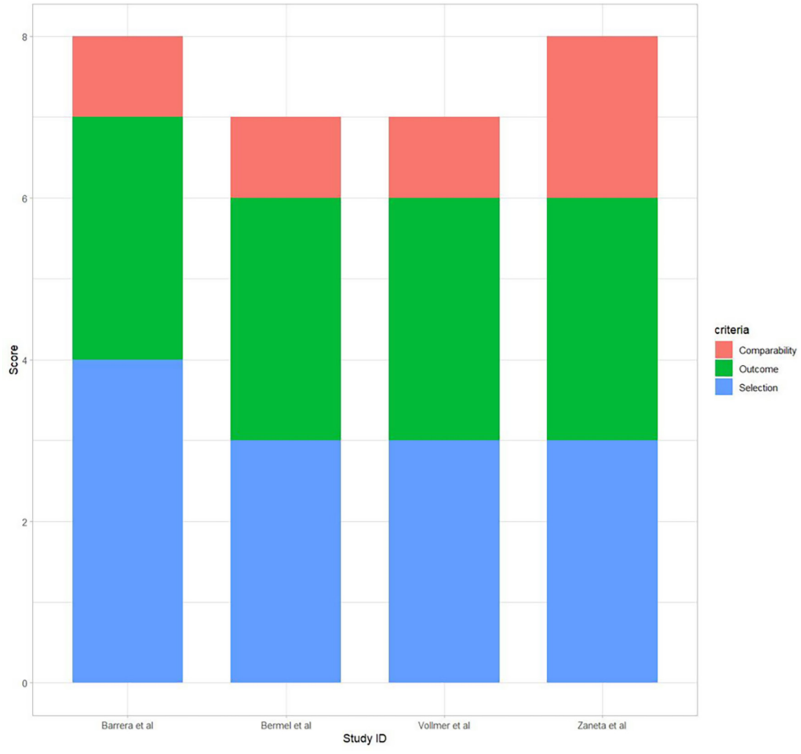


Figure 2. Newcastle-Ottawa Scale (NOS) assessment for non-randomized studies. Quality assessment scores of the included non-randomized studies based on the NOS criteria

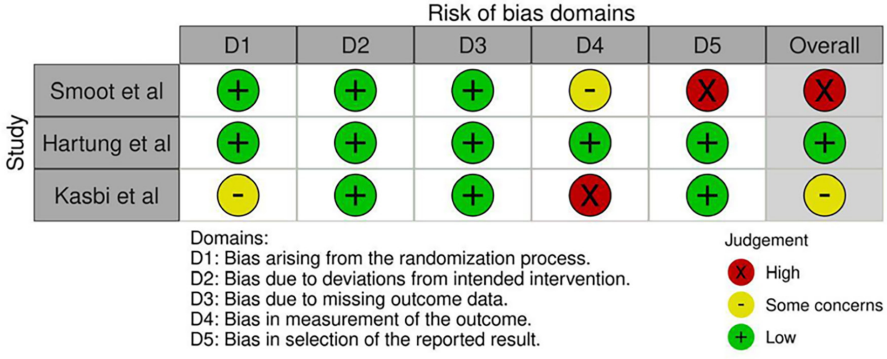


Figure 3. Risk of bias by domain for randomized studies. Domain-specific risk of bias assessments for randomized trials, evaluated using the ROB2 tool and categorized by level of concern

ROB2: Cochrane's Risk of Bias Tool

Outcomes

Conventional vs. Shorter Infusion

One sub-study, comparing conventional and shorter infusion groups in patients receiving six doses of ocrelizumab 600 mg, found a similar number of patients experiencing IRRs after the first dose (101/373 vs. 107/372 patients, respectively) (14). Across all six doses in the sub-study, the proportion of patients experiencing IRRs was similar between groups (41.6% vs. 46.2%). Most IRRs were mild or moderate (Grade 1-2), occurring in 99.4% of patients in the conventional infusion group and 97.7% in the shorter infusion group. Only five reactions were severe (Grade 3): one in the conventional infusion group and four in the shorter infusion group.

No Grade 3 or higher IRRs were reported after the second dose, and no patients discontinued treatment due to IRRs. The most common IRRs during the first infusion were throat irritation (18.8% vs. 29.9%) and dysphagia (6.9% vs. 7.5%) in the conventional and shorter infusion groups, respectively. Within 24 hours post-infusion, headache (25.7% vs. 17.8%) and fatigue (22.8% vs. 18.7%) were the most frequently reported adverse events.

In another sub-study (15), patients receiving a single dose of ocrelizumab (600 mg) via shorter infusion experienced no severe or life-threatening IRRs. Grade 1-2 IRRs were reported in 12.4% of patients, consistent with findings from the main study, particularly at dose 3. Infusion rate reduction or treatment interruption was required for nine patients, as observed at dose 3, and all IRRs resolved without further medical intervention.

In study, patients receiving a single dose of home-based ocrelizumab (600 mg) infusion over 2 h were assessed, with 25.3% (95% confidence interval: 16.7-33.8%) experiencing an IRR of any grade (17). Of these, 18.2% were Grade 1 and 7.1% were Grade 2, with no IRRs ≥ Grade 3 reported.

Another study evaluated patients receiving varying numbers of ocrelizumab 600 mg doses with an infusion time reduced from 3.5 to 2 h (18). Overall, 25 patients (8.8%) in the rapid infusion group and 13 patients (15.1%) in the conventional group experienced IRRs. The frequency of IRRs did not differ significantly between the two groups. Most IRRs were mild (Grade 1, 81.6%) or moderate (Grade 2, 18.4%).

Full First Dose (600 mg) vs. Split Dose (300 mg)

One study compared IRRs of the first dose 600 mg vs. two 300 mg showed that most of the IRRs were mild in both (two 300 mg doses and one 600 mg dose) groups (16).

Shorter Full Dose vs. Shorter Split Dose

In sub-study, patients were divided into two cohorts: cohort 1 (n=95) received 600 mg of ocrelizumab over 2 hours, while cohort 2 (n=46) received a split dose of 300 mg over 1.5 hours (13). The results were as follows:

In cohort 1, 35 patients experienced IRRs during the first dose and 30 during the second dose, whereas only 7 patients in cohort 2 experienced IRRs. No observed Grade 3 or 4 IRRs were reported in either cohort.

In cohort 1, 14% of patients experienced IRRs that required interruption or slowing of the infusion, while no such interruptions occurred in cohort 2.

Premedication

IRRs were compared between groups that received different premedications in the study (9): one group received oral cetirizine (10 mg), and the other received diphenhydramine (25 mg). Following the first infusion of the initial dose, each group reported six IRRs (corresponding to 60% of the cetirizine group and 67% of the diphenhydramine group). At the end of the study (after two doses), 80% of patients in the cetirizine group and 89% in the diphenhydramine group experienced at least one IRR. The incidence of IRRs was similar between groups, with no increase in severity and no Grade 3 events reported (Table 3).

Patient Satisfaction

After blinding in the study, most patients in the conventional group chose to switch to short-infusion (79.7% (n=279/350), whereas most patients in the short-infusion group opted to continue with short-infusions (94.6%; n=331/350) (14). Among patients who preferred conventional infusions (n=90), 57.7% (n=51/90) had experienced IRRs, compared to 42.0% (n=256/610) of those who preferred shorter infusions.

A significant improvement in the overall infusion experience was reported by patients receiving at-home infusions (17). They described feeling more comfortable, safer, and respected. They also noted that nurses provided clearer explanations compared with the hospitals.

Discussion

This systematic review provides the most recent data about the procedural interventions to reduce IRRs in patients receiving ocrelizumab for MS. Management of IRRs is rarely discussed in general, and specifically for ocrelizumab. In patients with MS, experiencing IRRs is critical as it may lead to treatment delays or discontinuation; therefore, preventing these reactions is essential for successful treatment.

"Do no harm" is a fundamental principle in medical practice. Despite this, fewer than 10% of systematically published reviews each year assessed harm associated with medical interventions as their primary objective (22).

Short vs. Conventional

Shorter infusions did not significantly increase the incidence or severity of IRRs in any of the studies (2-6). However, in one study, only 0.53% of patients could not tolerate the short infusion and

Table 3. Summary of interventions and IRR outcomes. Comparative overview of intervention strategies, infusion-related reaction (IRR) rates, and key findings across the included studies evaluating ocrelizumab administration in patients with multiple sclerosis

Study	Design	Intervention	Comparator	IRR rate	IRR severity	Key finding
Zanetta et al. (18)	Cohort	600 mg over 2 h (Shortened)	600 mg over 3.5 h (Conventional)	8.8% vs. 15.1%	Mild-moderate	Shortened infusion showed fewer IRRs
Abbasi Kasbi et al. (16)	RCT	One 600 mg dose	Two 300 mg doses	Similar	Mostly mild	Both dosing strategies are safe
Vollmer et al. (13)	Open-label phase IIIb	600 mg (2 h) or 300 mg (1.5 h)	None	Cohort 2 had fewer IRRs	No Grade ≥3	Shorter infusions well-tolerated
Smoot et al. (9)	RCT	Cetirizine premedication	Diphenhydramine premedication	80% vs. 89%	No Grade 3	Both premedications are similarly effective
Hartung et al. (14)	RCT	600 mg over 2 h	600 mg over 3.5 h	41.6% vs. 46.2%	Mild-moderate	No significant difference in IRRs
Bermel et al. (15)	Single-arm phase IIIb	600 mg over 2 h	None	12.4%	Grade 1-2 only	No severe IRRs, consistent with prior data
Barrera et al. (17)	Open-label phase IIIb	600 mg at home (2 h)	Historical control	25.3%	Grade 1-2 only	At-home infusion is safe and well-tolerated

IRR: Infusion-related reaction, RCT: Randomized controlled trial

continued ocrelizumab treatment, representing a very small percentage (14).

Short infusion is a feasible and patient-preferred option, with 80% of patients opting to switch to shorter infusions (14). Reducing infusion time also helps optimize clinic scheduling and reduce staff workload. Additionally, at-home short infusions demonstrated positive outcomes and increased patient comfort, providing an alternative for stable MS patients (17).

This is primarily because peak ocrelizumab concentrations were similar between shorter and conventional infusions, suggesting no increase in drug exposure-related toxicity (14). Additionally, premeditation reduced cytokine release and hypersensitivity reactions.

The incidence of IRRs varies widely across studies due to multiple factors. Higher IRR rates in open-label studies suggest ascertainment bias, where clinicians and patients may over-report mild symptoms due to heightened awareness (13). Some studies included treatment-naïve patients (9), who typically experience higher IRR rates compared with pre-exposed patients (18). Additionally, some studies captured IRRs only during infusion (13), while others included events occurring within 24 hours post-infusion (14). Non-standardized IRR definitions across all studies further contribute to variability in reported rates.

Premedication

Methylprednisolone and antihistamines were administered universally (9). Cetirizine was non-inferiority to diphenhydramine in preventing IRRs and was associated with fewer sedative side effects. Some studies allowed on-demand dose adjustments, which may also contribute to variability in reported IRR severity (9).

The First Dose

As per the standard protocol, the first dose is administered in two infusions to reduce IRR rates. However, a single 600 mg dose may be considered, as there is no difference in 24-hour post-infusion or life-threatening reactions. Slightly higher IRR rates can be managed by increasing premedication or reducing the infusion rate (16).

Study Limitations

The included studies were highly heterogeneous, which influenced the reported incidence of IRRs and prevented a meta-analysis. Additionally, long-term safety data were lacking, limiting the generalizability of our findings for long-term management and hindering the detection of complications that may develop over time, such as malignancies and infections. The primary progressive MS cohorts were small compared to the relapsing-remitting MS cohorts. Additionally, only a few studies reported details on premedication administered before infusion.

Future Directions

Further studies are needed to investigate different strategies for reducing IRRs and to establish a safer infusion protocol for ocrelizumab. In particular, additional trials on premedication strategies would significantly contribute to the literature. Long-

term observational studies are also warranted to provide a deeper understanding of ocrelizumab adverse events. Finally, standardizing the definition of IRRs would allow for more consistent and comparable results across studies.

Conclusion

Short and at-home infusions demonstrated safety comparable to conventional infusions, while offering a more comfortable, patient-preferred option. The single 600 mg first infusion was associated with slightly higher IRR rates, which can be easily managed. Both cetirizine and diphenhydramine were effective as premedications, showing similar reductions in IRR incidence.

Footnotes

Authorship Contributions

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

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DOI: 10.4274/jmsr.galenos.2025.2025-9-1

J Mult Scler Res 2026;6:9-14

REVIEW

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Visual Impairment in Multiple Sclerosis: A Comprehensive Review of Clinical Impact and Pathogenesis

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Abstract

Multiple sclerosis (MS), a chronic immune-mediated disease of the central nervous system with frequent visual involvement and frequently causes visual dysfunction through demyelination, neurodegeneration, and vascular impairment. Among the earliest and most disabling manifestations are optic neuritis, ocular motor dysfunction, and reduced contrast sensitivity, and for optometrists early recognition and consistent monitoring of these deficits are essential for timely referral, rehabilitation, and quality-of-life support. This review discusses the implications for optometric practice by synthesizing recent evidence on visual pathway alterations in MS. A narrative review of literature published between 2018 and 2025 was conducted using PubMed, Scopus, and Web of Science, and keywords included "multiple sclerosis,""optic neuritis,""visual function,""optical coherence tomography," and "optometry." Articles focusing on visual dysfunction, assessment tools, and management strategies relevant to optometry were prioritized. Emerging evidence highlights the utility of optical coherence tomography (OCT) and visual evoked potentials for detecting subclinical optic nerve damage, while functional deficits such as impaired contrast sensitivity, reduced stereoacuity, and visual field loss significantly impact daily activities. Through comprehensive eye examinations, monitoring of visual performance, and identification of red flags requiring neurological referral, optometrists play a central role in early detection. Recent studies also emphasize low-vision rehabilitation, prisms, and tailored visual aids as effective strategies to improve quality of life in affected patients. Visual dysfunction is a common and often under-recognized component of MS, and optometrists are well positioned to provide functional support, detect early signs, and collaborate in multidisciplinary management. Integrating advanced imaging, functional testing, and low-vision strategies into routine optometric care may improve both visual outcomes and patient quality of life. The present review summarizes pathophysiological mechanisms, clinical manifestations, diagnostic tools, and rehabilitation approaches, while new advances in OCT, OCT-angiography, and artificial intelligence-based analytics are discussed.

Keywords: Multiple sclerosis, optic neuritis, visual function, optical coherence tomography, optometry, low vision

Introduction

Multiple sclerosis (MS), a chronic immunemediated demyelinating disorder of the central nervous system that primarily affects young adults with peak onset between 20 and 40 years, is characterized by multifocal lesions, inflammation, demyelination, and neurodegeneration in brain, spinal cord, and optic nerves, and often leads to progressive neurological dysfunction (1). As of 2023, MS affected ~2.9 million individuals globally, with females more commonly affected than males (2), and visual disturbance is often an early sign reflecting the disease's predilection for the optic nerves and visual pathways (3).

Visual impairment in MS encompasses a broad spectrum, ranging from acute optic neuritis (ON) to chronic, subclinical dysfunction. ON presents as the initial symptom in about one fifth of MS cases, and up to half of patients experience at least one episode during the disease course (4,5). Persistent visual deficits, including reduced contrast sensitivity, color desaturation, visual field defects, diplopia, or ocular motility disorders, are also common often impairing daily functioning even when high contrast visual acuity (HCVA) remains relatively preserved (6,7).

Beyond acute inflammation, MS produces chronic retinal neurodegeneration even in eyes without clinical ON. Optical

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Received: 19.09.2025 **Accepted:** 20.10.2025 **Epub:** 04.11.2025 **Publication Date:** 27.01.2026

Cite this article as: Kumari R. Visual impairment in multiple sclerosis: a comprehensive review of clinical impact and pathogenesis. J Mult Scler Res. 2026;6:9-14

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coherence tomography (OCT) demonstrates thinning of the retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GCIPL), correlating with both visual dysfunction and global central nervous system changes (8,9). These findings reinforce the value of visual system biomarkers for assessing disease activity and monitoring progression.

This review aims to integrate recent findings (2018-2025) on visual impairment in MS and to outline the clinical implications for both optometric and neurological practice.

Methodology

Search Strategy and Selection Criteria

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar for publications between January 2018 and September 2025, using the keywords "multiple sclerosis," "optic neuritis," "visual dysfunction," "low contrast acuity," "retinal nerve fiber layer," "OCT," "OCT-angiography (OCT-A)," "visual rehabilitation," and "artificial intelligence (AI) in MS," with Boolean operators ("and," "or") applied to combine terms. Studies were included if they comprised (a) peer-reviewed original research articles, systematic reviews, or meta-analyses, (b) English-language publications, and (c) work focusing on visual or ocular manifestations of MS. Exclusion criteria consisted of (a) case reports, conference abstracts, or commentaries lacking primary data; (b) non-English articles, and (c) studies unrelated to visual outcomes. Reference lists of included papers were also screened to identify additional relevant studies. From a total of 136 publications, 92 met the inclusion criteria and were used to inform this review.

Epidemiology and Clinical Context

Visual disturbances are a hallmark of MS and commonly constitute one of its earliest clinical manifestations. ON represents the most frequent acute visual event, functioning as presenting symptom in ~20% of patients and occurring in nearly half during the disease course (4,10), while subclinical optic nerve damage is even more widespread (11,12).

The global burden of MSrelated visual impairment is substantial: more than 60% of patients report visual symptoms—including acute ON, persistent low contrast loss, blurred vision, or diplopia—at some stage (13). These impairments occur across both relapsing and progressive forms, including secondary progressive MS and primary progressive MS (14).

Demographically, onset usually falls between ages 20 and 40 with a marked female predominance (~3:1), and visual symptoms follow similar distributions (2,15). When ON presents after age 50, alternative etiologies such as ischemic or inflammatory non-MS causes are more likely (16).

ON and Risk of Multiple Sclerosis

Prognostic Significance

The ON treatment trial demonstrated that about 50% of individuals with isolated ON develop clinically definite MS over ~15 years (5,17), and risk rises markedly when white matter lesions are present on brain magnetic resonance imaging (MRI) at presentation. Patients with at least one demyelinating lesion have ~72% chance of conversion (5,18). Under the 2017 McDonald criteria, ON is incorporated as diagnostic evidence when MRI or cerebrospinal fluid findings are supportive, enabling earlier diagnosis and earlier initiation of disease-modifying therapies (DMTs) (19).

Clinical Course and Recovery

Recovery after ON is variable: highdose IV corticosteroids accelerate restoration of vision, particularly contrast sensitivity and visual fields, but they do not improve long term HCVA outcomes (5,17,20). Oral prednisone alone is contraindicated because of elevated risk of recurrence (17). Even after apparent recovery occurs, persistent deficits in contrast sensitivity, color perception, and visual fields are common, reflecting incomplete remyelination or axonal injury (21).

Neuroimaging Correlates

MRI is central in evaluating ON, with acute ON typically showing optic nerve T2 hyperintensity and frequently gadolinium enhancement during active inflammation (17). Brain white matter lesions not only support the diagnosis but predict both conversion and future disability. Advanced techniques such as diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) detect microstructural changes in optic nerve and retrochiasmal pathways even in eyes without clinical ON (22).

Chronic Visual Dysfunction Beyond ON

Persistent visual deficits are experienced by many MS patients even without a history of ON, and up to ~40% exhibit low contrast letter acuity (LCLA) deficits that are missed by highcontrast tests (7,20). These chronic impairments include reduced contrast sensitivity, color desaturation, visual field irregularities, motion perception anomalies, and reading fatigue (6,21).

Structural retinal changes account for much of this dysfunction: OCT demonstrates RNFL and GCIPL thinning in both ON affected and unaffected eyes, and these correlate with quality-of-life measures such as the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ25) (22). RNFL thinning in eyes without ON is also associated with greater disability (as per Expanded Disability Status Scale) and brain atrophy (8,9,23,24), reinforcing the value of routine visual function monitoring as a component of MS assessment.

Pathophysiology of Visual Dysfunction in MS

ON and Demyelination

ON involves perivascular inflammation with disruption of the blood-brain barrier, immune cell infiltration, and demyelination of optic nerve axons. Clinically, patients typically present with subacute unilateral vision loss accompanied by pain with eye movement, color desaturation, reduced contrast sensitivity, and a relative afferent pupillary defect (25,26). In demyelination, visual evoked potentials (VEPs) (pattern and multifocal) demonstrate prolonged latency together with reduced amplitude (27-29).

Axonal Injury and Retinal Neurodegeneration

Significant axonal loss begins early, and ON may result in loss of up to ~40% of optic nerve axons within weeks (30,31). Even when eyes appear clinically unaffected, OCT reveals progressive thinning of the RNFL and GCIPL, correlating with visual deficits, brain atrophy, and disability scores (8,9,12,25,32).

Subclinical Visual Pathway Damage

Eyes without clinical ON frequently demonstrate deficits in lowcontrast acuity, motion perception, and binocular vision (20,33,34), and multifocal VEPs show delayed responses or reduced amplitudes in these unaffected eyes (27,35). Lesions in optic radiations or visual cortex contribute to visual field defects, slowed processing, and interactions with cognitive impairment (36).

Mechanisms of Retinal Injury

Retinal damage can occur independently of optic nerve inflammation: histopathology demonstrates microglial activation, retinal ganglion cell loss, and retinal atrophy even without clinical ON (8,37). A subset of patients develops microcystic macular edema (MME), which is associated with worse visual function and inflammatory disease activity. Proposed mechanisms include Muller cell dysfunction, disruptions of bloodretina barrier and retrograde degeneration (38,39).

Inflammation and Neurodegeneration: A Dual Framework

Inflammation and demyelination account for acute events such as ON, whereas chronic retinal thinning and visual pathway damage reflect ongoing neurodegeneration. This dual framework has therapeutic implications: immunomodulatory therapies reduce relapses and ON frequency but do not prevent longterm axonal loss or retinal thinning (33,40).

Clinical Features and Diagnostic Evaluation

Clinical Features of ON

• ON typically presents with subacute unilateral vision loss evolving over hours to days and is frequently accompanied by pain on eye movement (41).

• Color desaturation, particularly of red hues, and contrast sensitivity deficits are common (42,43).

• Visual field defects are often central or centrocecal. Optic disc swelling is seen in ~35% of cases, whereas the optic disc remain normal in retrobulbar ON (44,45).

Other Ocular Manifestations

• Diplopia from internuclear ophthalmoplegia (medial longitudinal fasciculus involvement), nystagmus or gazeevoked oscillations to brainstem or cerebellar lesions (46,47).

• Homonymous visual field defects arise from optic radiation or occipital lesions.

• More subtle deficits: motion perception, reading fatigue, or binocular dysfunction (34).

Diagnostic Tools

A wide range of diagnostic tools is available to assess visual function in MS, each offering distinct clinical insights. These methods allow detection of both structural and functional abnormalities, from subtle visual deficits to significant neurodegenerative change, and Table 1 presents a comparative overview of the most commonly used techniques, highlighting their utility in diagnosis, monitoring, and prognosis.

- **High Contrast Visual Acuity (HCVA)**

Measures central vision clarity and remains the standard clinical test, although it is less sensitive to subtle visual deficits in MS patients (7,20).

- **Low Contrast Letter Acuity (LCLA)**

Measures contrast sensitivity deficits and detects impairments even when HCVA is preserved; LCLA correlates with RNFL and GCIPL thinning, and is a sensitive functional measure in MS (22,33,48).

- **Color Vision Testing**

Assesses color desaturation, particularly relevant during or after episodes of ON (44).

- **Visual Field Testing**

Detects scotomas and central or peripheral visual field defects, providing lesion localization within the visual pathways (45,36).

- **Optical Coherence Tomography (OCT)**

Measures structural parameters including RNFL and GCIPL thickness and detects MME; OCT is a sensitive biomarker for both acute inflammatory and chronic neurodegenerative damage in MS (8,12,39,40).

- **VEPs and multifocal VEPs**

Evaluate latency and amplitude of visual signal transmission and reveal demyelination and conduction delays even in subclinical cases (27,35,49,50).

Table 1. Comparative summary of major diagnostic tools

Diagnostic tool	Primary parameter assessed	Clinical advantages	Limitations	Relevance in MS-related visual dysfunction
OCT	RNFL and ganglion cell complex thickness	Non-invasive, quantitative, sensitive to axonal loss	Limited correlation with cortical demyelination	Standard tool for detecting retinal neurodegeneration
OCT-A	Retinal microvasculature and perfusion	Visualizes microvascular impairment; complements structural OCT	Motion artifacts; limited field of view	Emerging biomarker for neurovascular coupling and disease activity
VEP	Electrical response of visual cortex to stimuli	Detects subclinical demyelination, functional measure	Influenced by fatigue, non-specific to lesion site	Essential for early detection and monitoring of optic pathway damage
MRI	Demyelinating plaques and optic pathway lesions	Whole-brain visualization, correlates with disease burden	Expensive, less sensitive to subtle retinal changes	Gold standard for diagnosing and staging MS
AI-based image analysis	Multimodal pattern recognition (OCT, MRI)	Automated detection, predictive analytics	Requires validation, potential for algorithmic bias	Promising adjunct for precision diagnosis and prognosis

OCT: Optical coherence tomography, OCT-A: OCT-angiography, VEP: Visual evoked potentials, MRI: Magnetic resonance imaging, AI: Artificial intelligence, RNFL: Retinal nerve fiber layer, MS: Multiple sclerosis

- **Magnetic Resonance Imaging (MRI)**

Detects lesions, active inflammation, and optic radiation involvement; advanced techniques such as DTI and MTI provide microstructural information. MRI remains the gold standard for diagnosis and prognosis in MS (17,22,36).

- **Patient Reported Outcomes (e.g., NEI VFQ-25)**

Capture quality of life and real-world visual impact, providing an essential complement to objective clinical testing (22).

Treatment of Visual Dysfunction in MS

Acute Management of ON

High dose intravenous corticosteroids (e.g., methylprednisolone 1 g/day for 3-5 days with taper) shorten time to visual recovery, particularly contrast, fields, and color perception, although they do not improve long term HCVA (5,17,20). For severe or steroid non-responsive cases, plasma exchange is reserved.

Disease-Modifying Therapies (DMTs)

DMTs (interferon beta, glatiramer acetate, fingolimod, ocrelizumab, cladribine) reduce ON recurrence and suppress MRI inflammatory activity, yet their effect on slowing retinal thinning and neurodegeneration remains modest (46,47,51).

Neuroprotective and Remyelinating Strategies

Strategies under investigation include:

- Phenytoin, which has been shown to reduce RNFL loss in acute ON cohorts (44,45).
- Clemastine fumarate, anti-LINGO1 antibodies, neurotrophic and antioxidant therapies all of which remain in study phases (45).

Symptomatic and Supportive Therapies

- Lowvision aids, magnifiers, electronic reading devices to assist reading and mobility.
- Prism therapy for diplopia and oculomotor exercises with vision therapy for improving gaze stability.
- Vision rehabilitation and occupational therapy further support and maximize independence (46).

Digital Monitoring and AI Integration

Smartphonebased tests for visual acuity and contrast sensitivity correlate with OCT metrics and may enable remote follow-up (46). AI/machine learning models that combine OCT, VEP, MRI, and biomarkers (serum neurofilament light chain) show growing promise for prediction of disease progression and for personalized treatment planning (33).

Rehabilitation of Visual Dysfunction in MS

Visual rehabilitation plays a central role in improving functional outcomes and quality of life in MS-related visual impairment. Conventional strategies such as contrast sensitivity and reading training are now complemented by contrast enhancement filters, digital magnification, and adaptive lighting systems to optimize residual vision, while occupational therapy emphasizes mobility and orientation training for safe navigation and spatial awareness. Adaptive software solutions, including screen-reading programs, speech-to-text converters, and AI-assisted visual scene interpreters, significantly enhance patient independence. Multidisciplinary rehabilitation models integrating neurologists, optometrists, and low-vision specialists are increasingly recommended to deliver holistic, goal-oriented care.

Illustrative Case Example: A 34-year-old woman with relapsing-remitting MS reported fluctuating vision and difficulty with contrast discrimination. OCT revealed thinning of the RNFL, while OCT-A demonstrated reduced vessel density in the superficial plexus. A customized rehabilitation plan involving contrast filters, adaptive magnification, and mobility training resulting in a 25% improvement in LCLA and increased

subjective quality-of-life scores on the NEI VFQ-25 scale after 12 weeks, illustrating the functional impact of integrating structural assessment with rehabilitative care (52).

Emerging Research and Future Directions

Growing evidence supports OCT-A as a sensitive biomarker in MS, detecting reduced retinal vessel density—particularly in macular and peripapillary regions—which may precede structural damage and help distinguish ON-affected eyes.

Parallel research has accelerated development of AI and machine learning models capable of predicting MS progression using OCT, VEP, MRI, and clinical data, with increasing emphasis on model explainability for clinical adoption (12).

An expanding literature also highlights sex differences and lifestyle influences: although MS is more common in women, men may experience greater visual decline, and modifiable factors such as smoking, vitamin D, diet, and physical activity are under investigation for their effects disease progression and visual outcomes.

Explainable Artificial Intelligence in MS-Related Vision Research

Artificial intelligence has substantial potential for early detection and monitoring of optic nerve and retinal changes in MS, but translation to clinical use depends on transparency and interpretability. Explainable AI frameworks aim to demonstrate which image features or biomarkers drive predictions, increasing diagnostic confidence, reducing bias, and supporting ethical integration of AI systems into multidisciplinary MS care. Ongoing research should prioritize clinician-interpretable AI models for OCT and MRI analysis to ensure real-world applicability.

Conclusion

Visual dysfunction in MS is multifactorial, involving acute inflammatory injury (ON), chronic neurodegeneration, and subclinical visual pathway damage. Diagnostic tools—OCT, VEP, MRI—permit early detection and longitudinal monitoring. Current DMTs lessen ON recurrence and reduces relapses but provide limited protection against long term axonal loss and retinal thinning. Emerging strategies, including neuroprotective and remyelinating therapies, AI-based predictive tools, OCTA vascular metrics, and structured rehabilitation, are increasingly important for preserving vision and quality of life. Personalized multimodal monitoring together with early intervention holds the greatest promise for improving outcomes.

Footnotes

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

Acknowledgement

We thank all co-authors and institutional collaborators for their contributions. The authors declare that AI-based language assistance (ChatGPT, OpenAI) was utilized solely for grammar refinement, formatting, and reference organization, and affirm that the intellectual content, analysis, and conclusions remain the authors' original work.

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DOI: 10.4274/jmsr.galenos.2025.2025-11-1

J Mult Scler Res 2026;6:15-21

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REVIEW

Impact of Acquired Brain Injury on Vision: Patterns, Assessment, and Rehabilitation

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Abstract

Acquired brain injury (ABI), including stroke and traumatic brain injury, is frequently associated with visual system impairments that range from basic sensory deficits to complex perceptual dysfunctions, substantially affecting patient independence, safety, and quality-of-life. This narrative review synthesizes current evidence on the patterns, underlying mechanisms, assessment strategies, and management of vision impairments following ABI, while also highlighting gaps in clinical care and research. A comprehensive literature search was conducted using PubMed, Scopus, and Google Scholar to identify studies addressing post-ABI visual deficits, their pathophysiology, rehabilitation approaches, and outcomes in both adult and pediatric populations. Visual impairments after ABI include visual field defects (e.g., homonymous hemianopia), oculomotor dysfunction, cortical visual impairment, and higher-order visual perceptual disorders such as visual neglect and visual agnosia. Accurate assessment requires interdisciplinary collaboration and the use of tools such as perimetry, visual evoked potentials, neuroimaging, and neurocognitive testing. Rehabilitation strategies encompass compensatory training, prism adaptation, vision therapy, and assistive technologies; however, the strength of evidence supporting these interventions remains variable, and standardized care pathways are lacking. Early screening, coordinated interdisciplinary management, and individualized rehabilitation programs are essential to optimize visual recovery. Further research is needed to establish robust evidence-based interventions and to integrate visual assessment and rehabilitation into comprehensive neurorehabilitation services.

Keywords: Acquired brain injury, visual impairment, cortical visual impairment, visual field loss, traumatic brain injury, stroke rehabilitation, neuro-ophthalmology

Introduction

Acquired brain injury (ABI), encompassing traumatic brain injury (TBI) as well as non-traumatic etiologies such as stroke, hypoxia, infection, and tumors, represents a leading cause of long-term neurological disability worldwide. In addition to cognitive and motor impairments, visual dysfunction is among the most common yet underrecognized sequelae of ABI. The visual system occupies nearly one-third of the human cerebral cortex, rendering it particularly susceptible to both focal and diffuse neural damage. As a result, even localized lesions may disrupt multiple visual pathways, producing a broad spectrum of deficits that substantially affect independence, mobility, and quality-of-life (1).

Epidemiological studies suggest that approximately 50-80% of individuals with ABI experience some degree of visual impairment, ranging from basic sensory deficits, such as visual field loss, to higher-order perceptual disturbances, including visual neglect, visual agnosia, and cortical visual impairment (CVI) (2). These abnormalities frequently coexist with oculomotor dysfunctions—such as strabismus, convergence insufficiency, and saccadic dysmetria—which further compromise binocular vision and reading efficiency. Despite their high prevalence, visual impairments are often overlooked during acute management and rehabilitation, where attention is typically directed toward more apparent motor or language deficits. This underrecognition may delay appropriate intervention and adversely affect functional recovery (3).

Growing recognition within neuro-ophthalmology and vision rehabilitation has underscored the importance of

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Received: 04.11.2025 **Accepted:** 13.12.2025 **Publication Date:** 27.01.2026

Cite this article as: Kumari R. Impact of acquired brain injury on vision: patterns, assessment, and rehabilitation. J Mult Scler Res. 2026;6:15-21

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integrating systematic visual assessment into multidisciplinary ABI care. Early identification through standardized screening tools, including perimetry, ocular motility assessment, and evaluation of visual perceptual function, allows for timely and targeted interventions that may meaningfully improve patient outcomes. Rehabilitation approaches—such as compensatory scanning training, prism adaptation, vision therapy, and assistive technologies—have demonstrated increasing potential benefit; however, their implementation remains inconsistent across clinical settings (4).

Given the heterogeneity of ABI and the complexity of visual processing, a comprehensive understanding of post-ABI visual dysfunction is essential for the development of effective diagnostic and therapeutic frameworks. Accordingly, this narrative review aims to synthesize current evidence on the mechanisms, clinical manifestations, assessment strategies, and management of visual impairments following ABI, while identifying key gaps in research and clinical practice that must be addressed to optimize patient care.

Epidemiology of Visual Impairments After ABI

Visual dysfunction is among the most prevalent yet frequently underestimated sequelae of ABI. Epidemiological studies consistently report that approximately 50-80% of individuals with ABI experience some form of visual impairment during the acute or chronic phases of recovery (5). However, the true prevalence is likely higher, as subtle sensory deficits and higher-order visual perceptual disturbances may remain undetected in the absence of specialized assessment. Moreover, heterogeneity in study design, visual assessment methods, and patient populations contributes substantially to the wide variability observed in reported prevalence rates.

Global and Regional Prevalence

Globally, the World Health Organization estimates that more than 60 million people live with long-term neurological disability resulting from stroke and TBI combined, a substantial proportion of whom experience visual impairment (6). Among individuals with stroke, visual field defects—such as homonymous hemianopia and quadrantanopia—are reported in approximately 30-50% of cases. Oculomotor abnormalities, including gaze palsy, diplopia, and nystagmus, affect nearly 40% of stroke survivors, while visual neglect occurs in up to 30%, particularly following right hemispheric lesions (7).

TBI, another major contributor to ABI, is associated with an even higher burden of visual sequelae. Recent studies indicate that 60-70% of individuals with moderate-to-severe TBI experience one or more visual dysfunctions, ranging from accommodative and vergence abnormalities to deficits in visual processing (8). Although often considered less severe, mild TBI—commonly related to sports injuries or blast exposure—can also result in subtle yet functionally significant visual symptoms, including photophobia, blurred vision, and impairments in reading and visual attention.

Determinants and Outcomes

The likelihood and severity of visual dysfunction following ABI are influenced by several factors, including lesion location, the extent of diffuse axonal injury, patient age, and the presence of concomitant cognitive deficits. Early identification of visual impairments is frequently impeded by the limited integration of comprehensive vision assessment into routine neurological evaluation and rehabilitation protocols. Consequently, unrecognized visual deficits may contribute to delayed functional recovery, impaired mobility, increased risk of falls, and reduced reintegration into activities of daily living and employment.

Although the epidemiological burden of post-ABI visual impairment has been relatively well characterized in high-income Western countries, data from low- and middle-income regions remain limited. In the context of the rising global incidence of cerebrovascular disease and traumatic injury, enhanced epidemiological surveillance and the implementation of standardized visual screening protocols are essential to accurately define the scope of vision loss secondary to ABI.

Types and Mechanisms of Visual Impairments After ABI

The human visual system relies on the integrated functioning of ocular, cortical, and subcortical structures. ABI—whether caused by ischemic stroke, TBI, or hypoxic insult—can disrupt these networks at multiple levels, resulting in a broad spectrum of visual impairments. The type and severity of deficits depend on lesion location, extent of neural damage, and individual neuroplastic potential.

1. Visual Field Defects

Visual field loss is among the most prevalent visual consequences of ABI, particularly following occipital lobe lesions or posterior cerebral artery strokes. Disorders such as homonymous hemianopia, quadrantanopia, and scotomas arise from injury along the geniculocalcarine pathway, extending from the optic tract to the primary visual cortex. These deficits can significantly impair navigation, reading, and spatial orientation. Although spontaneous partial recovery may occur, persistent field loss often necessitates compensatory strategies, including visual scanning training or prism adaptation. Functional neuroimaging studies suggest that perilesional cortical reorganization may contribute to recovery in selected cases (9).

2. Oculomotor Dysfunction

Oculomotor abnormalities—including impaired saccades, smooth pursuit deficits, nystagmus, and convergence insufficiency—are

common following ABI, particularly in TBI. These deficits result from disruption of cortical-subcortical control circuits involving the frontal eye fields, cerebellum, and brainstem. Affected individuals frequently report diplopia, eye strain, or difficulty with reading. Quantitative assessment tools, such as eye movement recordings and infrared oculography, support accurate diagnosis and guide rehabilitation strategies, including vergence and pursuit training. Persistent oculomotor dysfunction may exacerbate dizziness and postural instability (10).

3. Cortical Visual Impairment

CVI arises from damage to the visual cortex or its associated white matter tracts, leading to deficits in visual perception despite normal ocular health. Although traditionally recognized in pediatric populations, CVI is increasingly identified in adults with ABI. Clinical manifestations include reduced visual acuity, impaired visual attention, and difficulty recognizing faces or objects. Neuroimaging studies indicate functional disconnection among occipital, temporal, and parietal regions. Rehabilitation emphasizes structured visual stimulation, environmental modifications, and targeted perceptual retraining (11).

4. Visual Neglect and Spatial Attention Deficits

Damage to the parietal or temporo-parietal junction can lead to visual neglect, characterized by the failure to attend to one side of space despite intact visual fields. This condition is particularly common after right-hemisphere stroke and is associated with severe disability and safety risks. Visual neglect arises from disrupted attentional control and interhemispheric imbalance rather than primary sensory loss. Interventions such as prism adaptation, scanning therapy, and non-invasive brain stimulation have demonstrated promising, albeit variable, benefits. Early detection using standardized assessments, such as the behavioral inattention test, improves rehabilitation outcomes (12).

5. Higher-order Visual Perceptual Disorders

In addition to primary visual deficits, ABI can result in complex perceptual disorders, including visual agnosia, prosopagnosia, and alexia, typically due to damage in the ventral visual stream connecting the occipital and inferotemporal cortices. These disorders often cooccur with cognitive or language deficits, which can complicate recognition and recovery. Management strategies primarily include cognitive-perceptual training and compensatory cueing, although large-scale trials assessing their efficacy remain limited.

Mechanistic Insights and Clinical Implications

Contemporary neuroimaging suggests that visual dysfunction following ABI arises not only from focal damage but also from network-level disconnection and maladaptive neuroplasticity. Injury to white matter tracts and trans-synaptic degeneration contributes to persistent deficits. Rehabilitation strategies that leverage visual neuroplasticity—such as repetitive stimulation and adaptive visual tasks—may facilitate recovery in selected patients. However, variability in injury patterns and the absence of standardized diagnostic criteria continue to limit widespread application.

A clear understanding of the mechanisms underlying visual dysfunction after ABI is essential for developing personalized interventions. The integration of neuro-optometric assessment, neuropsychology, and occupational therapy remains critical for achieving functional improvement and enhancing quality-of-life.

Types and Mechanisms of Visual Impairment in ABI

Visual dysfunction following ABI is diverse and reflects the complexity of the visual system, which involves multiple cortical and subcortical pathways. These impairments may result from direct structural damage to the visual cortex, optic radiations, or visual association areas, as well as secondary factors such as cerebral edema, ischemia, or diffuse axonal injury. The most commonly observed visual sequelae after ABI include visual field loss, oculomotor dysfunction, CVI, and higher-order perceptual disorders.

Visual field defects occur in approximately one-third of patients with stroke or TBI and typically present as homonymous hemianopia or quadrantanopia. These defects generally arise from lesions in the retrochiasmal visual pathways, particularly the optic radiations and occipital cortex. Patients with visual field loss often experience spatial disorientation, difficulty reading, and impaired mobility. Although partial recovery may occur within the first six months, persistent visual field loss requires compensatory strategies, such as visual scanning training or prism adaptation therapy (13).

Oculomotor dysfunction, including convergence insufficiency, saccadic dysmetria, strabismus, and impaired smooth pursuit, is also common after ABI. Lesions in the brainstem, cerebellum, or cortical eye movement centers disrupt binocular coordination, leading to symptoms such as diplopia, blurred vision, and eye strain. These dysfunctions are often underdiagnosed despite their significant impact on balance, mobility, and reading efficiency (14).

CVI represents a distinct form of visual loss resulting from cortical or subcortical injury, despite anatomically normal eyes. Individuals with CVI frequently exhibit fluctuating visual responses, difficulty recognizing complex scenes, and challenges with visual crowding. Functional magnetic resonance imaging (MRI) studies suggest that these symptoms are associated with altered connectivity and compensatory neuroplasticity in occipito-temporal pathways (15).

Higher-order perceptual disorders, including visual neglect, simultanagnosia, prosopagnosia, and visual agnosias, result from lesions affecting the parietal and temporal cortices. Visual neglect, particularly when associated with right parietal lobe damage, reduces awareness of the contralesional visual field and severely impacts daily functioning and spatial attention (16).

Mechanistically, ABI-induced visual deficits arise from both focal and diffuse neural injury. Hypoperfusion, excitotoxicity, inflammation, and axonal shearing contribute to secondary degeneration of interconnected visual networks. Advanced neuroimaging has revealed disrupted connectivity between fronto-parietal and occipito-temporal regions, which underlies persistent dysfunction. Understanding these mechanisms facilitates accurate diagnosis and informs targeted rehabilitation strategies (17).

Assessment of Visual Dysfunction After ABI

Evaluation of visual dysfunction following ABI requires a comprehensive, multidisciplinary approach that integrates neurological, ophthalmological, and optometric perspectives. Because visual deficits can range from basic sensory loss to complex perceptual disorders, no single test can capture the full spectrum of impairments. Early, structured visual assessment is essential to identify functional limitations, guide rehabilitation, and improve quality-of-life.

Clinical screening typically begins with a standard ophthalmic assessment, including visual acuity, refraction, and ocular health evaluation, to exclude preexisting ocular pathology. Visual field testing—performed using automated or manual perimetry—remains the cornerstone for detecting hemianopia, quadrantanopia, or scotomas. Goldmann and Humphrey perimetry can precisely delineate the extent and pattern of field loss, providing critical information for both diagnosis and rehabilitation planning (18). In acute settings where formal perimetry is impractical, bedside confrontation tests may serve as an initial screening tool.

Oculomotor assessment is equally important, as dysfunctions in vergence, saccades, and pursuit movements are common after ABI. Objective techniques, such as eye-tracking or video-oculography, can detect subtle abnormalities that routine clinical examination might miss. Specific assessments, including the developmental eye movement test and the King-Devick test, are useful for evaluating reading-related eye movements and can indicate underlying oculomotor inefficiencies (19). Additionally, pupillary responses and near point of convergence testing provide further insight into cranial nerve and brainstem function.

Assessment of visual attention, neglect, and higher-order perceptual deficits often requires neuropsychological evaluation. Standardized tests, such as the behavioral inattention test and the Bells test, are commonly used to detect unilateral neglect, whereas object and face recognition tasks can identify agnosias or prosopagnosia (20). Functional visual assessment, including observation of reading, navigation, and visually guided reaching, provides ecological validity to formal test results.

Neuroimaging techniques, particularly MRI and diffusion tensor imaging (DTI), are invaluable for identifying lesions within visual pathways and associated networks. These modalities can correlate structural damage with clinical symptoms and monitor recovery over time (21). Electrophysiological assessments, including visual evoked potentials, offer objective evidence of postchiasmal dysfunction and are particularly useful when behavioral responses are unreliable, such as in pediatric or severely impaired patients (22).

Given the complex interplay between visual, cognitive, and motor domains, interdisciplinary collaboration is essential. Optometrists, ophthalmologists, neurologists, and neuropsychologists should work together to ensure comprehensive evaluation and integrated management. The implementation of standardized vision screening protocols in neurorehabilitation programs has been shown to improve detection rates and facilitate timely intervention (23). Emerging digital technologies, including virtual reality (VR)-based visual field mapping and mobile vision assessment platforms, further enhance accessibility and accuracy in post-ABI visual evaluation (24).

Rehabilitation and Management Approaches in Visual Dysfunction After ABI

Rehabilitation of visual dysfunction following ABI aims to restore visual performance, enhance compensatory mechanisms, and improve functional independence. The complexity of visual processing and the heterogeneity of impairments necessitate a multimodal, interdisciplinary approach that integrates optometric, neurological, and occupational rehabilitation strategies.

Management begins with a comprehensive assessment of the type and severity of visual impairment, followed by individualized therapy plans. For patients with visual field deficits, compensatory techniques such as visual scanning training, systematic eye movement exercises, and reading retraining are commonly employed. Scanning therapy promotes systematic exploration of the blind hemifield, facilitating adaptation and improving detection of peripheral stimuli. Prism adaptation therapy, using yoked or sectoral prisms, has demonstrated efficacy in shifting the visual field and enhancing awareness of the impaired field (25,26). Recently, VR-based rehabilitation platforms have emerged as effective adjuncts, providing immersive environments for repetitive, feedback-based training (27).

Restorative approaches aim to enhance neural plasticity and residual visual field function through visual restitution therapy (VRT) and perceptual learning. These interventions involve repetitive visual stimulation near the border of the visual field defect to strengthen synaptic activity and cortical representation. Although the evidence remains mixed, some studies report measurable improvements in detection sensitivity and functional outcomes following sustained training (28,29).

Oculomotor rehabilitation targets common deficits after traumatic or ischemic brain injury, including convergence insufficiency, saccadic dysmetria, and pursuit impairments. Techniques such as vergence exercises, accommodative therapy, and dynamic saccadic training can restore binocular control and improve reading fluency. Computer-assisted oculomotor training and neuro-optometric rehabilitation have demonstrated promising results in enhancing fixation stability and visual endurance (30). Furthermore, integrating vestibular and balance training can further support overall recovery, particularly in patients experiencing postural instability or dizziness.

Management of CVI and higher-order perceptual disorders primarily emphasizes compensatory strategies and environmental modifications. Simplifying visual scenes, enhancing contrast, and providing structured routines can reduce visual crowding and cognitive load. For patients with visual neglect, interventions such as prism adaptation, optokinetic stimulation, and non-invasive brain stimulation techniques—including transcranial direct current stimulation—are under investigation for their potential to improve spatial awareness (31,32).

Assistive technologies are playing an increasingly important role in vision rehabilitation. Electronic magnifiers, head-mounted display systems, and augmented reality (AR) devices facilitate reading and mobility. Mobile applications offering gaze-tracking, text-to-speech, and scene interpretation have enhanced accessibility for individuals with visual-perceptual deficits (33). Emerging evidence also supports the integration of artificial intelligence-based adaptive vision aids, which can adjust display and contrast parameters in real time according to user needs (34).

Ultimately, successful rehabilitation depends on individualized goal setting, patient engagement, and early initiation of therapy. Interdisciplinary coordination among ophthalmologists, optometrists, neuropsychologists, and occupational therapists ensures comprehensive care. Despite advances, gaps remain in the standardization of rehabilitation protocols and the measurement of long-term outcomes, highlighting the need for high-quality, controlled trials to establish evidence-based best practices (35).

Discussion and Future Directions

Despite growing recognition of visual dysfunction following ABI, significant gaps remain in understanding its mechanisms, diagnosis, and management. The heterogeneity of ABI—including stroke, TBI, hypoxic injury, and intracranial hemorrhage—contributes to variability in visual outcomes and complicates the development of standardized rehabilitation approaches. Recent advances in neuroimaging, digital technologies, and neurorehabilitation have opened promising avenues for personalized interventions; however, integrating these approaches into routine clinical practice remains challenging (36,37).

Current evidence highlights the critical role of neuroplasticity in postinjury visual recovery. Functional MRI and DTI studies have demonstrated cortical reorganization within the occipital and parietal regions following targeted rehabilitation, particularly through VRT and perceptual learning paradigms (38). The extent of cortical plasticity, however, appears to depend on lesion location, size, and chronicity. This variability underscores the potential benefit of tailoring rehabilitation strategies to individual neural profiles, using imaging biomarkers as predictive tools to optimize outcomes (39).

Technological innovations—particularly VR, AR, and telerehabilitation—offer unprecedented opportunities for visual training. These tools create immersive, adaptive, and feedback-rich environments that can enhance patient engagement and facilitate home-based rehabilitation (40). Artificial intelligence powered gaze-tracking systems and machine-learning algorithms can further personalize therapy intensity and objectively monitor progress. Nevertheless, accessibility, cost, and the need for rigorous clinical validation remain significant barriers, especially in low-resource settings (41).

Multidisciplinary collaboration is another key determinant of successful outcomes. Integrated care models involving neuro-ophthalmologists, optometrists, occupational therapists, and neuropsychologists ensure that visual, cognitive, and perceptual deficits are addressed holistically (42). Despite this, vision rehabilitation remains underrepresented in many neurorehabilitation programs, often overshadowed by motor and language therapies. Incorporating vision screening protocols into early post-stroke and post-TBI care pathways can substantially improve detection rates and recovery potential (43).

Future research should prioritize three key areas. First, large-scale randomized controlled trials are necessary to establish evidence-based protocols for specific interventions, including prism adaptation, visual scanning, and non-invasive brain stimulation. Second, long-term follow-up studies should assess sustained functional gains and quality-of-life outcomes rather than focusing solely on short-term visual metrics. Third,

interdisciplinary and patient-centered research frameworks should incorporate patient-reported outcomes to address the psychosocial and occupational impacts of visual dysfunction (44).

In conclusion, although substantial progress has been made in understanding and managing visual impairments following ABI, the field remains in an evolving state. Bridging the gap between neuroscience, technology, and rehabilitation practice will be critical to achieving meaningful visual recovery and enhancing life participation among affected individuals (45).

Conclusion

Visual dysfunction following ABI remains a significant yet frequently underrecognized contributor to long-term disability. Early screening and targeted rehabilitation can substantially enhance functional recovery and quality-of-life. Incorporating visual assessment into standard neurorehabilitation programs is essential for comprehensive care. A coordinated, multidisciplinary approach—augmented by advancing technologies such as VR and telerehabilitation—offers promising opportunities for improving visual outcomes. Ongoing research and the standardization of evidence-based practices will be critical to ensuring that vision rehabilitation becomes an integral component of brain injury recovery globally.

Footnotes

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

Acknowledgment

The author declare that AI-based language assistance (ChatGPT, OpenAI) was employed solely for grammar refinement, formatting, and reference organization. All intellectual content, analyses, and conclusions remain the original work of the authors.

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DOI: 10.4274/jmsr.galenos.2026.2025-10-2

J Mult Scler Res 2026;6:22-25

CASE REPORT

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Multidomain Improvement with a Device-free SONAPS Program in Primary Progressive Multiple Sclerosis: A Case Report

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Abstract

Rapid, multidomain functional improvement is uncommon in primary progressive multiple sclerosis (PPMS). We report the case of a 44-year-old man with long-standing PPMS who completed a 15-session, device-free somatic-neuropsychological adaptive programming system program over 90-days. Global disability, assessed using the composite disability and functional status scale, improved from 20/50 to 7/50. Lower-limb strength increased (Medical Research Council scale: left, 0→1; right, 2→4). The Babinski sign normalized on the right and attenuated on the left. Multiple physical and psychological symptoms improved across 0-10 severity scales. One routine rituximab infusion occurred during the intervention period. Clinical gains persisted at 3 and 9 months without relapse or regression, despite exposure to significant psychosocial stressors. No adverse events were observed. These findings warrant further investigation in controlled, blinded studies.

Keywords: Device-free, functional gain, multiple sclerosis

Introduction

Primary progressive multiple sclerosis (PPMS) is characterized by a steady accumulation of neurological disability, with limited potential for rapid or spontaneous improvement (1). Although disease-modifying therapies may slow disease progression, reversal of established functional deficits is rare (1). From a patient-centered perspective, disability in PPMS reflects impairment across both physical-structural-functional (PSF) and psychological-behavioral-cognitive (PBC) domains, each of which contributes substantially to daily functioning and quality of life (2).

Non-pharmacological rehabilitation approaches in PPMS typically produce modest gains and often require prolonged intervention periods. Reports describing short-term, multidomain functional improvements are therefore uncommon. In this context, we present a case of PPMS demonstrating substantial improvement across PSF and PBC domains following a brief, device-free somatic-neuropsychological adaptive programming system (SONAPS) program. This report is intended to be exploratory and hypothesis-generating, documenting the clinical course and outcomes to inform future controlled investigations (2).

Case Report

A 44-year-old man from Tehran, Iran, presented in December 2023 with a 10-year history of progressively worsening neurological symptoms consistent with PPMS. The disease course was marked by continuous progression without identifiable relapses. At baseline, the patient reported severe imbalance with frequent falls, dependence on two canes for ambulation, and pronounced nocturnal muscle spasms. Additional symptoms included neuropathic pain, heat sensitivity, persistent fatigue, anxiety, intrusive memories, claustrophobia, fear of sleeping alone, insomnia, and marked social withdrawal.

Neurological examination revealed bilateral extensor plantar responses (right greater than left), an intact Romberg test,

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Received: 15.10.2025 **Accepted:** 04.01.2026 **Publication Date:** 12.03.2026

Cite this article as: Najafpour H, Riazat A. Multidomain improvement with a device-free SONAPS program in primary progressive multiple sclerosis: a case report. J Mult Scler Res. 2026;6:22-25

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and significant lower-limb weakness. Dorsiflexion strength was graded as 0/5 on the left and 2/5 on the right using the Medical Research Council (MRC) scale. Upper-limb strength was relatively preserved (4/5). The baseline composite disability and functional status scale (CDFSS) score was 20/50. Severity ratings for PBC symptoms ranged from 7 to 10 on 10-point scales (Table 1).

The patient had received at least 17 lifetime rituximab infusions administered every six months, yet clinical deterioration continued. A scheduled rituximab infusion occurred during the SONAPS intervention period (3). Concomitant medications included citalopram and intermittent marijuana use for pain and sleep. Brain magnetic resonance imaging (MRI) was not performed because of severe gadolinium hypersensitivity and claustrophobia. The patient reported no prior episodes of sustained functional improvement during approximately nine years of anti-CD20 therapy.

Baseline functional performance was documented using video recordings obtained on December 19, 2023. The SONAPS program commenced on December 20, 2023.

Intervention (SONAPS)

SONAPS is a structured, non-invasive, non-pharmacological, and device-free program delivered over 15 sessions (approximately 120 minutes per session) across a 90-day period. All sessions followed a standardized entry sequence and incorporated individualized, symptom-guided content spanning both PSF and PBC domains.

Session Structure

Each session included:

1. Interval symptom review, including motor function, balance, pain, sleep, and psychological symptoms.
2. Structured clinical assessment using predefined anchors, such as PSF and PBC ratings, functional task performance, and sensory-motor checks.
3. Individualized, multimodal intervention, targeting:

- Posture, coordination, balance, and muscle activation;
- Fatigue modulation;
- Emotional reactivity, anxiety-related themes, and intrusive memories (addressed through brief, focused tasks without psychotherapeutic dialogue);
- Autonomic-related complaints, including sleep disturbance and stress regulation.

4. Post-intervention reassessment, with documentation of both perceived and clinically observable changes.
5. Video documentation, when consent was provided, to capture objective functional findings when consented, of clinically observable findings.

Two sessions were extended to approximately four hours to allow evaluation of suspected food-related intolerances within the same device-free therapeutic framework.

Personnel and Fidelity

All sessions were conducted by a single treating physician with more than 20 years of clinical experience in managing complex neurological and psychological conditions. Treatment fidelity was ensured through strict adherence to a standardized session checklist, consistent use of PSF and PBC assessment anchors, and pre- and post-session video documentation.

No changes to the patient's medication regimen occurred during the intervention period, aside from the scheduled rituximab infusion.

Outcomes

1. Global Disability (CDFSS)

The CDFSS score improved from 20/50 at baseline to 7/50 following the program, representing an absolute reduction of 13 points. Improvements were observed across all subscales, as detailed below:

- Physical disability: 10/20→3/20
- Cognitive/psychological: 7/20→3/20
- Functional status: 3/10→1/10

Table 1. Prespecified outcomes before and after SONAPS (male, 44-year-old; PPMS)

Outcome/measure	Pre	Post	Delta/notes
CDFSS (global disability)	20/50	7/50	~65% reduction
Physical disability (CDFSS)	10/20	3/20	Subscale change
Cognitive/psychological (CDFSS)	7/20	3/20	Subscale change
Functional status (CDFSS)	3/10	1/10	Subscale change
Left dorsiflexion (MRC)	0/5	1/5	Gain of 1 grade
Right dorsiflexion (MRC)	2/5	4/5	Gain of 2 grades

SONAPS: Somatic-neuropsychological adaptive programming system, PPMS: Primary progressive multiple sclerosis, CDFSS: Clinical disability functional status scale; MRC: Medical Research Council scale

2. Neurological Examination

Neurological assessment demonstrated objective motor and reflex improvements:

- **Left ankle dorsiflexion:** 0/5→1/5
- **Right ankle dorsiflexion:** 2/5→4/5
- **Babinski sign:** Right converted to downward; left markedly attenuated
- **Romberg test:** Unchanged (negative).

3. PSF and PBC Symptoms

Marked improvements were observed across multiple patient-reported symptoms, as assessed on a 0-10 scale, with large absolute reductions:

- Muscle weakness: 8→5
- Spasticity: 10→6
- Coordination impairment: 10→4
- Neuropathic pain: 5→3
- Fatigue: 10→5
- Loss of balance: 8→2
- Anxiety: 8→1
- Claustrophobia: 8→1
- Stress: 10→1
- Negative parental memories: 10→1.

These changes are illustrated in Figure 1 and summarized in Table 1.

4. Durability of the Effect

At the 3-month follow-up (Tir 1404), both the patient and his father—who is also diagnosed with multiple sclerosis and received SONAPS independently—reported no recurrence of prior symptoms. At the 9-month follow-up (October 2025), functional improvements remained stable without evidence of regression.

Notably, during the 90-day program, the patient experienced several significant stressors, including a severe upper respiratory infection, the death of a close friend, and a traumatic accident involving a yet relative. Despite these events, no symptom exacerbation was observed.

No adverse events were recorded throughout the study period.

Discussion

Rapid, multidomain improvement in PPMS is uncommon. In this case, substantial gains were observed across motor, sensory, functional, and psychological domains following a short, device-free intervention. The magnitude and breadth of improvement—including increases in MRC strength scores, conversion of the Babinski response, and marked reductions in PSF and PBC symptom scores—are unexpected within the natural course of PPMS (1,2).

The persistence of clinical improvement over a 9-month follow-up period further supports the potential clinical relevance of these findings (2). However, causal inference is not possible in this single-case observation. Confounding effects from long-term anti-CD20 therapy, including a routine infusion administered during the intervention period, cannot be exclude. In addition, placebo effects, increased clinical attention, and regression to the mean may have contributed to the observed changes.

Despite these limitations, the temporally clustered and harmonized pattern of physical and psychological improvement—occurring within a 90-day intervention window after approximately nine years of steady disease progression—

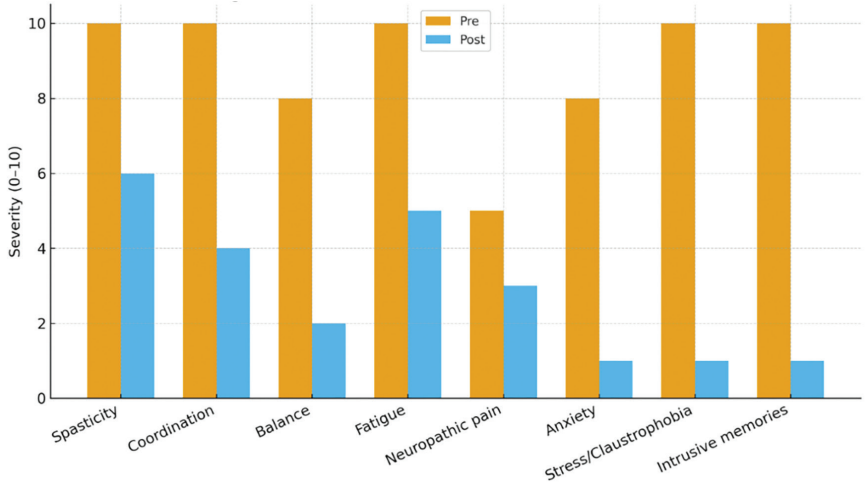


Figure 1. Graphical representation of symptom changes across PSF and PBC domains following the SONAPS intervention

PSF: Physical-structural-functional, PBC: Psychological-behavioral-cognitive, SONAPS: Somatic-neuropsychological adaptive programming system

suggests a potential therapeutic signal that warrants further investigation in controlled clinical trials (2).

The mechanisms underlying such broad improvement are unclear but may involve modulation of maladaptive neural circuits (4-9) and stress response systems, areas accessible to non-invasive intervention such as transcranial stimulation (10,11). While other physical modalities like pulsed electromagnetic field therapy have been studied in MS (12,13), the device-free, multi-domain approach of SONAPS appears distinct.

Patient Perspective

The patient reported meaningful improvements in mobility, emotional stability, sleep quality, confidence while walking outdoors, and a reduced fear of sleeping alone. He emphasized that these changes were "unlike any improvement" experienced during the preceding nine years of treatment.

Study Limitations

This report has several important limitations:

- Single-patient, non-blinded case.
- Routine rituximab infusion occurred within interval (potential confounder) (3).
- Use of self-reported symptom scales (4,5).
- No MRI was performed due to gadolinium reaction and claustrophobia.
- No blinded assessment or objective gait metrics (e.g., T25FW) were obtained (6).

Future controlled studies should incorporate blinded evaluators, standardized functional outcome measures, and objective physiological endpoints to better characterize efficacy and underlying mechanisms.

Conclusion

In a patient with advanced PPMS, a brief, device-free SONAPS program was associated with substantial improvement across multiple clinical domains, sustained for up to 9 months and without reported adverse events. Controlled and blinded studies are needed to evaluate reproducibility and to elucidate potential mechanisms of action (2,7-13).

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

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

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

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

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DOI: 10.4274/jmsr.galenos.2026.2026-1-1

J Mult Scler Res 2026;6:26-30

CASE REPORT

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Multidomain Functional Improvement Following a Device-free SONAPS Program in Late-onset Multiple Sclerosis: A Case Report of a 75-year-old Patient

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Abstract

Functional improvement in late-onset secondary progressive multiple sclerosis is uncommon, particularly in elderly patients with a long disease duration. We report the case of a 75-year-old man with symptom onset after the age of 50 and more than 20 years of progressive multiple sclerosis who experienced sustained, multidomain functional improvement following a short, non-invasive, non-pharmacological, device-free Somatic-neuropsychological adaptive programming system program delivered over approximately 60 days. The patient had not received disease-modifying therapy or physiotherapy for several years prior to the intervention. Global disability, assessed using the composite disability and functional status Scale, decreased from 29/50 to 3/50, accompanied by improvements across physical, functional, and psychological domains. Clinical improvements remained stable at 3-, 9-, and 12-month follow-up, with no adverse events reported. These findings should be interpreted as hypothesis-generating clinical observations rather than as evidence of treatment efficacy.

Keywords: Late-onset multiple sclerosis, secondary progressive multiple sclerosis, multidomain functional improvement, non-pharmacological intervention, case report

Introduction

Progressive multiple sclerosis (MS) is characterized by the gradual accumulation of neurological disability across motor, sensory, cognitive, and behavioral domains. In advanced stages of the disease, sustained functional improvement is considered biologically challenging, particularly in elderly patients with a long disease duration.

Late-onset MS, defined as symptom onset after the age of 50 years, represents a relatively uncommon phenotype and is often associated with more rapid disability progression and a greater comorbidity burden.

In this context, documenting multidomain clinical improvement in elderly individuals with long-standing progressive MS may provide valuable observational insights. The present report describes a hypothesis-generating clinical observation of functional improvement following a short, non-invasive, non-pharmacological, device-free intervention program.

Case Report

A 75-year-old retired businessman presented with long-standing neurological disability consistent with secondary progressive MS (SPMS).

Neurological symptoms began at the age of 55 years, with intermittent lower-limb spasm and gait instability. Over the following two decades, neurological function gradually deteriorated. Although brief partial remissions occurred earlier in the disease course, recovery remained incomplete, and disability accumulated progressively. A formal diagnosis of MS was established at the age of 65 years.

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Received: 29.01.2026 **Accepted:** 23.03.2026 **Publication Date:** 07.04.2026

Cite this article as: Najafpour H, Riazat A. Multidomain functional improvement following a device-free SONAPS program in late-onset multiple sclerosis: a case report of a 75-year-old patient. J Mult Scler Res. 2026;6:26-30

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At presentation, the patient reported the following symptoms:

- Severe fatigue
- Imbalance
- Lower-limb spasticity
- Numbness and paresthesia
- Tremor
- Neuropathic pain
- Heat sensitivity
- Urinary urgency with nocturia (5-6 episodes per night) caused chronic sleep disruption
- Cognitive complaints included subjective cognitive slowing and mental fog
- Ambulation was limited to cane-assisted walking, accompanied by a fear of falling

Neurological examination demonstrated the following findings:

- Spastic gait
- Bilateral lower-limb weakness
- Tremor affecting fine motor tasks
- Positive Romberg sign
- Bilateral extensor plantar responses

Global disability, assessed using the composite disability and functional status scale (CDFSS), was 29/50.

The CDFSS is a clinician-administered, multidomain disability scale developed in our clinic to assess neurological disability across three domains:

- Physical disability score (0-20)
- Cognitive-psychological score (0-20)
- Functional status (0-10)

Unlike the Expanded Disability Status scale, which is heavily weighted toward ambulation, the CDFSS provides a broader multidomain assessment of physical, cognitive, and functional status.

Baseline findings and outcome measures are summarized in Table 1.

Intervention [Somatic-neuropsychological Adaptive Programming System (SONAPS) Program]

The patient completed eight intervention sessions over approximately 60 days. A schematic overview of the patient's clinical timeline is presented in Figure 1. The intervention was non-invasive, non-pharmacological, and device-free. The SONAPS is a clinic-developed intervention framework designed to facilitate systemic functional regulation across physical—structural—functional and psychological—behavioral—cognitive domains. The approach operates within a real-time, closed-loop clinical framework in which patient responses during structured tasks are continuously monitored and used to guide adaptive adjustments in task sequencing.

Sessions included the following components:

- Structured symptom review
- Observational functional assessment
- Individualized, multimodal sensorimotor tasks

Rather than directly targeting isolated symptoms, the intervention aimed to improve systemic functional regulation.

For example, during early sessions, the patient demonstrated the following:

- Inability to independently button clothing
- Tremor during mobile phone use
- Reduced voice intensity
- Impaired balance

Following adaptive task sequences involving posture control, sensory feedback, and coordinated motor engagement, improvements in fine motor control were observed.

Functional performance was documented using video recordings obtained with patient consent.

Outcome Measures

Symptom severity ratings were obtained using a structured 0-10 scale, where:

Table 1. Prespecified outcomes before and after SONAPS

Domain	Measure	Baseline	Postintervention
Disability	CDFSS (0-50)	29	3
Strength	MRC LL-left (0-5)	1	3
Strength	MRC LL-right (0-5)	2	4
Neurologic signs	Romberg	Positive	Negative
Neurologic signs	Babinski	Upgoing	Neutral/downgoing

SONAPS: Somatic-neuropsychological adaptive programming system, CDFSS: Composite disability and functional status scale

- 0 indicates the absence of symptoms
- 10 indicates the worst imaginable symptom severity

Ratings were obtained through structured patient interviews.

Outcomes

Following the intervention program, global disability decreased substantially, with CDFSS scores improving from 29/50 to 3/50 postintervention. Lower-limb strength improved bilaterally on the Medical Research Council scale.

Neurological examination demonstrated the following:

- Conversion of Romberg sign from positive to negative
- Babinski responses becoming neutral or intermittently downgoing

Changes in neurological findings are summarized in Table 1. Symptom improvements are illustrated in Figure 2A, whereas changes across CDFSS domain scores are illustrated in Figure 2B.

Discussion

Sustained functional improvement in elderly individuals with long-standing SPMS is uncommon due to the disease's underlying biology, which is dominated by chronic neurodegeneration and limited reparative capacity (1,3).

Neuroplasticity declines with advancing age and prolonged disease duration, further restricting recovery potential in progressive neurological disorders (2). Nevertheless, emerging research suggests that neural systems may retain some adaptive capacity even in long-standing disease states.

Studies of functional brain connectivity indicate that large-scale neural networks remain dynamically modifiable and may respond to structured sensorimotor engagement and behavioral inputs (3,4).

Rehabilitation interventions in progressive MS have traditionally focused on domain-specific improvements, such as gait training, balance exercises, or fatigue management. Previous multimodal rehabilitation programs have generally reported modest, domain-limited benefits (5-7).

In contrast, the present observation suggests the potential for broader, multidomain functional improvement within a closed-loop adaptive intervention framework.

The SONAPS approach emphasizes real-time adjustment of sensorimotor and behavioral tasks based on ongoing patient responses, aiming to facilitate systemic functional regulation rather than targeting isolated symptoms.

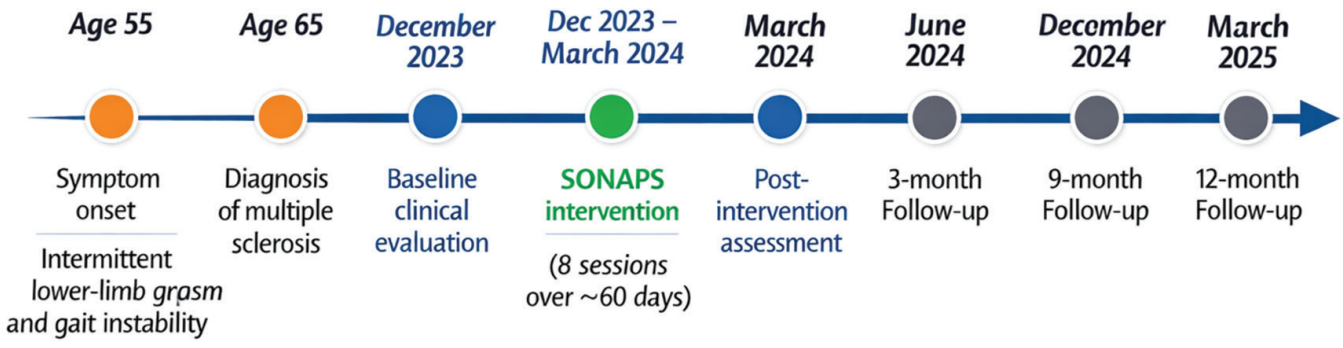


Figure 1. CARE timeline of the patient's clinical course from symptom onset to follow-up after the SONAPS intervention

Age 55: Symptom onset

Age 65: Diagnosis of MS

December 2023: Baseline clinical evaluation

December 2023 - March 2024: SONAPS intervention (8 sessions over ~60 days)

March 2024: Postintervention assessment

June 2024: 3-month follow-up

December 2024: 9-month follow-up

March 2025: 12-month follow-up

SONAPS: Somatic-neuropsychological adaptive programming system, MS: Multiple sclerosis

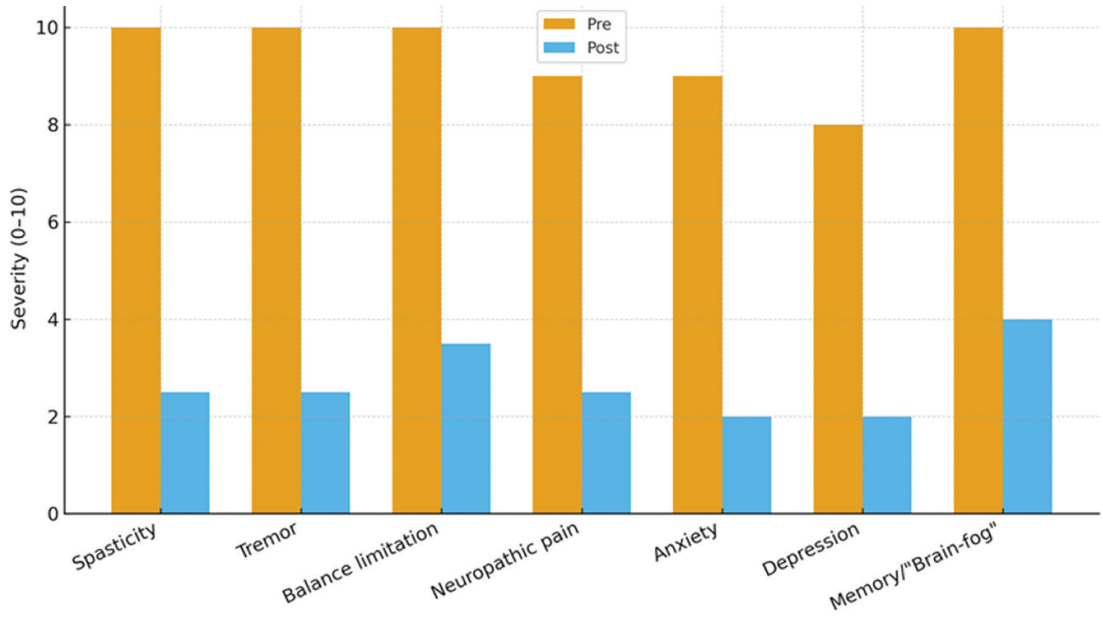


Figure 2A. Selected symptom severity scores (pre- vs. post-intervention)

PSF: Physical-structural-functional domain, PBC: Psychological-behavioral-cognitive domain

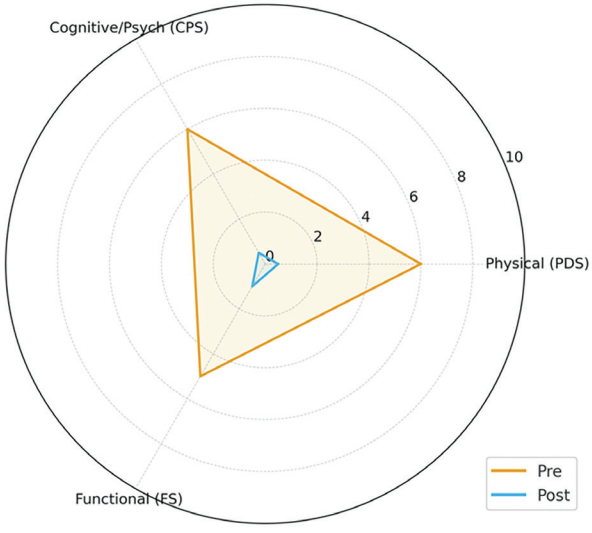


Figure 2B. Changes in CDFSS subscale scores, normalized to a 0-10 scale

CDFSS: Composite disability and functional status scale, PDS: Physical disability score, CPS: Cognitive-psychological score, FS: Functional status

Note: Error bars are not shown due to the single-case design

To our knowledge, sustained multidomain functional improvement of this magnitude in an elderly patient with long-standing SPMS has rarely been reported (1,4).

However, alternative explanations—including placebo effects, regression to the mean, or non-specific therapeutic influences—cannot be excluded.

Therefore, this report should be interpreted as a hypothesis-generating clinical observation that may inform future controlled studies.

Study Limitations

Several limitations should be acknowledged. First, this report describes a single, non-blinded case, and causal relationships cannot be established. Second, objective gait metrics and neuroimaging data were unavailable.

Third, several outcomes relied on patient-reported symptom ratings, which may be subject to reporting bias.

Additionally, the 0–10 symptom severity scales have not been validated for clinical responsiveness.

Fourth, the CDFSS has not yet undergone external validation.

Transparency and Independent Evaluation

To support transparency, video documentation of functional performance before and after the intervention sessions was obtained with patient consent. Short and extended video materials illustrating representative functional changes can be made available to reviewers upon request. Independent clinical evaluation by external investigators interested in examining the intervention under controlled research conditions is also welcome.

Conclusion

This case describes sustained multidomain functional improvement in a 75-year-old patient with late-onset SPMS following a short, device-free intervention program. These findings should be interpreted as hypothesis-generating clinical

observations rather than evidence of treatment efficacy. Further controlled and independently replicated studies are required.

Ethics

Informed Consent: Written informed consent was obtained from the patient and participating family members for the publication of clinical information and video documentation.

Footnotes

Authorship Contributions

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

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

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

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DOI: 10.4274/jmsr.galenos.2026.2025-6-1

J Mult Scler Res 2026;6:31-38

REVIEW

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Efficacy and Safety of BTKi in the Treatment of Multiple Sclerosis: A Systematic Review

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Abstract

Multiple sclerosis (MS) is an immune-mediated disease characterized by inflammatory demyelinating lesions within the central nervous system. Bruton's tyrosine kinase inhibitors (BTKis) modulate immune responses by inhibiting a key enzyme involved in B-cell receptor signaling and the activation of other immune cells. However, the efficacy and safety of BTKi remain controversial, and more comprehensive studies are required. We searched PubMed, Scopus, and the Cochrane Library for randomized controlled trials (RCTs) evaluating BTKis for MS through October 1, 2024, and identified six RCTs. A total of 2,960 patients from these trials were included to examine the efficacy and safety of BTKi in MS treatment. The included BTKi were evobrutinib [25,45, and 75 mg once daily; 75 mg twice daily (BID)], fenebrutinib (200 mg BID), and tolebrutinib. Across the included studies, evobrutinib—particularly at 75 mg BID—reduced the number of new T1 gadolinium-enhancing lesions and T2 lesion burden compared with placebo, with a favorable safety profile. In addition, its long-term efficacy was supported by stable outcomes and sustained safety. Other BTKi demonstrated promising short-term results; however, no long-term data are currently available. In contrast, none of the treatments showed significant changes in Expanded Disability Status Scale scores. Overall, BTKi have shown promising results in the treatment of MS. In particular, evobrutinib may serve as a suitable oral alternative for patients with mild to moderate disease due to its safety and selectivity. Nevertheless, further clinical trials are needed to better evaluate other BTKi and to provide a more comprehensive understanding of their long-term efficacy and safety.

Keywords: Systematic review, multiple sclerosis, BTKi, T1- and T2-weighted magnetic resonance imaging, randomized controlled trials, EDSS

Introduction

Multiple sclerosis (MS) is an autoimmune disorder characterized by the presence of plaques in the white and gray matter of the brain and spinal cord, caused by a chronic inflammatory process involving the central nervous system (CNS) (1), in which axons are demyelinated during the body's attack on its own axonal coverings, called myelin sheaths (2,3). This process results in a complex array of symptoms, including numbness and tingling, vision impairment, focal weakness, bladder and bowel dysfunction, and cognitive impairment, which accounted for 512,985 disability-adjusted life years and 4,738 deaths worldwide in 2021 (4). This represents a substantial burden on global productivity, as younger age groups had a considerable share of new-onset cases, primarily affecting individuals aged 20-44 years (4,5), while patients under the age of 18 were also significantly impacted, with 30,000 cases reported in 2020 (6).

The diagnosis of MS is primarily clinical, relying on patient history and physical examination findings. As no single laboratory test is diagnostic for MS, investigations such as magnetic resonance imaging (MRI) of the brain and spinal cord are used to support the diagnosis and monitor disease progression (7,8).

Although B-cells and plasma cells contribute to the demyelination process, the protective functions of local microglial cells and derived macrophages, which aid in remyelination, appear to be

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Received: 04.07.2025 **Accepted:** 01.04.2026 **Publication Date:** 20.04.2026

Cite this article as: Matar HI, Baniamer MN, Alsarayrah AI, Al-Rjoub AA, Altaweel AS, Baniamer BN, Aletaywi AN. Efficacy and safety of BTKi in the treatment of multiple sclerosis: a systematic review. J Mult Scler Res. 2026;6:31-38

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impaired due to the proinflammatory environment observed in MS and other neurodegenerative diseases (9). While current treatments have proven efficacy in preventing relapses and acute inflammatory episodes in active MS, no therapeutic option guarantees the prevention of disability accumulation associated with progressive MS, nor the regeneration of damaged neural components (10). Accordingly, MS remains an incurable disease (1).

Bruton tyrosine kinase inhibitors (BTKis) are a class of drugs that inhibit BTK, expressed on hematopoietic cells, primarily B lymphocytes, and play a key role in their differentiation, activation, signaling pathways, and overall function (11,12). Research has shown that BTK expression on microglial cells in the brain is upregulated in patients with MS, contributing to the chronic inflammation observed in the disease (13). BTK inhibitors can penetrate the CNS, thereby modulating both innate and adaptive immune systems involved in MS pathogenesis (11,13). Additionally, they have demonstrated the ability to promote axonal remyelination by enhancing microglial clearance of myelin debris (13), making them promising candidates for the treatment of MS.

Currently available oral treatments for MS, such as teriflunomide, dimethyl fumarate (DMF), and fingolimod, lack selectivity (teriflunomide is moderately selective), which results in multiple systemic side effects (14). In contrast, evobrutinib is highly selective, suggesting fewer systemic side effects. Its dual action on adaptive and innate immunity, combined with improved selectivity, positions it as a promising therapeutic candidate that may address some of the unmet needs in MS management.

Methods

The procedure of our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (15).

Research Strategy

A systematic literature search was independently conducted by three authors up to October 1, 2024. Databases searched included PubMed, Scopus, and the Cochrane Library, using a research strategy encompassing all known forms of BTK inhibitors and synonyms for MS. In addition, we manually screened the reference lists of relevant articles to ensure comprehensive inclusion of pertinent studies. Furthermore, we manually screened neurology.org.

("BTK Inhibitor" OR "tolebrutinib" OR "evobrutinib" OR "Ibrutinib" OR "Pirtobrutinib" OR "Orelabrutinib" OR "Tirabrutinib" OR "Fenebrutinib" OR "Bruton's tyrosine Inhibitor") AND ("Multiple Sclerosis" OR "MS" OR "Disseminated Sclerosis" OR "Cerebrospinal Sclerosis" OR "Autoimmune Demyelinating Disorder" OR "Encephalomyelitis Disseminata").

Eligibility Criteria

Inclusion criteria were determined using the PICO framework as follows: (1) population: participants diagnosed with MS, aged 18 years or older (up to 55 or 65 years); (2) intervention: administration of at least one class of oral BTKi for the treatment of any MS subtype, with comparisons made between various dosages and formulations of BTKi and placebo drugs; (3) outcomes: assessed using objective measures, specifically the Expanded Disability Status Scale (EDSS) and T1- and T2-weighted MRI; (4) exclusion criteria (1) absence of essential data, (2) studies presented solely as commentaries, book chapters, or animal studies, (3) studies with overlapping datasets, or (4) studies conducted solely *in vitro*.

Data Extraction and Quality Assessment

Data extraction was independently performed by two authors, with disagreements resolved by a third author. Fundamental study characteristics were meticulously collected, including authors, national clinical trial numbers, publication type, intervention type, study objectives, control groups, treatment groups, total participant numbers, study duration, and outcome events. Patient demographics, including gender and age, were also recorded. Additionally, inclusion and exclusion criteria, outcome assessments, and study conclusions were compiled. Study quality was assessed using the risk of bias tool to provide a comprehensive understanding of the included studies.

Outcomes

Primary outcomes included the number of new gadolinium-enhancing (Gd) T1 lesions, changes in T2 lesion volume (or number of new/enlarging T2 lesions where reported), and EDSS scores. Safety outcomes included treatment-emergent adverse events (TEAEs), categorized as grade 1 (asymptomatic), grade 2 (discomfort), grade 3 (severe), and grade 4 (life-threatening).

Results

Search Results

The literature search identified a total of 675 studies from PubMed, Scopus, and Cochrane using a preformatted search strategy. Using EndNote, 180 studies were duplicates, and 482 were excluded based on titles and abstracts. Fifty-five studies underwent full-text review, and six met the inclusion criteria; all were included in the systematic review (Figure 1).

Study Characteristics

All six included studies were multicenter trials, including a total of 2,960 patients. Three studies were placebo-controlled (16-18), two were active-controlled (19), and one was an open-label extension (OLE) (20). Study periods ranged from 12 (16) to 192 weeks (20). Mean ages were approximately 38.5 years, with EDSS scores below 6, including both relapsing-remitting MS (RRMS) and secondary progressive MS, with RRMS being the

majority. Sample sizes varied substantially among the studies, ranging from 109 (16) to 1,166 participants (19).

Two studies compared evobrutinib with teriflunomide (19), one study compared evobrutinib with placebo (18), one study compared fenebrutinib with placebo (16), and one study compared tolebrutinib with placebo (17). Doses ranged from evobrutinib 25 mg once daily (QD) to fenebrutinib 200 mg twice daily (BID).

Risk of Bias

Three of the six trials showed low risk of bias across all five domains (16-18). One study showed high risk of randomization bias due to the lack of randomization, as it was an OLE trial (20). The evolutionRMS 1 and 2 studies raised concerns due to high withdrawal rates (approximately 20%), increasing the risk of missing outcome data (19) (Figure 2).

Efficacy

- Number of New T1 Gd+ Lesions

All included studies assessed the number of new T1 Gd+ lesions. One study compared evobrutinib (25 mg QD, 75 mg QD, and 75 mg BID), placebo, and DMF (18). Patients in the evobrutinib 75 mg BID group showed a rapid onset of action and a marked reduction in the mean number of new T1 Gd+ lesions during the first 12 weeks. Patients in the evobrutinib 75 mg QD group

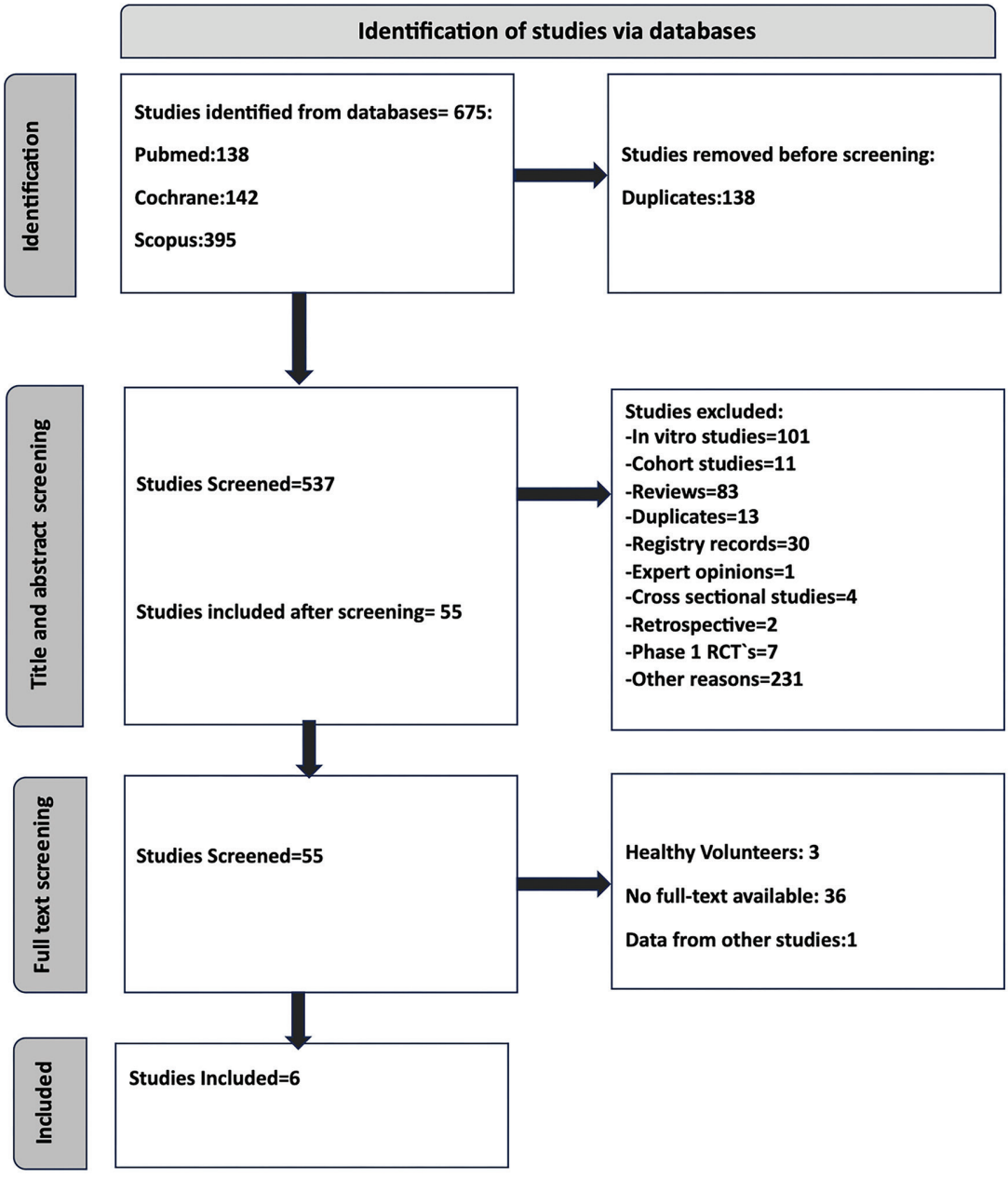


Figure 1. The literature search process

RCT: Randomized controlled trials

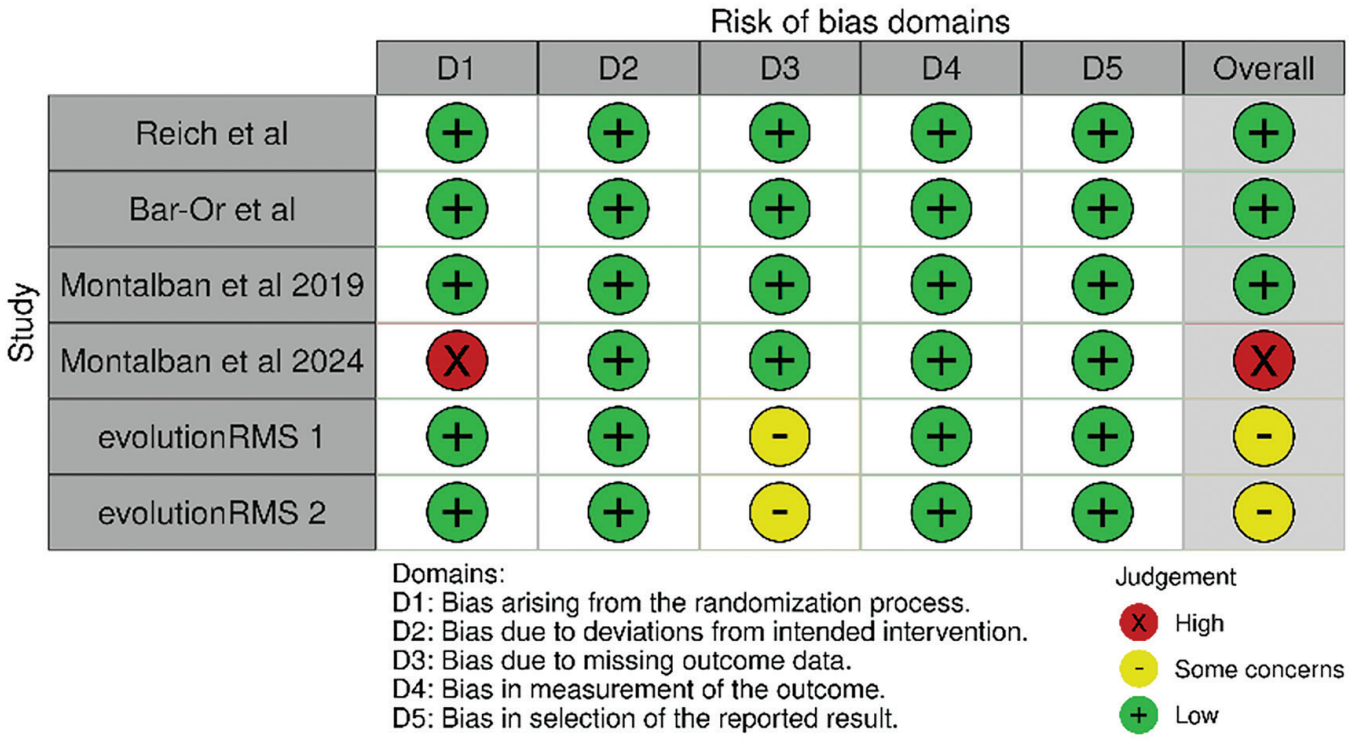


Figure 2. The quality assessment of the included studies

RMS: Relapsing multiple sclerosis

showed a significantly lower number of new T1 Gd+ lesions from week 12 to week 24, but not at other doses.

Two studies compared evobrutinib (45 mg BID) with teriflunomide (14 mg QD). Both studies indicated similar improvements in the first 24 weeks for both drugs, but lesion numbers increased with evobrutinib, unlike teriflunomide, after week 24 (19).

An OLE (75 mg QD and 75 mg BID) showed that the mean number of T1 Gd+ lesions changed according to dose. There was a temporary increase with evobrutinib 75 mg QD, followed by a decrease after switching to 75 mg BID in the OLE (20).

One study compared tolebrutinib (5,15,30, and 60 mg) with placebo. The maximal effect was observed at 60 mg, where 90% of participants had no new Gd-enhancing lesions (17).

A study comparing fenebrutinib 200 mg BID with placebo showed a 69% reduction in total new T1 Gd+ lesions at weeks 4, 8, and 12 combined, with a rapid reduction of 49% by Week 4, 92% by Week 8, and 90% by Week 12 (16).

- T2 Lesion Volume

All six studies assessed changes in T2 lesion volume. One study comparing evobrutinib (25 mg QD, 75 mg QD, and 75 mg BID) with placebo reported a T2 lesion volume of 0.42 at week 24 in the 75 mg BID group, indicating better response than other doses (18). Two studies comparing evobrutinib (45 mg BID) with teriflunomide (14 mg QD) showed that evobrutinib was not superior to teriflunomide (19). In the OLE (75 mg QD followed by 75 mg BID), T2 lesion volumes remained stable from baseline to week 192 across the double-blind treatment groups (20).

A study comparing fenebrutinib with placebo demonstrated relative reductions of 90% and 95% in T2 lesions at weeks 8 and 12, respectively (16).

Another study comparing tolebrutinib with placebo suggested a dose-dependent linear relationship with new or enlarging T2 lesions, significant across all six dose-response models (17).

- EDSS Score

Two studies assessed changes in EDSS scores (18,20). One study showed no significant change from baseline in patients receiving evobrutinib (25 mg QD, 75 mg QD, and 75 mg BID) (18). In the OLE, patients switched from 75 mg QD to BID after a mean duration of 50.6 weeks (±6.0), and EDSS scores remained stable, with no change in median baseline EDSS throughout the study, regardless of the initial treatment arm. This may reflect that EDSS is less sensitive to changes over a one-year period compared to Gd+ lesions (20).

Safety

One study comparing evobrutinib (25 mg QD, 75 mg QD, and 75 mg BID) with placebo and DMF reported the highest rate of serious adverse events (7%) in patients treated with evobrutinib 75 mg BID. The most common evobrutinib-related adverse events were nasopharyngitis and increased levels of alanine

aminotransferase, aspartate aminotransferase, and lipase. Evobrutinib also had lower rates of systemic adverse events, such as flushing, compared with DMF (18).

In the OLE, no new safety signals were identified with long-term evobrutinib treatment. TEAEs were mild to moderate, including nasopharyngitis (15%) and increased lipase (12%). No serious elevations in liver aminotransferases were observed during the double-blind period (20).

Two studies comparing evobrutinib (45 mg BID) with teriflunomide (14 mg QD) indicated a clinically relevant risk of drug-induced liver injury, limiting use in patients with pre-existing liver conditions (19).

One study comparing fenebrutinib with placebo reported no new safety concerns, consistent with earlier findings, suggesting a favorable benefit-risk profile (16).

Overall, BTK inhibitors rarely cause adverse events, with systemic adverse events being particularly uncommon. Table 1 provides further details.

Discussion

This systematic review synthesizes current evidence on BTKi for the treatment of MS and discusses their efficacy and safety. The findings suggest that BTKi represent a promising class of oral drugs for mild and moderate cases.

A systematic review of BTKi in MS is important as it consolidates all available evidence to establish their efficacy in reducing radiological disease activity, such as new lesions, and clarifies their distinct safety profile, particularly the risk of liver enzyme elevations. This provides clinicians and researchers with a critical, evidence-based foundation for evaluating this emerging therapeutic class.

The studies indicate that BTKi produce a positive and rapid improvement in MRI findings, particularly at the evobrutinib 75 mg BID dose. DMF is an oral DMT with moderate efficacy and a favorable safety profile (21), but current trials suggest that evobrutinib shows superior outcomes, especially in the short term (18). Evobrutinib 75 mg BID demonstrated an 83% reduction in new T1 Gd+ lesions, compared with 75% with DMF during the first 24 weeks of treatment (22), suggesting its potential as an alternative oral therapy for MS.

Table 1. Studies key findings

Study ID	Design	Intervention	Dosing arms & frequency	Key findings
Reich et al. (17)	Phase 2b RCT	Tolebrutinib	(5,15,30,60) mg once daily	The study demonstrated a dose-dependent reduction in new gadolinium-enhancing (Gd) lesions, with the 60 mg dose achieving an 85% reduction ($p=0.03$) and an 89% reduction in new or enlarging T2 lesions ($p<0.0001$). Higher tolebrutinib exposure correlated with fewer new lesions, and taking the drug with food significantly increased plasma concentration. Exploratory imaging showed a reduction in slowly evolving lesions at 60 mg, suggesting potential effects on chronic inflammation, while paramagnetic rim lesions were found in 50% of participants, indicating persistent neuroinflammation. Tolebrutinib was well tolerated, with headache (7%) as the most common adverse event and one serious adverse event (MS relapse in the 60 mg group), which did not lead to treatment discontinuation. Mild ALT elevations were seen in two patients but resolved without stopping treatment. These findings support the continued development of tolebrutinib in phase 3 trials for relapsing and progressive multiple sclerosis.
Bar-Or et al. (16)	Phase 2 RCT	Fenebrutinib	200 mg twice daily	Fenebrutinib demonstrated a 69% reduction in the total number of new T1 Gd+ lesions over 12 weeks, with a rapid onset of efficacy observed by week 4. At weeks 8 and 12, lesion reductions reached 92% and 90% for T1 Gd+ lesions, and 90% and 95% for T2-weighted lesions, respectively. Exploratory analyses showed that fenebrutinib penetrated the cerebrospinal fluid (CSF) at levels sufficient to inhibit B-cell and microglia activation, suggesting potential effects on chronic inflammation and progressive disease mechanisms. The treatment was well tolerated, with no serious adverse events reported. Most adverse events were mild or moderate (Grade 1 or 2), except for two Grade 3 asymptomatic liver transaminase elevations. These findings highlight fenebrutinib's early and significant anti-inflammatory effects in relapsing multiple sclerosis, supporting its further clinical development.

Table 1. Continued

Study ID	Design	Intervention	Dosing arms & frequency	Key findings
Montalban et al. (18) 2019	Phase 2 RCT	Evobrutinib	25 mg once, 75 mg once, 75 mg twice daily	Evobrutinib significantly reduced the total number of Gd+ lesions on T1-weighted MRI at weeks 12 through 24, with the 75 mg once-daily dose showing the greatest effect (rate ratio: 0.30, p=0.005) compared to placebo. However, the 25 mg once-daily and 75 mg twice-daily doses did not show a statistically significant difference. There was no significant reduction in the annualized relapse rate (ARR) or disability progression at any dose level. The treatment was generally well tolerated, but higher doses (75 mg once or twice daily) were associated with an increased incidence of liver enzyme elevations (ALT, AST) and lipase. While most patients remained relapse-free, the safety profile and need for hepatic monitoring warrant further investigation. These findings support further evaluation of evobrutinib in larger, longer trials to determine its role in multiple sclerosis management.
Montalban et al. (20) 2024	Phase 2 RCT	Evobrutinib	25 mg once, 75 mg once, 75 mg twice daily	Evobrutinib demonstrated a sustained reduction in disease activity over more than 3.5 years, with a stable ARR of 0.11 and consistently low T1 Gd+ lesion counts. A rapid onset of efficacy was observed within the first 12 weeks, with significant reductions in new T1 Gd+ lesions and a decrease in neurofilament light chain (NfL) levels, a biomarker of neuroaxonal damage. Evobrutinib effectively penetrated the CSF at concentrations sufficient to achieve high Bruton's tyrosine kinase occupancy, indicating potential modulation of both peripheral and central nervous system inflammation. The treatment was well tolerated, with no new safety signals identified, and most adverse events were mild or moderate. These findings support evobrutinib's long-term efficacy and safety in relapsing multiple sclerosis, reinforcing its potential as a disease-modifying therapy.
EvolutionRMS 1	Phase 3 RCT	Evobrutinib or teriflunomide	45 mg twice daily or 14 mg once daily	Evobrutinib did not demonstrate superiority over teriflunomide in reducing relapses, with an ARR of 0.15 vs. 0.14 (p=0.55). MRI results showed a higher number of new T1 Gd+ lesions in the evobrutinib group (0.50 vs. 0.35 per scan). There was no significant difference in 12-week and 24-week confirmed disability progression, and serum NfL levels remained comparable between the groups. However, higher liver enzyme elevations were observed in patients receiving evobrutinib, with 5% experiencing ALT increases above 5× the upper limit of normal, compared to less than 1% in the teriflunomide group. These findings suggest that evobrutinib does not offer a significant advantage over teriflunomide for managing RMS.
EvolutionRMS 2	Phase 3 RCT	Evobrutinib or teriflunomide	45 mg twice daily or 14 mg once daily	Evobrutinib showed no significant difference in the efficacy compared to teriflunomide, with both groups having an identical ARR of 0.11 (p=0.51). Evobrutinib was associated with a higher number of new T1 Gd+ lesions (0.50 vs. 0.31 per scan), indicating no added benefit in suppressing acute inflammation. Disability progression rates and neuroaxonal damage markers (NfL levels) remained similar between both treatments, further confirming the lack of superiority. The safety profile mirrored that of evolutionRMS 1, with higher rates of liver enzyme elevations observed in the evobrutinib group. Overall, these results reinforce that evobrutinib does not provide additional efficacy benefits over teriflunomide in treating relapsing multiple sclerosis.

RMS: Relapsing multiple sclerosis, RCT: Randomized controlled trial, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, MRI: Magnetic resonance imaging

However, evobrutinib showed stable T2 lesion volume across treatment groups, with only slight reductions at the 75 mg BID dose for both short- and long-term use (18), similar to DMF (22). Likewise, EDSS scores showed little to no change in both treatments (18).

Evobrutinib's high selectivity reduces systemic side effects (11). This is noteworthy because flushing is a common adverse effect of DMF—22% of patients receiving 120 mg twice daily for the first week, followed by 240 mg twice daily thereafter, experience flushing (18). Therefore, evobrutinib may be a suitable alternative in patients experiencing severe flushing.

Phase 3 studies comparing evobrutinib 45 mg BID with teriflunomide 14 mg QD were less promising (19), likely due to the relatively low dose, as long-term effects of evobrutinib 75 mg BID were markedly better than 75 mg QD (18).

Trials of other BTKi, such as tolebrutinib and fenebrutinib, were too short to provide strong evidence of their efficacy. Nevertheless, these trials demonstrated some promising results, highlighting the importance of advancing these agents to phase 3 trials.

Study Limitations

This systematic review has several limitations. Variations among included studies in terms of study duration, BTKi type, and dosing prevented a meta-analysis across all studies. Furthermore, additional studies on other BTKi formulations are needed to provide a comprehensive understanding of their efficacy and safety. Future research should focus on comparing the long-term efficacy of high-dose evobrutinib (75 mg BID) with other oral MS therapies, such as DMF and teriflunomide, in mild and moderate cases. Advancing trials for other BTKi and for evobrutinib 75 mg BID to phase 3 will provide more definitive evidence to guide clinical use.

Conclusion

Evidence from randomized trials confirms that BTK inhibitors provide a potent and rapid reduction in gadolinium-enhancing lesions in MS, highlighting their strong effect on suppressing inflammatory activity. The therapeutic effect is dose-dependent but may not be sustained across all dosing regimens. BTKi are generally well tolerated, with hepatic events being the most notable safety concern. Long-term stability of EDSS scores suggests the need for further investigation into their effects on disability progression. These findings support BTKi as a valuable addition to the MS treatment arsenal, with dose optimization and liver safety as key considerations for clinical use.

Acknowledgement

The authors thank Ramez Odat and Anas Zakarya for their assistance and support during this project.

Footnotes

Authorship Contributions

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

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DOI: 10.4274/jmsr.galenos.2026.2025-8-3

J Mult Scler Res 2026;6:39-45

RESEARCH ARTICLE

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Expression Levels of Intracellular Pathway Factors of B Lymphocytes in Patients with Multiple Sclerosis with and without Optic Neuritis Onset

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Abstract

Objective: Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system with a heterogeneous clinical course. Patients presenting with a first episode of optic neuritis (ON) generally exhibit a more favorable prognosis. Although T lymphocytes have traditionally been regarded as the primary drivers of MS pathogenesis, increasing evidence highlights the importance of B lymphocytes and their intracellular signaling pathways. This study aimed to investigate whether differences exist in B-cell-related intracellular pathway gene expression between patients with MS with and without ON onset and to assess their potential pathogenic implications.

Materials and Methods: A total of 26 patients with MS were enrolled, including 10 with ON onset and 16 without ON at disease onset. Disability was evaluated using the Expanded Disability Status Scale (EDSS), and cognitive performance was assessed using standardized neuropsychological testing. Peripheral blood samples were analyzed for B-cell-related gene expression [*B-lymphoid tyrosine kinase (BLK), B-cell scaffold protein with ankyrin repeats 1 (BANK1), transforming growth factor beta (TGFB), and ATPase Na^+/K^+ transporting subunit beta 3* (*ATP1B3*)] using quantitative polymerase chain reaction, and immune cell subset ratios were evaluated using flow cytometry.

Results: Although patients with ON-onset MS experienced a higher number of ON attacks during disease course, they demonstrated EDSS scores comparable to those of patients without ON onset. No significant differences were observed in immune cell subset ratios or in BLK, BANK1, or TGFB expression levels. However, ATP1B3 expression was significantly reduced in patients with ON onset compared with those without ON onset (p=0.011).

Conclusion: Reduced expression of *ATP1B3*, a gene implicated in B lymphocyte proliferation, appears to be associated with ON onset and increased frequency of ON attacks. These findings suggest that *ATP1B3* may be a potential biomarker associated with ON occurrence in MS. This hypothesis requires validation in larger longitudinal cohorts.

Keywords: Multiple sclerosis, optic neuritis, B lymphocyte, *ATP1B3*

Introduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system (CNS) that predominantly affects young adults and progresses through episodes of inflammation and myelin damage. Approximately 20% of patients with MS experience their first attack as optic neuritis (ON). Moreover, nearly half of patients with MS experience recurrent episodes of ON within 15 years of the initial attack (1).

In addition to genetic predisposition, environmental factors and infections are also implicated in the etiology of MS, presumably through the modulation of immune functions (2-5). Naïve $CD4^+$ and $CD8^+$ T-cells are believed to play a key role in the development of MS. After entering the CNS, T-cells induce an

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Received: 28.10.2025 **Accepted:** 19.04.2026 **Publication Date:** 08.05.2026

Cite this article as: Firat Z, Ozkan Yasargun D, Yilmaz V, Turkoglu R, Tuzun E, Arsoy E. Expression levels of intracellular pathway factors of B lymphocytes in patients with multiple sclerosis with and without optic neuritis onset. J Mult Scler Res. 2026;6:39-45

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inflammatory milieu that leads to oligodendrocyte apoptosis, demyelination, and eventually neuronal degeneration (6-11). Although MS has long been considered a T-cell-mediated disease, growing evidence suggests that B-cells also play an important role. Memory B-cells and plasma cells are responsible for the rapid and abundant production of antibodies in response to antigen exposure. Analysis of the cerebrospinal fluid (CSF) of patients with MS has shown that elevated B-cell counts are associated with more rapid disease progression (12). Additional evidence supporting the role of B-cells in MS pathogenesis includes intrathecal immunoglobulin production, the presence of oligoclonal bands (OCBs) in CSF, clinical improvement following treatment with monoclonal antibodies targeting B lymphocytes, and correlations between CSF plasmablast and immunoglobulin M levels with clinical progression and the number of contrast-enhancing lesions in MS (13,14).

Certain intracellular signaling pathways are preferentially involved in B-cell activation. The *B-cell scaffold protein with ankyrin repeats 1 (BANK1)* gene, located on chromosome 4, encodes a B lymphocyte-specific scaffold protein involved in B-cell receptor-mediated calcium mobilization within the intracellular space. B-lymphoid tyrosine kinase (BLK), a non-receptor tyrosine kinase belonging to the Src family of protooncogenes, participates in the regulation of cell proliferation and differentiation (15,16). The *BLK* gene has been implicated in the pathogenesis of autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (SLE) (17,18). Sodium, potassium-adenosine triphosphatase (Na^+/K^+-ATPase) is a major membrane protein involved in ion transport and provides the electrochemical gradient necessary for action potential generation in nerve and muscle cells. Among genes encoding membrane channel proteins, *ATPase Na^+/K^+ transporting subunit beta 3 (ATP1B3)* encodes the beta subunit of the Na^+/K^+-ATPase complex and is involved in lymphocyte activation (19). This gene contributes to Na^+/K^+-ATPase function, which increases intracellular sodium levels required for clonal expansion of T and B lymphocytes following antigen presentation (20-23). Reduced Na^+/K^+-ATPase activity has been suggested to trigger B-cell lymphoma-2 mediated apoptosis in cells. Thus, failure to suppress Na^+/K^+-ATPase activity may theoretically allow the persistence of autoreactive B-cells, thereby contributing to B-cell-mediated tissue damage (24). Transforming growth factor beta (TGFB) is expressed by regulatory B-cells, and selective inhibition of TGFB in B cells has been shown to increase the proportion of autoreactive B-cells (25,26). This cytokine has also been implicated in the development of gliosis, particularly in demyelinating plaques of the spinal cord (27).

Previous reports suggest that MS presenting with ON may involve heterogeneous disease mechanisms, which may influence long-term outcomes (28). Therefore, given the established importance of B cells in MS pathogenesis, we aimed to investigate whether patients with MS with and without ON onset exhibit differences in B-cell-mediated mechanisms by assessing peripheral blood B-cell subsets and measuring the expression levels of intracellular B lymphocyte pathway factors (*BANK1, BLK, ATP1B3,* and *TGFB*).

Materials and Methods

Participants and Neuropsychological Assessment

This study included 26 patients diagnosed with MS who were followed at the same MS outpatient clinic. The patients were divided into two groups: those with ON as the initial clinical manifestation of MS (n=10) and those without ON onset (n=16). An episode of ON was defined as painful vision loss or visual blurring lasting at least 24 hours, with no other identifiable cause. Demographic data, Expanded Disability Status Scale (EDSS) scores, number of ON relapses, type of first relapse (optic nerve or other region), and disease duration were recorded for all patients. None of the participants had coexisting systemic, neurological, autoimmune, or infectious disorders. No patients had experienced a relapse or received immunosuppressive treatment within 3 months prior to blood sample collection. In addition, none had received B-cell-depleting therapies before their current treatment. All patients were receiving immunomodulatory therapy, including interferon-β, fingolimod, dimethyl fumarate, or teriflunomide. To evaluate cognitive function, participants underwent standardized neuropsychological assessments in Turkish, including the Selective Reminding Test, 10/36 Spatial Recall Test, and Symbol Digit Modalities Test (SDMT), which assess verbal memory, visual memory, and sustained attention/information processing speed, respectively. Test selection and interpretation followed Turkish MS cognitive assessment literature, based on Brief Repeatable Battery of Neuropsychological Tests related norms and validated Turkish adaptation procedures (29). For the SDMT, Turkish validation studies support standardized administration in MS, including the oral version, with the number of correct responses recorded over 90 seconds (30). All neuropsychological assessments were performed by an evaluator blinded to clinical diagnosis and magnetic resonance imaging findings. Motor function was additionally assessed using the 9-Hole Peg Test and the timed 8-meter walk test. Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkiye, Haydarpasa Numune Education and Research Hospital, (decision no: HNEAH-KAEK2018/KK/31, date: 12.03.2018). Written informed consent was obtained from all participants.

Real-Time (RT)-Quantitative Polymerase Chain Reaction (qPCR)

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll density gradient centrifugation, resuspended in freezing medium, and stored in liquid nitrogen (1×10^6 cells in fetal bovine

serum supplemented with 10% dimethyl sulfoxide). Total RNA was extracted from frozen PBMCs using the RNeasy Mini Plus Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. RNA purity and concentration were assessed using a spectrophotometer. Samples with an optical density ratio at 260/280 nm between 1.9 and 2.1 were included in the analysis. Total RNA was reverse-transcribed into complementary DNA (cDNA) using the Transcriptor First Strand cDNA Synthesis Kit (Roche, Basel, Switzerland). RT-qPCR was performed using the Agilent Technologies Mx3005P qPCR system with SYBR Green Master Mix (LightCycler® 480 SYBR Green I Master, Roche, Basel, Switzerland) and gene-specific primers obtained from DNA Technology® (DN-10) (Table 1). Relative gene expression was calculated using the $2^{-\Delta\Delta CT}$ method, with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) serving as the internal normalization control.

Flow Cytometry

To identify the proportions of major immune cell subsets in peripheral blood, frozen PBMCs were thawed and washed in complete medium (supplemented with 10% fetal calf serum, 1% minimum essential medium vitamins, 1% L-glutamine, 1% sodium pyruvate, 1% non-essential amino acids, and 1% penicillin-streptomycin). Cells were stained with fluorescently labeled monoclonal antibodies [anti-human CD3-FITC, CD16/CD56-PE, CD19-APC (Becton Dickinson (BD), Multitest™), CD27-FITC, CD24-PerCP, CD38-Alexa Fluor 700, IgD-APC/Cy7, and CD138-PE (BioLegend)]. Subsequently, six-color immunofluorescence analysis was performed using a BD FACSAria II flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). Data were analyzed using CellQuest and FlowJo v7.6.5 software. The gating strategy for flow cytometry analysis is shown in Supplementary Figures 1 and 2.

Table 1. Primers used in real-time PCR studies

Gene	Primer sequence
BLK F	TAGATCACAGGGTCGGAAGG
BLK R	GGCAGCGGATCTTATAGTGC
TGFB F	GTACCTGAACCCGTGTTGCT
TGFB R	CAACTCCGGTGACATCAAAA
BANK1 F	GTTCAGACCCCGCACATATT
BANK1 R	CCTTCCCCTTCCATTTCATT
ATP1B3 F	AATCGCTACCAGGAACGCAA
ATP1B3 R	CGATCTCCACTCCTTCCAGC
GAPDH F	CCATCAATGACCCCTTCATT
GAPDH R	TTGACGGTGCCATGGAATTT

BLK: B-lymphoid tyrosine kinase, BANK1: B-cell scaffold protein with ankyrin repeats 1, TGFB: Transforming growth factor beta, ATP1B3: ATPase Na+/K+ transporting subunit beta 3, F: Forward, R: Reverse, PCR: Polymerase chain reaction

Statistical Analysis

Data distribution was assessed using the Kolmogorov-Smirnov test to evaluate normality. Because most variables were non-normally distributed, the Mann-Whitney U test was used for comparisons of continuous variables. Categorical variables were analyzed using the chi-square test. Spearman's rank correlation coefficient was used to assess associations between variables. The Bonferroni correction was applied for multiple comparisons. Statistical significance was set at $p<0.05$.

Results

Comparison of Clinical Features of the Study Groups

Patients were stratified into groups with and without ON at disease onset. No significant differences were observed between the two groups in age, sex, disease duration, treatment type, or EDSS scores. However, patients with ON onset had a significantly higher number of ON attacks during the disease course. Regarding cognitive and motor function tests, only SDMT scores differed significantly between groups (Table 2). After Bonferroni correction ($p<0.0062$), only the difference in the number of ON attacks remained statistically significant.

Flow Cytometry and PCR Results

In peripheral blood immunophenotyping of patients with MS, no clear association was observed between groups with and without ON onset in the proportions of T-cells, B-cells, NK-cells, regulatory B-cells (Bregs), plasmablasts, plasma cells, or memory B-cells (Figure 1).

In the next step, expression levels of B-cell-associated genes involved in B lymphocyte proliferation were measured using qPCR. No significant differences were observed in the mRNA expression levels of BLK, BANK1, or TGFB between the two groups. In contrast, ATP1B3 expression was significantly lower in patients with ON onset compared with those without ON onset ($p=0.011$) (Figure 2). This difference remained below the Bonferroni-adjusted significance threshold ($p<0.0125$).

Spearman's correlation analysis was performed to assess potential associations between clinical and cognitive parameters listed in Table 2 and expression levels of B-cell-associated intracellular molecules. A positive correlation was observed only between BLK expression and 8-meter walk test time ($p=0.009$, $R=0.644$). This correlation did not survive the Bonferroni-corrected threshold ($p<0.001$) and was therefore considered a chance finding. No significant correlations were observed between B-cell subset proportions and clinical or cognitive parameters in patients with MS.

Discussion

In our study, no significant correlations were observed between peripheral blood B-cell subset proportions and clinical measures of disability or cognitive performance in patients

Table 2. Comparison of MS patients with and without ON* at disease onset				
	With ON at disease onset (n=10)	**Without ON at disease onset (n=16)**	**p-value**	**Cohen's d-value**
Age	42.5 (11.2)	41.5 (6.7)	0.499	0.1
Gender (F/M)	7/3	13/3	0.508	NA
EDSS	2.5 (1.5)	3.0 (2.5)	0.128	0.4
Number of ON attacks	3.0 (2.2)	1.0 (2.0)	**0.006**	1.0
Disease duration	12.0 (6.5)	12.0 (5.0)	0.322	0.3
Immunomodulating treatment types **Interferon-β** **Fingolimod** **Dimethyl fumarate** **Teriflunomide**	 3 3 2 2	 4 5 4 3	0.988	NA
Selective recall test	9.0 (2.2)	8.0 (3.0)	0.069	0.5
Spatial recall test	4.5 (3.2)	4.0 (3.0)	0.477	0.0
Symbol Digit Modalities Test	44.0 (11.0)	32.0 (14.0)	**0.014**	0.9
9-hole peg test (seconds)	22.0 (7.0)	22.0 (7.7)	0.369	0.2
8-meter walk test (seconds)	7.5 (3.2)	8.5 (6.0)	0.108	0.4

Bold characters indicate statistically significant differences before Bonferroni correction. Continuous and categorical variables were compared with Mann-Whitney U and chi-square tests, respectively. Continuous variables are denoted as median (interquartile range)

*: Painful vision loss or blurring that lasts for at least 24 hours, with no other identifiable cause, was considered an episode of ON, ON: Optic neuritis, F: Female, M: Male, EDSS: Expanded Disability Status Scale, NA: Not applicable

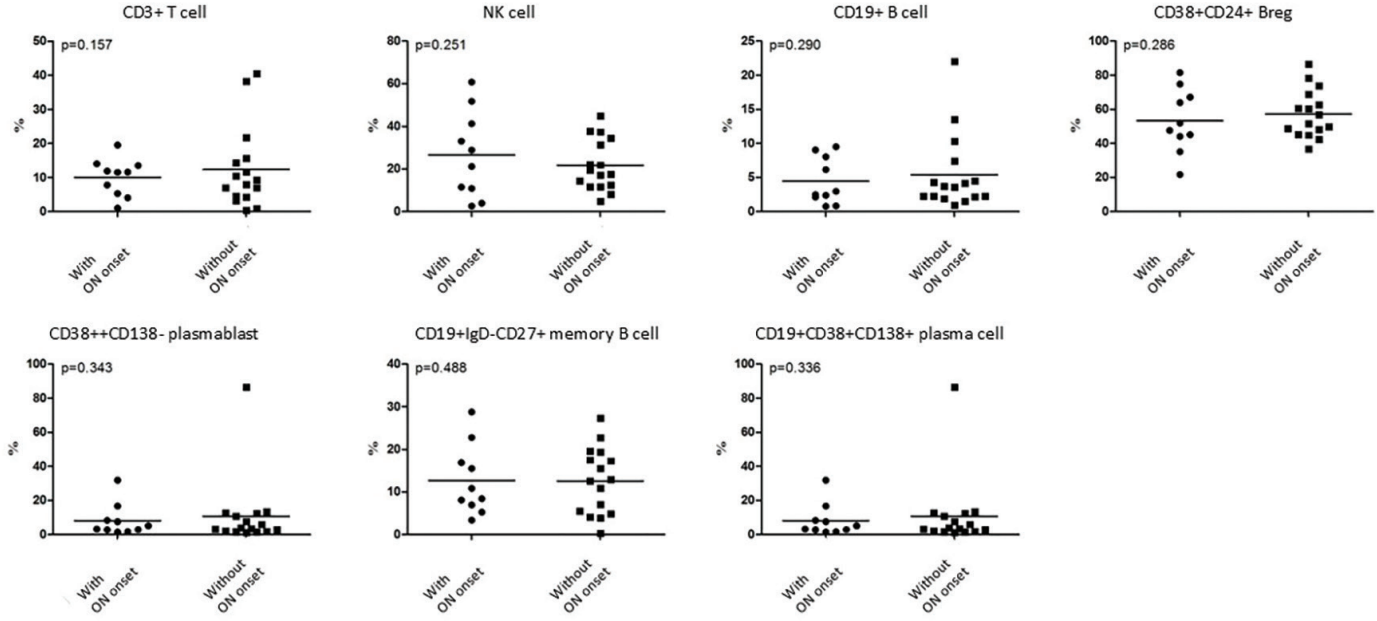


Figure 1. Comparison of peripheral blood immune cell subset ratios in patients with MS with and without ON onset. P-values are indicated in the upper left corner; horizontal lines represent median values

MS: Multiple sclerosis, ON: Optic neuritis, IgD: Immunoglobulin D

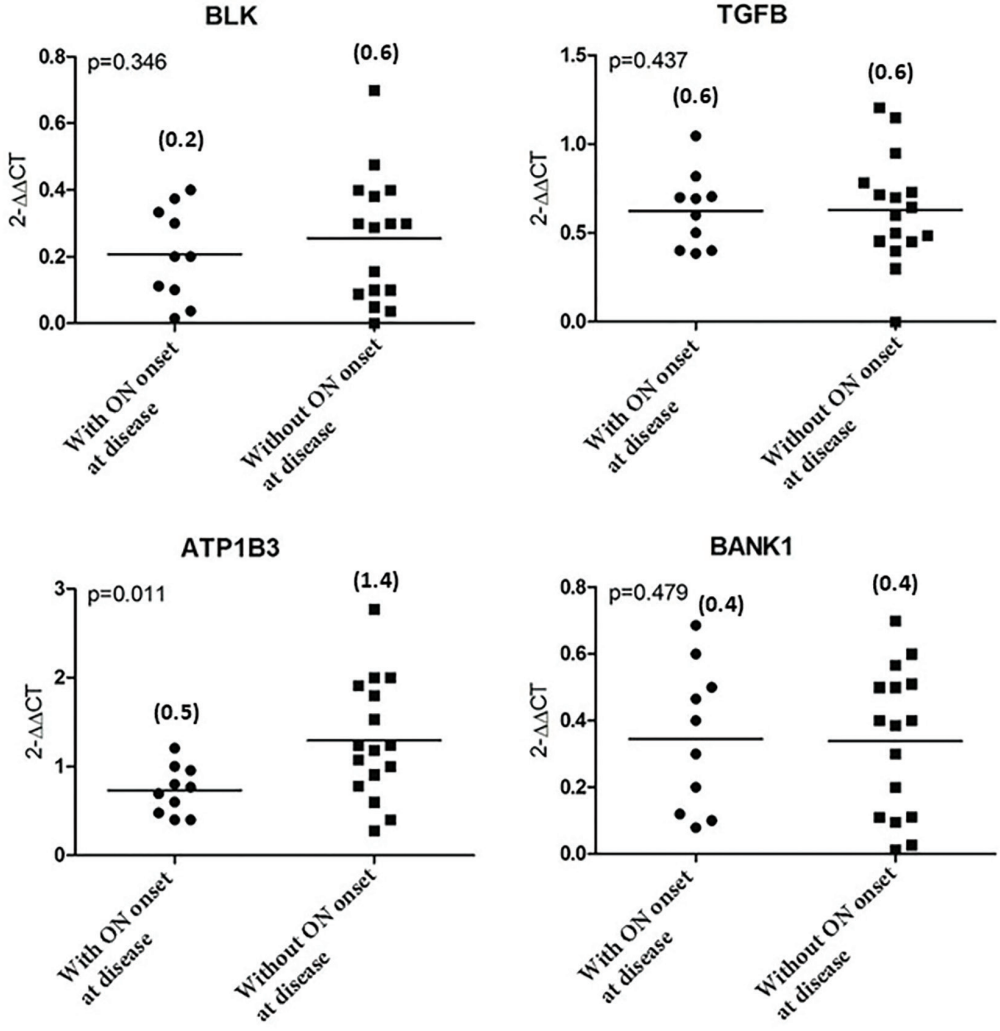


Figure 2. Comparison of expression levels of B-cell-associated genes in MS patients with and without ON onset. P-values are indicated in the upper left corner; horizontal lines represent median values, and values in parentheses indicate interquartile ranges

BLK: *B-lymphoid tyrosine kinase, BANK1: B-cell scaffold protein with ankyrin repeats 1, TGFB: Transforming growth factor beta, ATP1B3: ATPase Na^+/K^+ transporting subunit beta 3*, ON: Optic neuritis

with MS with ON-onset. These findings suggest that alterations in peripheral B-cell subset distribution do not directly reflect the degree of neurological or cognitive impairment in MS. Specifically, variations in the relative frequencies of naïve, memory, and regulatory B-cell populations in peripheral blood were not associated with EDSS scores or measures of cognitive processing efficiency.

Moreover, when participants were stratified according to disease onset type, no significant differences were observed in peripheral B-cell subset distributions between patients with ON-onset MS and those without ON-onset MS. Collectively, these findings indicate that peripheral blood immunophenotyping provides only a partial representation of the complex immune processes underlying disease activity and disability progression in MS.

In a previous study, significant differences were reported in the expression levels of *CR2, BLNK, RASGRP3*, and *BLK* genes between patients with MS and healthy controls. Correlation analysis further demonstrated that these genes had strong diagnostic utility (31). Another study reported that BLK expression was lower in patients with neuromyelitis optica compared with healthy individuals; however, during untreated acute attacks, BLK levels increased by 1.8-fold relative to healthy controls (32). In addition, reduced BLK expression has been associated with the development of immune complex-mediated glomerulonephritis in experimental models (33).

When gene expression levels were compared between patients with and without ON-onset MS, only *ATP1B3* expression was significantly lower in patients with ON-onset MS. In other autoimmune diseases, such as SLE, Na^+/K^+-ATPase activity

has been associated with increased B-cell survival and B-cell-mediated tissue damage (34). ATP1B3 has also been shown to enhance interferon-α production in lymphocytes (35). However, there is insufficient evidence to suggest that ATP1B3 is involved in antigen presentation or proinflammatory cytokine production, which are additional key functions of B-cells in autoimmune conditions. The reduced expression of this gene, which is implicated in B lymphocyte expansion, in patients with ON-onset MS may therefore suggest a less prominent B-cell-mediated pathophysiology in this subgroup of MS. This interpretation is supported by reports emphasizing the predominance of T-cells in ON (36,37). However, these findings should be interpreted with caution, as peripheral blood lymphocyte expression profiles may not accurately reflect those of lymphocytes in the CNS, which are more directly relevant to the pathophysiology of ON and MS. Therefore, further studies—preferably using CSF lymphocytes—are needed to validate these hypotheses regarding the role of ATP1B3 in MS pathogenesis.

However, ATP1B3 expression may potentially serve as a prognostic biomarker in patients with MS. Many currently used MS biomarkers are either B-cell derived (e.g., OCBs and kappa free light chains) or involved in B-cell chemotaxis to the CNS (e.g., CXCL13) (38,39). Thus, if future studies with larger MS cohorts reproduce our findings, ATP1B3 may be considered for inclusion in panels of B-cell-related biomarkers used to support MS diagnosis and prognosis assessment.

Study Limitations

We acknowledge several limitations of this study, including the small sample size (particularly for a gene expression study aimed at identifying prognostic biomarkers), the absence of healthy controls, and the single-center, cross-sectional design, all of which may limit the generalizability and interpretation of the findings. Therefore, our results should be considered preliminary observations suggesting a potential association and highlighting the need for validation in larger, independent cohorts. Additionally, due to the cross-sectional design, we were limited to correlating current gene expression levels with the type of first attack, which occurred in the past. Because gene expression may vary significantly throughout the disease course, we cannot confidently conclude that ATP1B3 expression levels were altered at disease onset. Longitudinal gene expression studies are therefore needed to address this limitation. Finally, although immunomodulatory treatment type may act as a potential confounder, this effect could not be statistically assessed due to the small number of patients per treatment group, resulting in limited statistical power.

Conclusion

Our preliminary findings suggest a putative association between ATP1B3 expression and ON onset in MS. This supports the notion that future research should integrate peripheral immunophenotyping with CSF analyses, neuroimaging markers, and longitudinal clinical data to provide a more comprehensive understanding of the immune mechanisms underlying disability accumulation. Validation of these findings in larger cohorts, including both MS patients and healthy controls, will be essential to confirm their relevance and clarify their potential as prognostic biomarkers.

Supplementary Figures 1 and 2: https://d2v96fxpocvxx.cloudfront.net/dd8262ff-66e6-418e-b233-a064eb1ea82f/content-images/d37ee4e4-3c98-493e-8c05-62d3236a8a3a.pdf

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkiye, Haydarpasa Numune Education and Research Hospital, (decision no: HNEAH-KAEK2018/KK/31, date: 12.03.2018).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.F., D.O.Y., R.T., E.A., Concept: Z.F., V.Y., R.T., E.T., Design: Z.F., V.Y., R.T., E.T., Data Collection or Processing: Z.F., D.O.Y., R.T., E.A., Analysis or Interpretation: Z.F., V.Y., E.T., E.A., Literature Search: Z.F., D.O.Y., Writing: Z.F., D.O.Y. Z.F., D.O.Y., V.Y., R.T., E.T., E.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.

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DOI: 10.4274/jmsr.galenos.2026.2026-2-1

J Mult Scler Res 2026;6:46-49

CASE REPORT

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Multidomain Functional Improvement in a Wheelchair-dependent Patient with Very Early-onset Secondary Progressive Multiple Sclerosis Following a Device-free SONAPS Program: A Case Report

Hossein Najafpour, Azam Riazat

SONAPS Clinic, Tehran, Iran

Abstract

Clinically meaningful functional improvement in advanced secondary progressive multiple sclerosis (SPMS) is uncommon. A 34-year-old man with very early-onset multiple sclerosis, currently classified as SPMS, completed a device-free, non-pharmacological SONAPS program (19 sessions over approximately 120-150 days). At baseline, the patient was fully wheelchair-dependent and exhibited severe multidomain impairment. Composite disability assessed using the Composite Disability and Functional Status Scale improved from 38/50 to 15/50. Improvements were observed across physical, functional, and psychological domains and were accompanied by gains in muscle strength (upper limbs: 3→4; lower limbs: 0→2, Medical Research Council Scale). Functional improvements were corroborated by video-documented observations and supported by descriptive graphical representations. No adverse events were reported. This hypothesis-generating observation suggests that multidomain functional improvement may be achievable in advanced SPMS. However, controlled and blinded studies are required to confirm these findings.

Keywords: Secondary progressive multiple sclerosis, wheelchair dependence, SONAPS program, non-pharmacological intervention, multidomain functional improvement

Introduction

Secondary progressive multiple sclerosis (SPMS) is characterized by the progressive accumulation of neurological disability with limited potential for recovery (1-3). Functional improvement in advanced disease, particularly among patients with prolonged wheelchair dependence, is considered uncommon (1).

Non-pharmacological interventions in progressive MS typically demonstrate modest and domain-specific effects (4). Reports describing rapid multidomain improvement remain rare.

The somatic-neuropsychological adaptive programming system (SONAPS) framework is a non-pharmacological, non-invasive, and device-free intervention designed to facilitate adaptive regulation across physical-structural-functional (PSF) and psychological-behavioral-cognitive (PBC) domains.

Case Report

A 34-year-old male diagnosed with multiple sclerosis at 16 years of age following an initial episode of optic neuritis presented with progressive neurological decline consistent with SPMS (2). The disease duration was approximately 16 years. The patient had been wheelchair-dependent for approximately four years prior to presentation. A schematic overview of the patient's clinical course is presented in Figure 1.

Written informed consent was obtained from the patient for the publication of this case report, including accompanying clinical images and videos.

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Received: 16.02.2026 **Accepted:** 15.05.2026 **Publication Date:** 03.06.2026

Cite this article as: Najafpour H, Riazat A. Multidomain functional improvement in a wheelchair-dependent patient with very early-onset secondary progressive multiple sclerosis following a device-free SONAPS program: a case report. J Mult Scler Res. 2026;6:46-49

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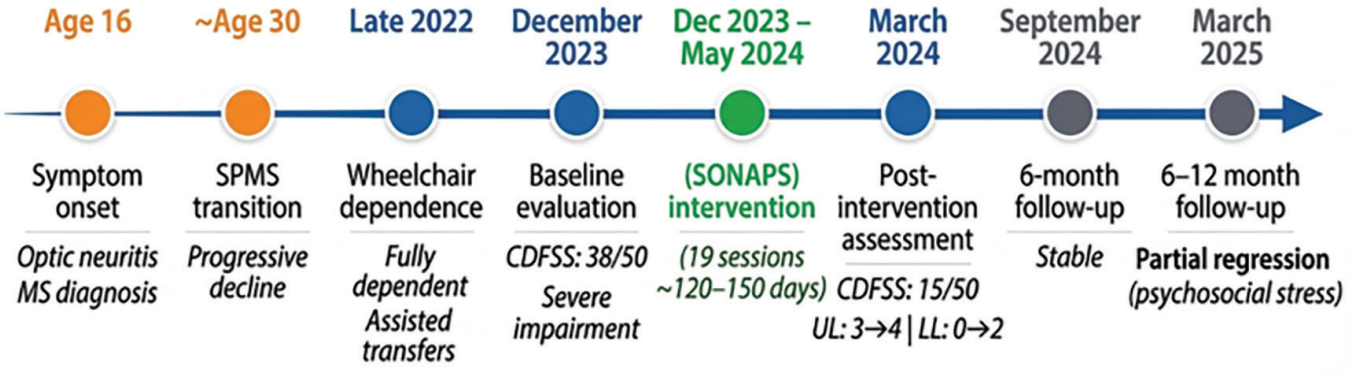


Figure 1. CARE-compliant timeline of the patient's clinical course from symptom onset through the 12-month follow-up after the SONAPS intervention

SONAPS: Somatic-neuropsychological adaptive programming system, CDFSS: Composite Disability and Functional Status Scale

Baseline Symptoms

- Severe lower-limb weakness and spasticity
- Upper-limb tremor
- Neuropathic pain
- Urinary dysfunction
- Severe insomnia
- Cognitive fatigue and anxiety

Neurological Examination

- Lower-limb strength: 0/5 bilaterally
- Upper-limb strength: 3/5
- Positive bilateral Babinski signs
- Impaired trunk control and balance

Baseline Disability

Composite Disability and Functional Status Scale (CDFSS) score: 38/50

SONAPS Intervention

The patient completed 19 sessions (approximately 120 minutes each) over a period of 90-110 days.

SONAPS is a structured, non-invasive, and device-free intervention that operates within an adaptive closed-loop clinical framework integrating PSF and PBC domains. The intervention content is dynamically adjusted according to patient responses during structured tasks.

The intervention was entirely device-free and consisted of structured, task-oriented sensorimotor and behavioral components.

Core elements included guided postural adjustments, coordination-focused motor tasks, graded muscle activation, and real-time therapist feedback based on observed patient responses.

No external devices, electrical stimulation, or pharmacological modifications were used during the intervention period.

Session Structure

Each session included the following components:

- Interval symptom review
- Structured assessment using PSF and PBC anchors
- Individualized multimodal intervention targeting:
  - Postural control
  - Sensorimotor integration
  - Coordination
  - Fatigue modulation
  - Behavioral and emotional regulation
- Adaptive task sequencing
- Post-session reassessment

Although individualized, all sessions followed a consistent structural framework to support conceptual reproducibility.

Outcome Measures

Primary Outcome

CDFSS

Secondary Outcomes

Muscle strength (Medical Research Council MRC scale)

Patient-reported symptom severity (0-10 scale)

Results

Composite disability improved from 38/50 to 15/50, representing an approximately 61% reduction (Table 1).

Subscale Changes

Physical: 19 → 8

Cognitive/psychological: 11 → 1

Functional: 8 → 6

Muscle Strength

Upper limbs: 3 → 4

Lower limbs: 0 → 2

Table 1. Prespecified outcomes before and after the SONAPS intervention

Domain	Measure	Baseline	Post
Disability	CDFSS	38	15
Strength	MRC upper limb	3	4
	MRC lower limb	0	2
PSF	Spasticity (0-10)	10	6
	Tremor (0-10)	10	4
	Balance limitation (0-10)	10	6
	Neuropathic pain (0-10)	9	5
PBC	Anxiety (0-10)	9	5
	Depression (0-10)	8	5
Cognition	Brain fog (0-10)	10	4

CDFSS: Composite Disability and Functional Status Scale, MRC: Medical Research Council Scale, PSF: Physical-structural-functional, PBC: Psychological-behavioral-cognitive

Functional Changes

Improved assisted sit-to-stand ability

Improved trunk stability

Improved fine motor control

Representative images of the patient's functional status before and after the intervention are presented in Supplementary Figures 1 and 2.

Changes in symptom severity and CDFSS subscale scores are presented in Figures 2A and B. No adverse events were observed.

Follow-up

At 6 months: Clinical status remained stable.

Between 6 and 12 months: Partial regression was observed during periods of psychosocial stress.

All outcomes should be interpreted as exploratory given the absence of validated measurement instruments.

Discussion

Functional improvement in advanced SPMS is uncommon due to progressive neurodegenerative mechanisms and limited recovery potential (1,3).

In this case, multidomain improvement was observed; however, causal inference cannot be established. Alternative explanations—including behavioral engagement, expectancy effects, and measurement bias—should also be considered.

The absence of standardized outcome measures [e.g., Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW),

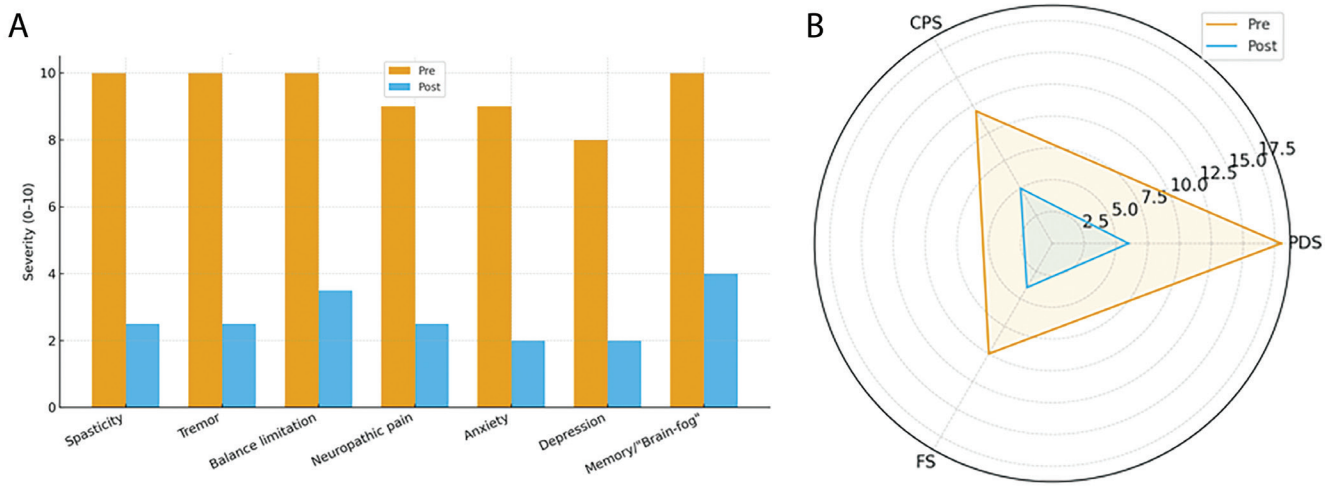


Figure 2. Changes in symptom severity and CDFSS subscale scores. **(A)** Changes in selected PSF and PBC symptom severity scores before and after the intervention (bar chart). **(B)** Changes in CDFSS subscale scores before and after the intervention (line graph)

PSF: Physical-structural-functional, PBC: Psychological-behavioral-cognitive, CDFSS: Composite Disability and Functional Status Scale

and Nine-Hole Peg Test (9HPT), baseline magnetic resonance imaging (MRI) data, and validated assessment tools further limits interpretability (4).

Neurobiological constraints related to aging and neuroplasticity may also limit recovery potential (5). Mechanistic interpretations remain speculative and require validation using objective neurophysiological methods, such as electroencephalography- or magnetoencephalography-based connectivity analyses (6,7).

Observed functional improvements were limited to assisted postural transitions and trunk control and did not include independent ambulation.

Study Limitations

Single-case, non-blinded design.

Absence of standardized outcome measures (EDSS, T25FW, 9HPT, and cognitive batteries).

No baseline MRI assessment.

Use of a non-validated CDFSS.

Reliance on subjective symptom ratings.

Conclusion

Multidomain functional improvement was observed in this case of advanced SPMS following a device-free intervention. These findings are exploratory in nature and require confirmation in controlled, blinded studies.

Ethics

Informed Consent: Written informed consent was obtained from the patient and participating family members for the publication of clinical information and video documentation.

Data Availability Statement

The clinical protocols and de-identified data supporting the findings of this case report are available from the corresponding author upon reasonable request. the SONAPS Clinic welcomes scientific inquiries and independent verification of the observed functional outcomes to support the development of structured non-pharmacological interventions in advanced MS.

Footnotes

Authorship Contributions

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

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

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

Supplementary Figures 1 and 2: https://d2v96fxpocvxx.cloudfront.net/17d041fe-057c-4c8e-a75d-948e33c0152a/content-images/75b54567-8dfe-44ef-a892-9ef175f61658.pdf

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DOI: 10.4274/jmsr.galenos.2026.2026-2-2

J Mult Scler Res 2026;6:50-53

CASE REPORT

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Concurrent Trigeminal Nerve and Cauda Equina Root Enhancement in Multiple Sclerosis: A Rare Case Report

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Abstract

Peripheral nerve and nerve root involvement are rare manifestations of multiple sclerosis (MS) and may pose diagnostic challenges by mimicking other inflammatory or systemic disorders. We report the case of a 26-year-old man who presented with acute right-sided facial numbness, mild hearing impairment, and imbalance. Brain magnetic resonance imaging (MRI) demonstrated demyelinating plaques in the pons and the periventricular and subcortical white matter, accompanied by contrast enhancement of the cisternal and intrapontine segments of the right trigeminal nerve. Spinal MRI revealed focal cervical and thoracic cord lesions with symmetric enhancement of the proximal cauda equina nerve roots. Cerebrospinal fluid analysis showed a normal cell count, an immunoglobulin G index of 0.68, and a type 3 oligoclonal band pattern. The patient demonstrated marked clinical and radiologic improvement following treatment with high-dose intravenous methylprednisolone and was subsequently started on disease-modifying therapy. This case highlights a rare radiologic manifestation of MS and underscores the importance of considering MS in the differential diagnosis of concurrent cranial nerve and cauda equina root enhancement.

Keywords: Multiple sclerosis, trigeminal nerve, cauda equina, cranial nerve enhancement, magnetic resonance imaging

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS). Magnetic resonance imaging (MRI) plays a crucial role not only in establishing the diagnosis but also in excluding imaging mimics, particularly when atypical findings are encountered (1). Trigeminal nerve involvement is uncommon and may occur with or without classic trigeminal neuralgia (2,3). Spinal cord involvement in MS typically presents as short-segment lesions, which may help distinguish MS from other demyelinating disorders (4). Cranial nerve enhancement has been increasingly recognized with the use of high-resolution MRI, and a pattern-based approach can aid in differentiating demyelinating involvement from infectious, neoplastic, or granulomatous etiologies (5). In contrast, cauda equina nerve root enhancement is exceedingly rare in MS and more commonly suggests infectious, granulomatous, neoplastic, or systemic autoimmune conditions (4). We present a rare case of MS with concurrent trigeminal nerve and proximal cauda equina root enhancement and discuss the key differential diagnostic considerations.

Case Report

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

A 26-year-old man presented with a 1-week history of right-sided facial numbness accompanied by mild right-sided hearing impairment, facial heaviness, imbalance, and fatigue. Neurologic examination revealed hypoesthesia in the distribution of the right trigeminal nerve, with no other focal neurologic deficits.

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Received: 03.03.2026 **Accepted:** 24.06.2026 **Publication Date:** 13.07.2026

Cite this article as: Cetindamar T, Arıcı Duz O, Cila A. Concurrent trigeminal nerve and cauda equina root enhancement in multiple sclerosis: a rare case report. J Mult Scler Res. 2026;6:50-53

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Post-contrast MRI demonstrated linear enhancement involving the cisternal and intrapontine segments of the right trigeminal nerve (Figure 1A and 1B). Brain MRI revealed multiple demyelinating plaques in the periventricular, subcortical, and pontine regions (Figure 2A and 2B). Spinal MRI demonstrated focal lesions in the cervical and thoracic spinal cord (Figure 3A and 3B), along with symmetric enhancement of the proximal cauda equina nerve roots (Figure 3C and 3D).

Cerebrospinal fluid analysis revealed a normal cell count without pleocytosis, an immunoglobulin G (IgG) index of 0.68, and a type 3 oligoclonal band pattern characterized by identical oligoclonal IgG bands in both serum and cerebrospinal fluid, together with additional cerebrospinal fluid-restricted bands. Serum angiotensin-converting enzyme levels were within normal limits. Antinuclear antibody testing showed weak positivity (1:100), whereas anti-double-stranded DNA antibodies, the extractable nuclear antigen panel, anti-aquaporin-4 antibodies, and anti-myelin oligodendrocyte glycoprotein antibodies were negative. Additional laboratory investigations performed to exclude infectious, systemic inflammatory, and autoimmune etiologies were unremarkable.

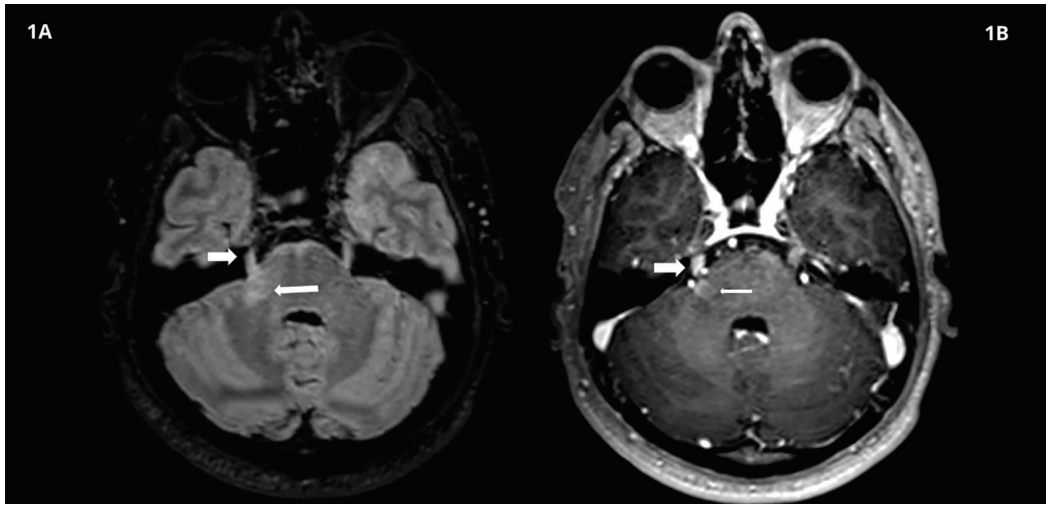


Figure 1. Brain MRI demonstrating trigeminal nerve involvement

(A) Axial FLAIR image showing thickening and edema of the cisternal segment of the right trigeminal nerve (thick arrow) and an active demyelinating plaque along the intrapontine pathway (thin arrow). (B) Post-contrast T1-weighted image demonstrating enhancement of both the cisternal segment of the trigeminal nerve (thick arrow) and the demyelinating plaque (thin arrow). Subpial plaques along the anterior pons show no contrast enhancement

MRI: Magnetic resonance imaging

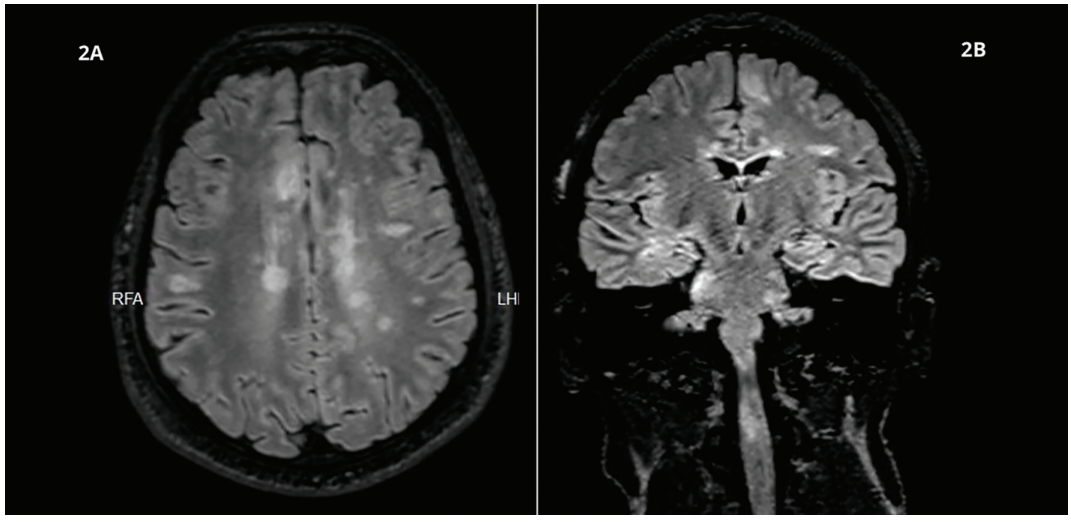


Figure 2. Cerebral demyelinating plaques

(A) Axial FLAIR image showing multiple demyelinating plaques in the periventricular, centrum semiovale, and subcortical regions. (B) Coronal FLAIR image demonstrating demyelinating plaques involving the cerebral parenchyma, brainstem, and cervical spinal cord

FLAIR: Fluid-attenuated inversion recovery

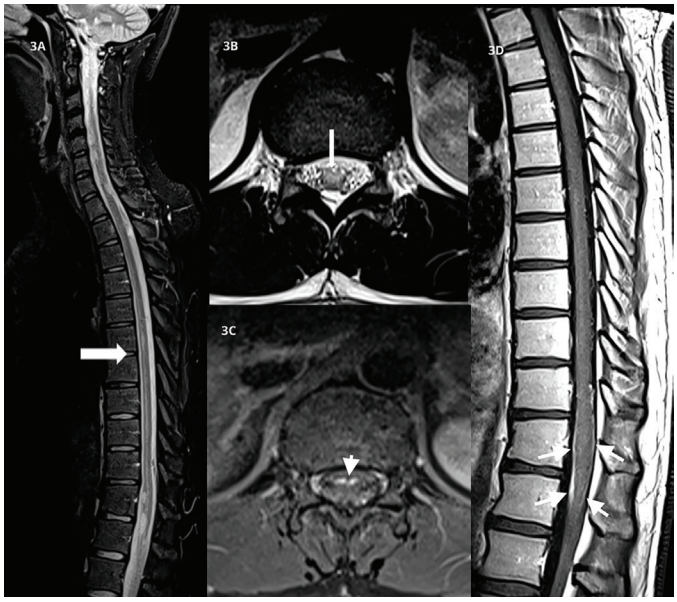


Figure 3. Spinal MRI demonstrating spinal cord and cauda equina involvement

(A) Sagittal STIR image showing extensive demyelinating plaques and edema (arrow) along the anterior subpial surface of the conus medullaris. (B) Axial T2-weighted turbo spin-echo image showing a conus medullaris plaque (arrow) localized to the anterior half of the spinal cord. (C,D) Post-contrast axial and sagittal images demonstrating symmetric enhancement of the proximal cauda equina nerve roots (arrows)

STIR: Short-tau inversion-recovery

The patient was treated with intravenous methylprednisolone (1 g/day for 7 days), resulting in near-complete clinical recovery. Follow-up MRI demonstrated resolution of the trigeminal nerve and cauda equina root enhancement. Disease-modifying therapy with ocrelizumab was subsequently initiated.

Discussion

Cranial nerve enhancement in MS is uncommon but is being increasingly recognized with the widespread use of high-resolution MRI. Trigeminal nerve involvement most often reflects inflammatory demyelination at the root entry zone or cisternal segment and may occur even in the absence of trigeminal neuralgia (2,3). A pattern-based approach to cranial nerve enhancement is essential for distinguishing demyelinating involvement from infectious, neoplastic, and granulomatous etiologies (5).

Spinal cord lesions in MS are typically short-segment and peripherally located, most commonly involving the cervical and thoracic spinal cord. This characteristic distribution can aid in differentiating MS from other antibody-mediated demyelinating disorders (4). Although cauda equina root enhancement is rare in MS, its coexistence with cranial nerve enhancement necessitates careful exclusion of alternative diagnoses, including connective tissue diseases and overlap syndromes (6,7).

Although MS is classically defined as a demyelinating disease of the CNS, pathologic and imaging studies suggest that inflammatory activity may extend beyond conventional CNS boundaries, particularly at sites where central and peripheral myelin interface. These transitional regions, such as the root entry zones of cranial and spinal nerves, may be especially vulnerable to inflammatory infiltration and demyelination. In addition, perivascular inflammation, blood-brain barrier disruption, and immune-mediated processes involving both adaptive and innate immune responses have been implicated in lesion formation and extension in MS. Collectively, these mechanisms may provide a plausible explanation for the rare occurrence of nerve root enhancement, including cauda equina involvement, in otherwise typical cases of MS (8).

Previous reports have described cranial nerve enhancement in MS, most commonly involving the trigeminal nerve (9), as well as occasional peripheral nerve or nerve root involvement in atypical presentations (6,7). In a large MRI cohort, cranial nerve enhancement was observed in 8.2% of patients, with trigeminal nerve involvement representing the most frequent finding (9). However, the simultaneous presence of both trigeminal nerve enhancement and cauda equina root involvement has rarely been documented. Compared with previously reported cases, our patient demonstrated a combination of cranial and spinal peripheral involvement in conjunction with typical demyelinating lesions of the brain and spinal cord, thereby expanding the spectrum of atypical radiologic manifestations of MS.

Trigeminal neuralgia is a recognized manifestation of MS, with a pooled prevalence of approximately 3.4% reported in a recent systematic review and meta-analysis (10). Furthermore, cranial nerve enhancement has been associated with greater lesion burden and a more severe disease course, underscoring its potential clinical significance (9). To our knowledge, simultaneous contrast enhancement of the trigeminal nerve and proximal cauda equina nerve roots has rarely been reported in patients with MS.

Conclusion

Concurrent trigeminal nerve and cauda equina root enhancement represents a rare manifestation of active MS. Recognition of this atypical imaging pattern is crucial to avoid misdiagnosis and to ensure timely initiation of appropriate disease-modifying therapy.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of anonymized clinical and radiologic data.

Footnotes

Authorship Contributions

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

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

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

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DOI: 10.4274/jmsr.galenos.2026.2026-5-2

J Mult Scler Res 2026;6:54-56

LETTER to the EDITOR

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SONAPPS: A Spatiotemporal Coherence-based Framework for Adaptive Self-regulatory Rehabilitation - A Hypothesis-generating Conceptual Letter

Hossein Najafpour[1], Sahar Najafpour[2], Azam Riazat[1]

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Keywords: Spatiotemporal coherence, PSF/PBC domain coupling, adaptive rehabilitation, noise taxonomy, practitioner competency, systems neuroscience, non-contact intervention, passive-state rehabilitation, falsifiable framework, validation roadmap

Dear Editor,

The phenotypic heterogeneity observed within diagnostic categories, such as progressive multiple sclerosis (MS) and autism spectrum disorder, wherein patients with the same diagnosis exhibit qualitatively distinct functional profiles and respond differently to identical interventions, challenges rehabilitation frameworks that target domain-specific deficits in isolation (1,2). We propose that this heterogeneity reflects disruptions in spatiotemporal coherence among regulatory contexts rather than isolated structural failures, and that this distinction has direct implications for rehabilitation design.

Self-organizing Neuro-adaptive Personalized Physiological System (SONAPPS) is proposed as a hypothesis-generating framework grounded in a spatiotemporal coherence model of pathology. This model conceptualizes dysfunction as a disruption in the coherent coupling among regulatory contexts—that is, within and across physical-structured functional and psychological-behavioral-cognitive domains—operating across multiple temporal and spatial scales (3,4). This perspective distinguishes SONAPPS from allostasis, which focuses on restoring homeostatic set points, and from conventional cybernetic control models, which rely on externally imposed regulatory correction. Rather than applying external regulatory templates, SONAPPS aims to restore endogenous inter-context coherence—the ability of each regulatory context to accurately represent and coordinate its relationship with all others (Figure 1).

A central feature of the model is a structured noise taxonomy that distinguishes five configurations of spatiotemporal incoherence: isolated intra-context noise, coherent intra-context pathology with inter-context incoherence, propagated noise, compensatory noise, and cross-domain decoupling (3,5). Each configuration is proposed to generate a distinct clinical phenotype and a corresponding prediction regarding intervention sequencing and response trajectories, thereby providing a basis for empirically testable and refutable hypotheses. The temporal dissociation pattern previously reported in MS case observations (6-9) is particularly consistent with cross-domain decoupling, illustrating how the model may generate testable clinical predictions.

We acknowledge concerns regarding the methodological structure of the framework. Operationally, SONAPPS is characterized by three core features: a passive resting state maintained by the patient throughout all sessions (i.e., without

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Received: 20.05.2026 **Accepted:** 22.06.2026 **Publication Date:** 05.08.2026

Cite this article as: Najafpour H, Najafpour S, Riazat A. SONAPPS: a spatiotemporal coherence-based framework for adaptive self-regulatory rehabilitation - a hypothesis-generating conceptual letter. J Mult Scler Res. 2026;6:54-56

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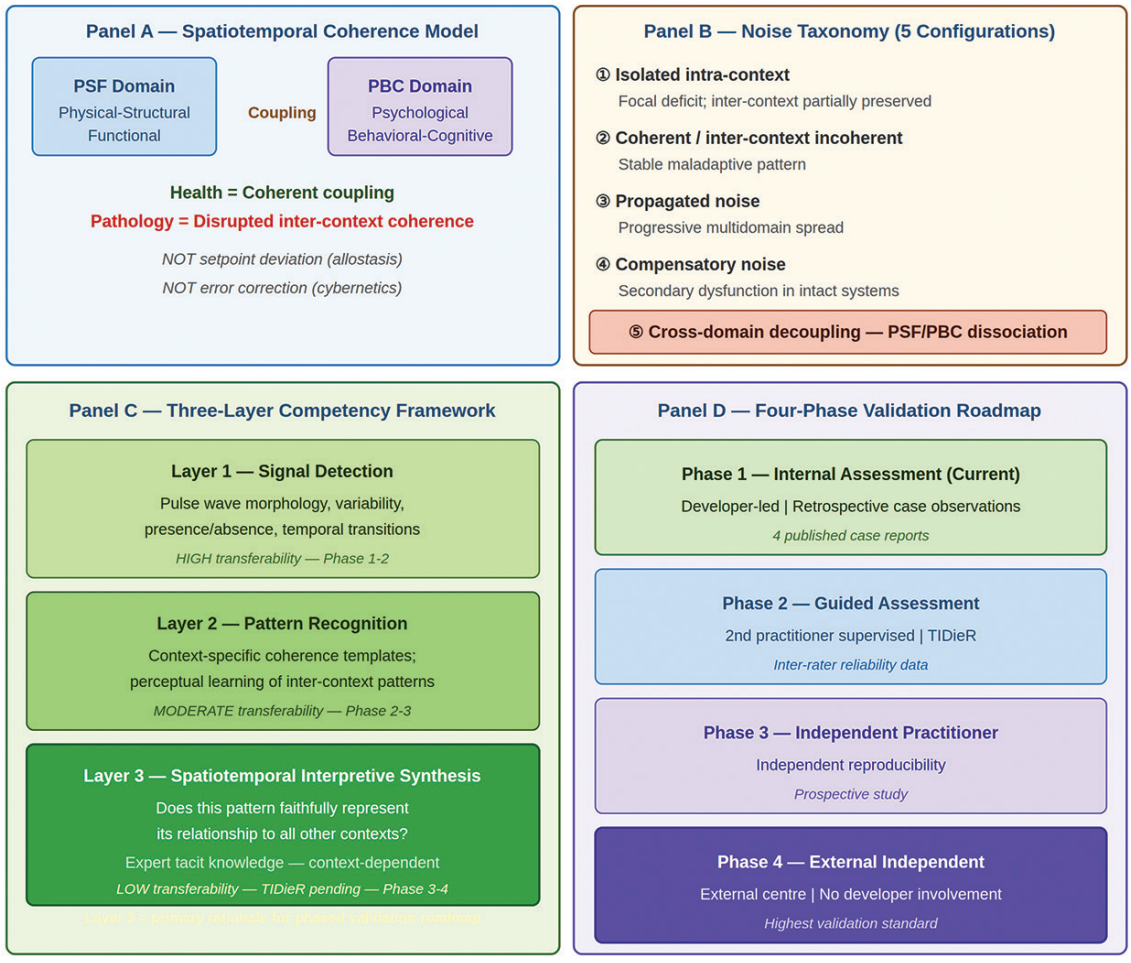


Figure 1. SONAPPS: spatiotemporal coherence-based rehabilitation framework

SONAPPS: Self-organizing Neuro-adaptive Personalized Physiological Systems

volitional movement or exercise), non-contact delivery at a distance of 1-1.5 m, and coherence-targeted modulation using practitioner pulse self-monitoring in conjunction with individualized patient-specific contextual reference materials. The proposed pulse-based assessment mechanism remains hypothetical and currently lacks direct empirical validation; its inclusion reflects the practitioner's clinical observational framework rather than an established physiological measure. Assessment is organized into three hierarchical practitioner competency levels—signal detection, pattern recognition, and spatiotemporal interpretive synthesis—with each level exhibiting distinct transferability characteristics and validation requirements. A TIDieR-compliant protocol description is currently in preparation and will be finalized following completion of Phase 2 of a four-phase validation roadmap (6).

The preliminary case observations (9,10) are anecdotal, uncontrolled, single-case descriptions and should not be interpreted as proof-of-concept findings or evidence of efficacy. They are cited solely as descriptive clinical observations intended to motivate further empirical investigation. The underlying mechanisms remain uncertain. Contemporary literature on predictive processing and active inference (3), multiscale physiological complexity (4), interpersonal physiological synchrony (7), and network neuroscience (5) provides a theoretical basis for the proposed mechanisms; however, these connections remain speculative and require direct empirical validation. Accordingly, the SONAPPS framework is presented not as a validated intervention but as a structured, falsifiable, and empirically testable conceptual architecture that warrants controlled prospective investigation.

In conclusion, SONAPPS proposes the restoration of spatiotemporal coherence as a distinct target for rehabilitation. The framework is differentiated from existing models, grounded in contemporary systems neuroscience, structured around a falsifiable noise taxonomy, and operationally defined through three competency levels supported by a phased validation roadmap. We invite empirical scrutiny and collaboration to evaluate its theoretical and clinical utility.

Footnotes

Authorship Contributions

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

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

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

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DOI: 10.4274/jmsr.galenos.2026.2026-6-1

J Mult Scler Res 2026;6:57-61

CASE REPORT

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Clinician-observed Psychosocial Stress as a Potential Modulator of Functional Durability Following Multidomain Improvement in Progressive Multiple Sclerosis: A Comparative Two-case Report

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Abstract

We report two patients with secondary progressive multiple sclerosis who demonstrated substantial multidomain functional improvement following the Self-organizing Neuro-adaptive Personalized Physiological System, a non-invasive, non-contact, passive-state, hypothesis-generating rehabilitation framework, and subsequently experienced complete functional regression at follow-up. Both patients shared a defining clinical feature: severe, chronic psychosocial stressors that were clinician-observed as persistent and apparently unresolvable throughout and beyond the intervention period. Case 1 (SH, 36F) received 20 sessions, with the Comprehensive Disability and Functional Status Scale (CDFSS) score improving from 26 to 9 before regressing to 18 at the 24-month follow-up. Case 2 (MH, 34M) received 19 sessions, with the CDFSS score improving from 32 to 11 before regressing to 24 at follow-up. In both cases, psychological-behavioral-cognitive domain scores regressed before or concurrently with the decline in physical domain scores. In contrast, four non-relapsing cases from the same observational series did not exhibit similar regression, suggesting that clinician-observed chronic psychosocial burden may be associated with reduced functional durability in progressive multiple sclerosis. This observation is strictly hypothesis-generating.

Keywords: Progressive multiple sclerosis, psychosocial stress; functional durability, psychological-behavioral-cognitive domain, Self-organizing Neuro-adaptive Personalized Physiological System, hypothesis-generating

Introduction

Durable functional improvement in progressive multiple sclerosis (MS) is uncommon, and the factors that determine whether initial rehabilitation gains are sustained or lost remain poorly understood (1,2). Chronic psychosocial stress is a recognized modulator of immune function, autonomic regulation, and neurological outcomes in MS (3,4). Stressful life events have been associated with an increased risk of relapse in relapsing MS (3); however, the relationship between persistent psychosocial burden and the durability of functional recovery following multidomain rehabilitation has not been systematically investigated.

We present two cases of secondary progressive MS (SPMS) in which substantial multidomain functional improvement was followed by complete functional regression at follow-up. A defining clinical feature observed in both cases was the presence of severe, chronic psychosocial stressors that appeared persistent and apparently unresolvable throughout and beyond the intervention period. In both cases, regression in the psychological-behavioral-cognitive (PBC) domain preceded

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Received: 03.06.2026 **Accepted:** 21.07.2026 **Publication Date:** 20.08.2026

Cite this article as: Najafpour H, Riazat A, Najafpour S. Clinician-observed psychosocial stress as a potential modulator of functional durability following multidomain improvement in progressive multiple sclerosis: a comparative two-case report. J Mult Scler Res. 2026;6:57-61

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or paralleled the decline in physical domain function. This comparative observation is presented strictly as a hypothesis-generating clinical signal that requires prospective validation.

Case Report

Written informed consent was obtained from both patients for the publication of this case report, including the accompanying clinical data.

SONAPPS Intervention Description

The Self-organizing Neuro-adaptive Personalized Physiological System (SONAPPS) is a non-invasive, non-pharmacological, non-contact, device-free, hypothesis-generating rehabilitation framework. Throughout all sessions, patients remained in a fully passive resting state, either seated or supine, with no volitional movement, physical exercise, or active behavioral participation required at any time. The practitioner was positioned approximately 1-1.5 m from the patient without making physical contact. Sessions were operationally guided by individualized, patient-specific contextual reference materials compiled from available clinical and biographical information, together with practitioner physiological self-monitoring. Each session lasted approximately 90-120 min. Preliminary clinical observations using this framework have been described in three previously published case reports (5-8). A Template for Intervention Description and Replication (TIDieR)-compliant protocol description is in preparation; the present description represents the most detailed operational account currently available. SONAPPS is presented as a hypothesis-generating framework rather than a validated therapeutic modality.

Outcome Measures

The Comprehensive Disability and Functional Status Scale (CDFSS) is a clinician-administered observational scale developed for use within the SONAPPS framework. It is scored from 0 (no disability) to 50 (maximum disability) across three subscales: physical-structural-functional (PSF; 0-25), PBC (0-15), and functional integration (0-10). The CDFSS has not undergone formal psychometric validation, and no established thresholds for the minimal clinically important difference have been determined. In these cases, it was used as a descriptive within-case monitoring instrument rather than as a validated inferential outcome measure. Lower and upper limb strength were assessed using the Medical Research Council (MRC) scale. Bladder dysfunction was evaluated based on patient self-report at each session and follow-up contact; however, no validated bladder-specific instrument was administered. Psychosocial stressors were characterized through structured clinical observation and interviews conducted at each session, and no validated psychometric instrument (e.g., the Perceived Stress Scale) was used. The Expanded Disability Status Scale (EDSS) was not assessed in either case because both patients were managed retrospectively before the clinic's current prospective assessment protocol was established.

Case 1 (SH) 36-year-old Woman with SPMS

SH first presented in November 2022 with an 18-year history of SPMS diagnosed according to the McDonald criteria. She ambulated with two canes and presented with severe bilateral lower limb weakness (MRC grade 0-1/5), patient-reported bladder dysfunction, fatigue, and a prominent PBC domain burden. She had not received disease-modifying therapy during the preceding year. A defining clinical feature observed by the clinician was the presence of severe, chronic psychosocial stressors that appeared persistent and apparently unresolvable, remaining present at baseline and throughout the intervention and follow-up periods. These stressors were not quantified using validated instruments, and their characterization was based solely on structured clinical observation.

SH underwent 20 SONAPPS sessions between February and June 2023 (approximately 150 days). No changes in medication occurred during the intervention period. The post-intervention assessment was performed after the completion of all 20 sessions.

Outcomes are summarized in Table 1. The CDFSS score improved from 26 to 9 (-65.4%). Lower limb strength improved from MRC grade 0-1/5 to 3/5. The Romberg sign was no longer elicited at the post-intervention assessment. Patient-reported bladder dysfunction resolved according to the patient's report. The PBC domain score improved from 36 to 24. At the 24-month follow-up (June 2025), complete functional regression was documented, with the CDFSS score worsening to 18 and the PBC domain score increasing to 38. Follow-up was conducted through a structured telephone interview, during which the patient reported being unable to return to work and that the psychosocial stressors had persisted.

Case 2 (MH) 34-year-old Man with SPMS

MH first presented in September 2024 with a 14-year history of SPMS. He was wheelchair-dependent and presented with bilateral lower limb paralysis (MRC grade 0/5), severe spasticity, patient-reported bladder dysfunction, prominent compulsive behaviors, and a severe PBC domain burden. He had not received disease-modifying therapy during the preceding period. Clinician-observed psychosocial stressors of considerable magnitude, including major financial litigation, family conflict, and complex personal circumstances, were present throughout and beyond the intervention period. These stressors were not assessed using validated instruments.

MH underwent 19 SONAPPS sessions beginning on December 10, 2024 (approximately 150 days). The post-intervention assessment was performed after completion of the final session. Discontinuation of treatment was attributable not to clinical deterioration but to logistical constraints associated with the ongoing psychosocial burden.

Table 1. Comparative clinical profiles and outcomes of cases SH and MH

Parameter	Case SH (36F)	Case MH (34M)
MS type/duration	SPMS/18 years	SPMS/14 years
First presentation	November 2022	September 2024
Intervention	20 sessions, February–June 2023	19 sessions, December 2024-May 2025
Timing of post-intervention assessment	After session 20 (June 2023)	After session 19 (May 2025)
Baseline CDFSS score	26/50	32/50
Post-intervention CDFSS score	9/50 (-65.4%)	11/50 (-65.6%)
Follow-up CDFSS score	18/50 (regression)	24/50 (regression)
Follow-up assessment method	Structured telephone interview (24-month follow-up)	Structured telephone interview (at follow-up)
Baseline MRC lower limb strength	0-1/5, bilateral	0/5, bilateral
Post-intervention MRC lower limb strength	3/5, bilateral	2-3/5, bilateral
Bladder function (patient-reported)	Resolved according to patient self-report	Partially resolved according to patient self-report
Baseline PBC score	36	43
Post-intervention PBC score	24	22
Follow-up PBC score	38 (regression)	38 (regression)
Psychosocial stressors	Severe; clinician-observed as persistent throughout	Severe; clinician-observed as persistent throughout
Pattern of PBC regression	PBC regression preceded physical regression	PBC regression paralleled physical regression

Notes: EDSS was not assessed because these were retrospective cases managed before implementation of the current prospective assessment protocol. Bladder function was evaluated by patient self-report only. Psychosocial stressors were characterized through structured clinical observation without the use of validated assessment instruments. Red shading indicates regression at follow-up

MS: Multiple sclerosis, CDFSS: Comprehensive Disability and Functional Status Scale (0-50; 0=no disability), PSF: Physical-structural-functional subscale (0-25), SPMS: Secondary progressive multiple sclerosis, PBC: Psychological-behavioral-cognitive subscale (0-15); MRC: Medical research council, EDSS: Expanded Disability Status Scale

Outcomes are summarized in Table 1. The CDFSS score improved from 32 to 11 (-65.6%). Lower limb strength improved bilaterally from MRC grade 0/5 to 2-3/5. Spasticity was assessed by the clinician as markedly reduced. Patient-reported bladder dysfunction partially resolved according to the patient's report. Compulsive behaviors were observed by the clinician to be substantially reduced. The PBC domain score improved from 43 to 22. At follow-up, the CDFSS score worsened to 24, and the PBC domain score increased to 38.

Note on MRC Improvement in a Passive-state Framework

The substantial improvements in MRC lower limb scores observed in both cases are clinically noteworthy because SONAPPS does not incorporate volitional movement or active exercise. The proposed mechanism—that restoration of coherence within the spatiotemporal regulatory network may facilitate neural reorganization without direct motor training—remains hypothetical and has not been established. Alternative explanations, including expectancy effects, assessor expectancy bias, natural fluctuation, and non-specific therapeutic influences, cannot be excluded and are explicitly acknowledged as important limitations of this retrospective, unblinded observational report.

Discussion

These two cases demonstrated a convergent pattern of substantial multidomain improvement followed by complete functional regression at follow-up in the context of clinician-observed, severe, and apparently unresolvable psychosocial stressors. In contrast, four non-relapsing cases showed sustained improvement in the presence of partially resolvable psychosocial stressors (Table 2), generating a specific hypothesis that warrants prospective investigation.

We propose that chronic, persistent psychosocial burden may be associated with reduced functional durability following multidomain improvement in progressive MS, potentially by sustaining dysregulation within the PBC domain, which may in turn undermine gains in the PSF domain through cross-domain regulatory interactions (5). This proposed association is descriptive and observational, and no causal or modulatory relationship can be inferred from this report. The proposed mechanism remains speculative and is consistent with, but not supported by, existing evidence that chronic stress influences autonomic function and neurological outcomes in MS (3,4).

Table 2. Comparison with non-relapsing cases in the same observational series

Case	CDFSS change	Follow-up CDFSS	Follow-up PBC	Psychosocial stressors (clinician-observed)
Case 1 (HY, 52F), SPMS	29→10 (-65.5%)	6 (stable)	24 (stable)	Partially resolvable
Case 2 (SH, 36F), SPMS	26→9 (-65.4%)	18 (regression)	38 (regression)	Persistent
Case 3 (63M), SPMS	43→22 (-48.8%)	37 (stable)	37 (stable)	Partially resolvable
Case 4 (62M), SPMS	41→14 (-65.9%)	12 (stable)	15 (stable)	Partially resolvable
Case 5 (47F), SPMS	35→12 (-65.7%)	14 (stable)	19 (stable)	Partially resolvable
Case 6 (MH, 34M), SPMS	32→11 (-65.6%)	24 (regression)	38 (regression)	Persistent

Note on case selection: Table 2 includes all six consecutive cases managed at the SONAPPS Clinic between 2022 and 2025 for which complete CDFSS and follow-up data were available. No cases were excluded, and case selection was not based on outcomes. The two relapsing cases (SH and MH) and the four non-relapsing cases constitute the complete available dataset for this period

Notes: All six cases represent the complete consecutive dataset from the SONAPPS Clinic for the 2022-2025 study period. Psychosocial stressors were characterized through structured clinical observation without the use of validated assessment instruments. This comparison is strictly observational and hypothesis-generating; therefore, no causal inferences can be drawn

CDFSS: Comprehensive Disability and Functional Status Scale, PBC: Psychological-behavioral-cognitive, SPMS: Secondary progressive multiple sclerosis, SONAPPS: Self-organizing Neuro-adaptive Personalized Physiological System

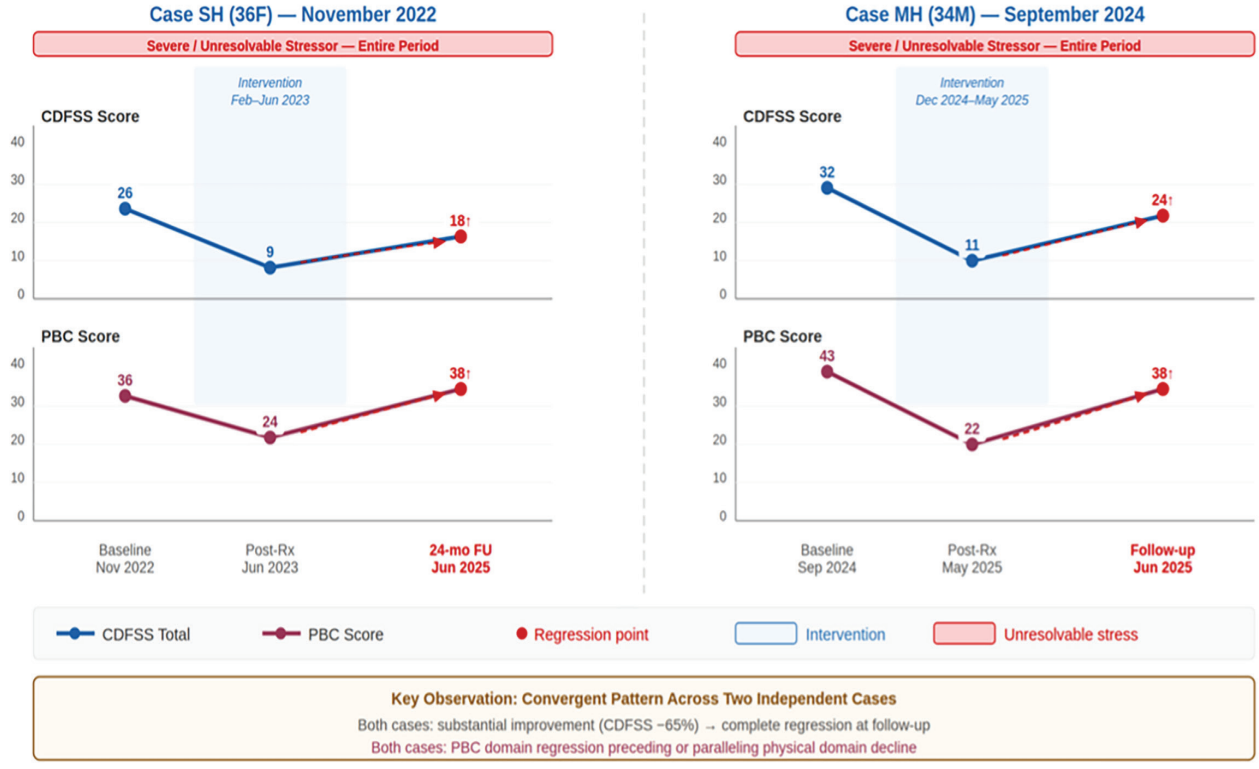


Figure 1. Comparative clinical trajectories of Cases SH and MH. The upper panel shows the CDFSS total score at three time points: baseline (before session 1), post-intervention (performed after completion of the final session—session 20 for SH and session 19 for MH), and follow-up. The lower panel shows the PBC domain total score at the corresponding time points. The orange bar indicates clinician-observed persistent psychosocial stressors throughout the observation period, and the shaded region represents the active intervention period. The post-intervention assessment was performed only after the intervention had been completed, not during the intervention period. Both panels illustrate a convergent observational pattern of substantial improvement followed by regression, with PBC domain regression preceding or paralleling the decline in physical domain function. No causal inference is implied

CDFSS: Comprehensive Disability and Functional Status Scale, PBC: Psychological-behavioral-cognitive

A notable feature in both relapsing cases was that PBC domain scores regressed before or concurrently with the decline in physical domain function (Figure 1). Whether this temporal pattern reflects a causal sequence, a shared response to ongoing psychosocial burden, or coincidence cannot be determined from these observations. Accordingly, the PBC-first regression pattern is presented as a descriptive observation rather than evidence of an underlying mechanism.

The natural progression of SPMS must be considered the primary explanation for the observed regression in both cases. SPMS is characterized by the progressive accumulation of disability (1,2). Without EDSS assessments performed by an independent neurologist, it is not possible to distinguish whether the observed regression was attributable to the natural disease course, the withdrawal of any potential treatment effect, the influence of psychosocial burden, or a combination of these factors. This discussion is not intended to minimize this alternative explanation, which remains at least as plausible as, and potentially more plausible than, the psychosocial stress hypothesis based on the available data.

The absence of EDSS, the Timed 25-Foot Walk, the Nine Hole Peg Test, the Symbol Digit Modalities Test, and validated psychosocial instruments (e.g., the Perceived Stress Scale) represents the most important methodological limitation of this study. Both cases were managed retrospectively before the establishment of the current prospective assessment protocol, which incorporates these measures from the outset (6-8). Therefore, all clinical observations should be interpreted as descriptive rather than inferential.

Conclusion

We report two patients with SPMS and clinician-observed persistent psychosocial burden who demonstrated nearly identical patterns of multidomain improvement followed by complete functional regression at follow-up. In contrast to four non-relapsing cases from the same observational series, these findings are consistent with the hypothesis that persistent psychosocial burden may be associated with reduced functional durability following rehabilitation in progressive MS. However, this association is observational, uncontrolled, and hypothesis-generating, and it requires prospective validation before any clinical conclusions can be drawn. Prospective studies incorporating validated psychosocial instruments, EDSS assessments performed by independent neurologists, standardized functional outcome measures, and longitudinal follow-up are warranted.

The principal limitations of this report include the following: (1) a retrospective two-case observational design that does not permit causal inference; (2) the absence of EDSS assessments performed by an independent, certified neurologist; (3) the use of a clinician-developed, non-validated outcome measure (CDFSS) for descriptive tracking; (4) clinician-observed characterization of psychosocial stressors without validated assessment instruments; (5) assessment of bladder dysfunction based solely on patient self-report; (6) the inability to exclude the natural progression of disease; (7) non-blinded outcome assessment; (8) the absence of a TIDieR-compliant protocol description (currently in preparation); and (9) a small sample size, which precludes generalization.

Ethics

Informed Consent: Written informed consent was obtained from both patients for the publication of this case report and the accompanying clinical data.

Acknowledgements

During the preparation of this manuscript, the authors used Claude (Anthropic) to assist with drafting and language editing. The authors reviewed and edited all generated content and take full responsibility for the final manuscript.

Footnotes

Authorship Contributions

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

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

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

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DOI: 10.4274/jmsr.galenos.2026.2026-6-2

J Mult Scler Res 2026;6:62-70

RESEARCH ARTICLE

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"It Shapes My Days and My Nights:" The 24/7 Biopsychosocial Experience of Living with Multiple Sclerosis: A Qualitative Study

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Abstract

Objective: This study was designed using a qualitative approach to explore the 24/7 experiences of patients with multiple sclerosis (MS).

Materials and Methods: Using purposeful maximum variation sampling, 17 patients with MS who met the 2017 McDonald criteria were included in the study. Data were collected between May and November 2024 using a semi structured interview form developed based on expert opinions; the interviews were audio-recorded and transcribed. Data analysis was performed using MAXQDA 2024 software, using Braun and Clarke's 6-phase thematic analysis framework.

Results: Five major themes regarding the 24/7 experiences of patients with MS were identified in our study: 1. diagnosis and acceptance process; 2. biopsychosocial effects of MS; 3. effects on family, marriage, and parenting roles; 4. sleep experiences and the psychosocial dimension of sleep; and 5. ways of coping with difficulties and problems encountered.

Conclusion: This qualitative study demonstrated that sleep changes were fundamentally linked to the biopsychosocial dimensions of the disease. Patients described sleep as both restorative and an emotional escape, noting that sleep disturbances led to fatigue, irritability, and reduced coping capacity. Beyond physiological causes, poor sleep may reflect a broader sense of loss of control and uncertainty associated with living with MS.

Keywords: Multiple sclerosis, sleep, biopsychosocial, multidimensionality, quality of life

Introduction

Multiple sclerosis (MS) is the most prevalent chronic inflammatory demyelinating disease of the central nervous system. It is a common condition that primarily affects young adult women, with both genetic and environmental risk factors playing significant roles in its development (1,2).

Understanding the comprehensive impact of MS on well-being requires moving beyond daytime symptomatology to acknowledge the profound nocturnal dimension of the disease. Current qualitative literature on patients with MS has extensively focused on various domains, including lived experiences (3), relapse (4), rehabilitation (5), stress and coping strategies (6), and caregiver experiences (7). However, given that MS is inherently a "24/7 condition" and that sleep has a pervasive influence both as a physiological necessity and a psychosocial construct, a more integrated focus is warranted. Because sleep experiences cannot be evaluated independently of patients' clinical journeys or their social identities within the family, this study aims to provide a comprehensive 24/7 perspective.

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Received: 25.06.2026 **Accepted:** 02.09.2026 **Publication Date:** 14.10.2026

Cite this article as: Ozkutlu O, Akin Altinci E, Ozgul Unluer N. "It shapes my days and my nights:" the 24/7 biopsychosocial experience of living with multiple sclerosis: a qualitative study. J Mult Scler Res. 2026;6:62-70

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Materials and Methods

Design

This study utilized a qualitative research method. The study was approved by the Health Sciences Ethics Committee of Ankara Yıldırım Beyazıt University (research code: 2023-401, decision no: 09-401, date: 23.11.2023). Detailed information about the study was provided to each participant, who provided informed consent prior to participation.

Participants

Recruitment was primarily conducted via social media platforms. The inclusion criteria were a diagnosis of MS based on the 2017 McDonald criteria (8), established by a specialist neurologist, and at least 1 year postdiagnosis. Participants with communication difficulties or additional chronic illnesses were excluded. A maximum variation purposive sampling strategy was used (9). The study was completed with 17 participants. Interviews were conducted in the interview room at the Gulhane Faculty of Physical Therapy and Rehabilitation.

Procedures

Semistructured interview questions were developed based on a comprehensive literature review, with input from existing scales (10) and qualitative interview forms (11,12). The original form was revised based on feedback from 2 professors from the departments of social work and mental health and disorders. The interview questions were also reviewed by 2 experts in qualitative research and sleep studies to ensure clarity and relevance. The final form featured open-ended questions, with the topics summarized in Table 1. EAA conducted audio-recorded interviews from May to November 2024 after obtaining participant consent.

Statistical Analysis

Thematic analysis was conducted with the assistance of MAXQDA 2024 software. The data were analyzed according to the 6-phase thematic analysis framework outlined by Braun and Clarke (13). Two researchers (EAA and OO) independently coded 4 randomly selected transcripts to foster diverse interpretations. They then engaged in reflexive discussions to negotiate and agree on the initial themes. EAA subsequently coded the remaining transcripts, while OO reviewed the process to challenge assumptions and confirm that the final themes were grounded in the data. EAA had no prior clinical contact with the participants. Reflexive journals were maintained by both researchers (EAA and OO) throughout the data collection and analysis phases. Peer debriefing was conducted through regular discussions with experts in social work and physiotherapy, who reviewed the coding process and emerging themes. The final themes and subthemes were reviewed and agreed upon by both researchers. Illustrative examples of interview statements and their corresponding classifications are presented in Table 2. Although the interview guide covered a range of topics, such as consulting a sleep expert and receiving guidance on sleep from health care professionals, these topics did not yield data that reached thematic saturation or emerged as salient patterns across the dataset. Therefore, they are not reflected in the final thematic framework, consistent with the principles of reflexive thematic analysis. The sample size was determined based on the richness and depth of the data, ensuring adequate information power to address the research aim (14).

Results

Interviews ranged in length from 22 to 46 minutes. Among the 3 male and 14 female participants, 11 were high school graduates and 11 were married. The participant who received the earliest diagnosis was diagnosed in 2003. Demographic data for each participant are summarized in Table 3. The coding and analysis process resulted in a final set of 5 themes and 14 codes (Figure 1).

Theme 1. Diagnosis and Acceptance

Recognizing MS and Its Diagnosis

The diagnosis process was described as a period of intense uncertainty, fear, and emotional turmoil following the onset of physical symptoms.

"At first, I couldn't feel my arm or leg. I felt weak and tired. I had no desire to do anything. I even had trouble moving. As the "dragging" sensations began and my vision deteriorated, I sought medical attention at a hospital, where I was eventually diagnosed" (Anka).

"I didn't know I was sick. I went to Moscow on official business, and my leg was locked up on the escalator. I couldn't move until I reached the end of the escalator. There were just a few steps left to reach the top, but when I took a step, I was in a lot of pain. My head hurt a lot, my brain hurt a lot, I could't stand the heat, I was very nervous, my reactions were harsh, and I didn't recognize myself anymore. I didn't understand; I was depressed, and nothing made me happy" (Balpetegi).

"It shapes my days and my nights" (Anka).

Accepting MS

Findings from participants indicated that acceptance following diagnosis was a long, emotionally turbulent process characterized by individual differences.

"I didn't accept it for the first five years. When did I accept it? When I came to my doctor, when I came to physical therapy, I was in a very bad way, I was throwing the needle. The drugs constantly had side effects on me. When I first went to physical therapy, after seeing the children there, I gave up on everything. I said, "I was wrong". I said I would never utter the word "sick" again. You have to accept it" (Mavis).

"I went to physical therapy years ago, and the physical therapist said something to me that I'll never forget: "Everyone in this world has something in their destiny, and this is what fell into yours". Since

then, I've accepted it. It lives with me. I see it as a guest. As long as we're not bad, we can get along" (Balpetegi).

Theme 2. Biopsychosocial Effects of MS

Physiological Effects

Findings from participants indicated that the physical effects of MS permeated every aspect of life, with the physical limitations of the disease directly affecting both participants' independence and quality of life.

"I have balance problems. When I stir soup during the day, it splashes everywhere. Sometimes, just as I'm about to swallow food, I don't know how to explain it; it's like a power outage. You know, when everything suddenly shuts off and the generator takes a moment to start. Whatever I'm holding can slip from my hand in an instant. Once, while driving, I meant to hit the brakes but pressed the gas instead. Thank God nothing happened" (Beyaz).

"I feel weak. It's this weakness and constant sleepiness... I don't normally fall asleep easily, but I constantly want to lie down. I can't lift my arms or legs. It's a strange kind of weakness without any apparent reason" (Tosbaga).

"I have difficulty walking. I cannot go far on my own" (Nb).

Table 1. Interview topics and subtopics on MS and sleep experiences

Main topic	Subtopic	Question example
Experience and meaning of MS	Diagnosis and disease progression	Can you share your experience with the MS diagnosis process and treatment options?
	Relationship between MS and sleep	Since your MS diagnosis, how has your sleep changed? Have these changes been more noticeable during specific periods (e.g., relapses or the early stages of the disease)?
Meaning of sleep	Definition of sleep	How do you personally understand sleep? What does good or poor sleep mean to you?
	Importance of sleep	Do you think good or poor sleep is important for your health and well-being?
	General sleep description	How would you describe your sleep in general (e.g., duration, depth, interruptions, and routine)?
	Influencing factors	Do you believe certain situations in your life affect your sleep (e.g., biological, psychological, social, or spiritual factors; medications; or secondary diagnoses)?
Sleep experience	Sleep process	Can you describe a typical night for you, from the moment you go to bed until you wake up? Consider sleep hygiene, partner-related factors, excessive sleep, insomnia, and other relevant experiences.
	Sleep evaluation	How would you describe the quality of your sleep?
	Concerns about sleep	What worries you the most about your sleep?
Sleep problem management	Coping strategies	Do you think you have sleep problems? If so, what strategies or treatments have you considered?
	Thoughts and feelings after poor sleep	When you do not sleep well one night, what do you usually think and feel? What do you think is the reason for your poor sleep?
	Actions after poor sleep	What do you do when you cannot sleep?
	Coping the next day	How does poor sleep affect your ability to cope the next day (e.g., memory, attention, and other daily activities)?
	Perceived control over sleep	Do you feel that you have control over your sleep?
Health care professional intervention	Guidance from health professionals on sleep	Have health care professionals ever discussed sleep with you as part of your treatment for MS? What have they told you?
Hope and future plans	Desired changes	If you had a magic wand to improve your sleep, what would you do?
	Future expectations for the sleep routine	Would you like to change your sleep routine? What is your outlook on your sleep in the future?
	Consult a sleep expert	If you could work with the world's leading sleep expert, what would you want to discuss or change about your sleep habits?

MS: Multiple sclerosis

Table 2. Statements and relevant initial classifications	
Selected statement	**Initial classification**
"My left foot would feel like it was stepping into an empty space. When playing soccer with friends, I would experience something like a cramp in my leg. I thought it was probably just fatigue. When it continued, I had an MRI. That's how I was diagnosed" (Ulucan)	Recognizing MS and the diagnosis process
"Let's go out, eat, go to the movies... Even going out is very difficult for me. And the next few days are difficult too. For example, there's a picnic activity. I force myself to find the strength that day, force myself to participate, force myself to smile so as not to disrupt the atmosphere and to fit in, and then I'm devastated for the next 3 days after coming back. I ruined all my friendships because of this" (Anka)	Changes experienced in social relationships
"If I can't sleep at night, I get irritable. I wait for the evening to come so I can sleep, or sometimes I go to the office and sleep if I can't sleep at home. If necessary, I will cancel my appointments. If necessary, I cancel my daily activities and sleep. I can't stay awake. I have MS, and if I don't sleep, I have attacks" (Gizem)	Changes MS creates in sleep patterns

MRI: Magnetic resonance imaging, MS: Multiple sclerosis

Table 3. Demographic characteristics of participants

Code name	Age, y	Sex	Educational level	Occupation	Employment status	Parental status (child's age, y/sex)	Year of diagnosis
Anka	31	Female	High school	Not working	Married	10/girl; 8/boy	2021
Balpetegi	50	Female	Bachelor's degree	Civil servant/not working	Single	None	2014
Geisha	26	Male	High school	Student	Single	None	2020
Gizem	34	Female	Bachelor's degree	Lawyer	Married	3 /boy	2017
Nb	38	Female	Elementary school	Housewife	Married	17/girl12/boy; 7/ boy	2024
Taco	30	Female	Postgraduate	Ceramics teacher	Single	None	2022
Tosbaga	24	Female	High school	Preschool assistant teacher	Single	None	2022
Ulucan	39	Male	High school	Cook/retired due to disability	Married	10 /girl	2014
Sirinlik	39	Female	Bachelor's degree	Sales representative	Married	5/boy; 10/girl	2014
Merdiven	37	Male	High school	Business owner	Married	11 /girl	2012
Rabia	28	Female	High school	Teacher	Single	None	2024
Yuksel	54	Female	Associate degree	Housewife	Married	34/boy32/girl; 20/ girl	2003
Nry	21	Female	High school	Student	Single	None	2022
Ayse	43	Female	High school	Worker	Married	17/girl; 20/girl	2009
Beyaz	45	Female	High school	Makeup artist/not working	Married	13/boy12/boy; 8/ girl	2006
Mavis	37	Female	High school	Accountant/retired due to disability	Married	16/boy; 8/boy	2011
Deniz	55	Female	High school	Civil servant/retired	Married	32/girl	2017

Psychological Effects

Our findings showed that the disease triggered feelings of hopelessness, anxiety, uncertainty, and loss of control, resulting in significant changes in self-perception and life satisfaction.

"Hopelessness, helplessness... There's nothing I can do. Not knowing anything is worse. I tell myself, "I'll just adjust myself to staying like this". They say we don't know. Is there any chance of improvement? We don't know... Complete uncertainty wears a person down even more. They say even the worst thing is better than uncertainty. That's exactly where I am right now" (Anka).

"You get obsessed. For example, you get into an emotional breakdown, you have an argument with someone. You feel guilty,

wondering whether you're the one to blame. These are patterns we pick up in childhood. Later comes excessive guilt, feeling like you're to blame... You immediately think, "Could it be MS?" I read that MS can cause such situations. We go through these ups and downs" (Yuksel).

Social Effects

Research findings showed that MS profoundly affects individuals' social lives, relationships, and social roles.

"Having MS is unbearable for both my close friends and strangers. I'm constantly tired. I'm even tired of saying it. They say I'm making excuses, but going out is torture for me. I go to a party, everyone has fun, and the next day I can't get out of bed for 2 days. The next few days are ruined. That's why I don't go anymore" (Anka).

"People react differently because they don't know anything about MS. They say, "Oh, poor thing". They shouldn't get hung up on that part. I stop contacting toxic people. I don't see people who stress me out. I also stop contacting people who constantly tell me their problems" (Sirinlik).

Theme 3. Reflections on Family, Marriage, and Parenting Roles

Reflections on Family Relations

Some participants stated that the intensive research and support efforts of family members to understand the disease empowered them, whereas others noted that differences in attention changed family dynamics.

"My family was scared too. Because it was an unknown disease. My uncle is a doctor. My dad shared it with him. I have a cousin who is an oncologist. When we asked them, they said there was nothing to be afraid of. Because there is a treatment. We learned by researching. My mom was researching tirelessly, day and night. Researching affects you a little" (Taco).

"We are three siblings. I am the youngest; I have an older sister and brother. My brother was the most valuable person in the house, the one who did everything, achieved everything, and was the hero of everything. With the illness, all the attention was on me" (Geisha).

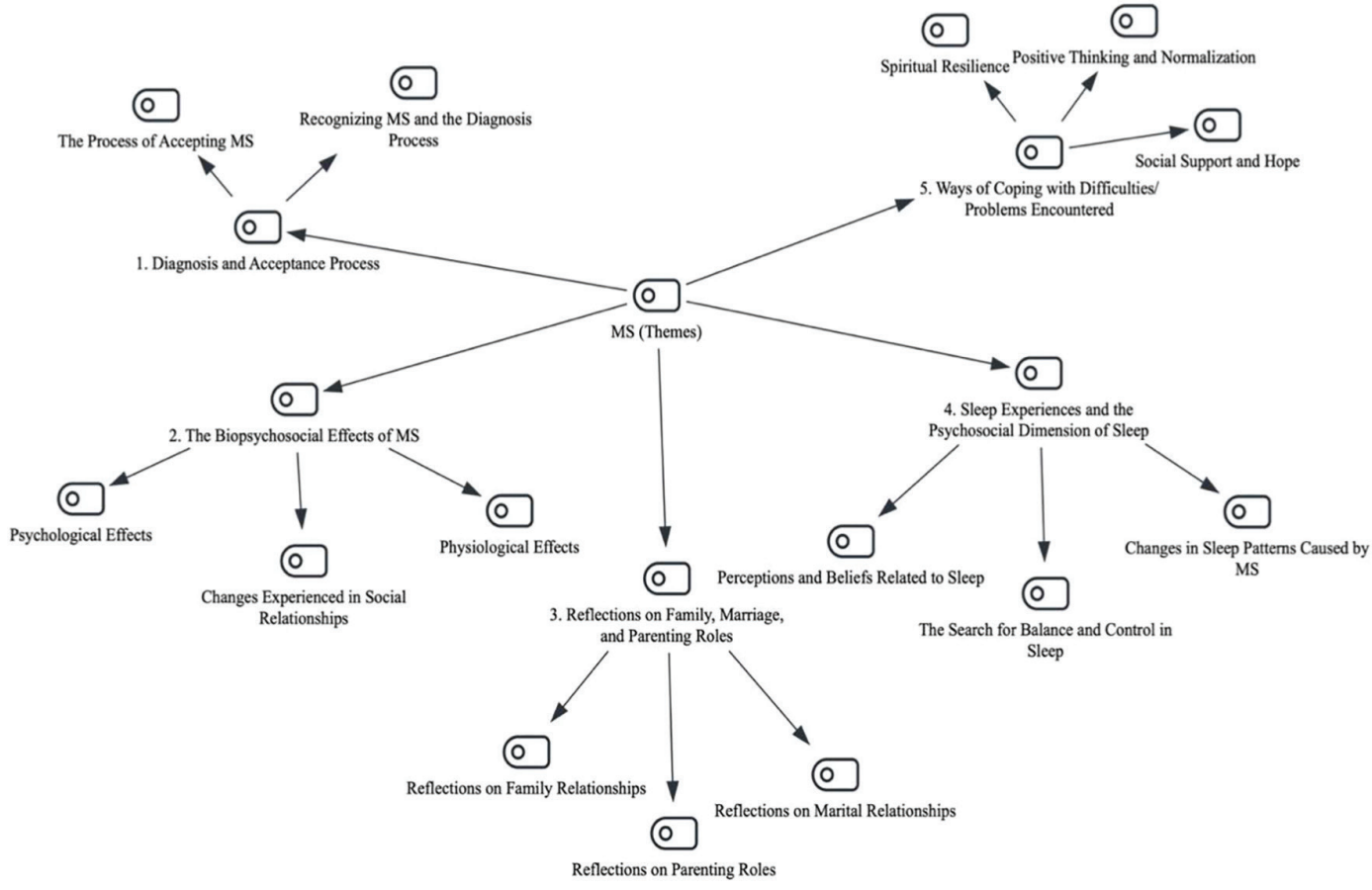


Figure 1. Thematic map of the coding structure. The map presents 5 main themes (central nodes), each with corresponding subthemes (surrounding branches), illustrating the hierarchical organization of the qualitative data analysis

MS: Multiple sclerosis

Reflections on Marital Relationships

Participants indicated that MS had mixed effects on marital relationships.

"I was very affected at first. I got angry quickly. I yelled at my wife. I yelled at my daughter. It was difficult... I directed my anger at them. I couldn't yell outside, so I came home and yelled at my wife. I was very sleepy during that period. I don't know if it was because of the disease" (Ulucan).

"Life is good if I live it according to my wife, but if I approach life a little bit from my perspective and live the way I want to live, that's when our problems start" (Anka).

Reflections on Parenting Roles

The findings obtained within the scope of the research showed that MS creates difficulties in parenting roles, both emotionally and practically.

"All I think about is my children. Will I be able to look after them? Will I be able to care for them? Will I be able to spend enough time with them?" (Anka).

"Sometimes I just want to sit down. I want to spend time at home. I'm sleepy, yes, I know I need to sleep, but then I can't spend time with the kids. I want to watch something or have a coffee by myself and relax, but we just can't do everything at once" (Ayse).

Theme 4. Sleep Experiences and the Psychosocial Dimension of Sleep

Perceptions and Beliefs Related to Sleep

Participants' statements indicated that sleep was viewed not only as physical rest but also as a means of mental, emotional, and physical renewal. Sleep aids in coping with illness, reduces stress, and alleviates the burdens of daily life. Participants described insomnia as a condition that increases both physical fatigue and emotional vulnerability.

"I wake up, and when I wake up, it's very difficult for me to fall asleep. Most of the time, I get up thinking my sleep is over, and the next day, I feel terrible because I couldn't sleep" (Anka).

"When I wake up in the morning, I feel like a formatted computer" (Merdiven).

Changes in Sleep Patterns Caused by MS

Participants stated that MS was a factor that directly affected sleep patterns. Problems such as difficulty falling asleep, frequent awakenings, and inability to sleep despite extreme fatigue were described in terms of both their physiological and psychological dimensions. Some participants resorted to medication or alcohol to cope with insomnia.

"I definitely can't sleep. I mean, I can't do it on my own, I can't manage it. I'm very tired, but I still can't sleep. I think this is related to MS" (Beyaz).

"I used to go to bed around 10 at night. But in the last year, it has greatly increased my sleep onset latency and my desire to sleep. Even if I don't sleep, I keep lying down trying to sleep, but I can't fall asleep. It has created a major problem with falling asleep" (Anka).

"It takes me a minimum of 20 minutes and a maximum of 60 minutes to fall asleep" (Rabia).

Search for Balance and Control in Sleep

Our results showed that the loss of control experienced due to the unpredictable nature of MS led participants to seek order and control in their daily lives. Participants attempted to establish balance through daily routines, sleep habits, and spiritual practices such as prayer to reduce the uncertainty associated with the disease.

"If I have pain, it takes me an hour or more to fall asleep. When I can't fall asleep, I think about nice things. I pray. I dream a lot. I think about my dreams, what I saw yesterday. That's how I fall asleep" (Yuksel).

"Sleep is the most crucial part for me. If I don't sleep well, the next day is miserable. Going to bed too late or being constantly woken up while sleeping affects me" (Sirinlik).

"Actually, it would be better if I went to sleep at 23:00. I'd like to fall asleep more easily at night, sort of like, "Let me stop thinking and rest; I'll think about it in the morning" (Nry).

Theme 5. Ways of Coping with Difficulties/Problems Encountered

Spiritual Resilience

Our results showed that faith and the concept of destiny played important roles in coping with physical and psychological burdens.

"My faith has a huge impact. After all, I know it comes from God and there's nothing I can do about it. I've always been grateful" (Ayse).

Positive Thinking and Normalization

Participants' statements indicated that positive thinking and normalization were effective strategies for coping with challenges.

"Actually, I tried to stay positive about everything... I always tried to think positively to myself. I still think positively. I usually forget that I'm sick" (Tosbaga).

"I went to physical therapy years ago, and the physical therapist said something to me that I'll never forget: "Everyone in this world has something in their destiny, and this is what fell into yours". Since then, I've accepted it. It lives with me. I see it as a guest. As long as we're not bad, we can get along" (Balpetegi).

Social Support and Hope

Our results showed that support from family members and close friends was an important protective factor in coping with the difficulties encountered.

"Everything in life is for us. I went through difficult times. The love of the people around me is probably what kept me going. My husband, my daughter, everyone was so kind to me that they were a great support in my fight against my illness" (Deniz).

"Life goes on no matter what. It goes on through pain. Nothing lasts forever. Whatever happens in life, MS patients in particular should take care of themselves. Stay positive and don't lose your energy. Don't give up on life. Sleep well" (Deniz).

Discussion

The themes and subthemes identified through data analysis included the diagnosis and acceptance process, biopsychosocial effects of MS, reflections on family, marriage, and parenting roles, sleep experiences and the psychosocial dimension of sleep, and ways of coping with difficulties/problems encountered.

Consistent with previous research, the present study confirmed that the diagnosis and acceptance process involves complex emotional trajectories. A meta-synthesis of qualitative studies focusing on the diagnosis of MS highlighted that individuals experienced intense emotional reactions and challenges that hindered their ability to comprehend and adjust to the diagnosis (15). The second theme identified in our study was the biopsychosocial impact of MS. Similar findings have been reported in a qualitative study of patients with MS aged 25-56 years, which also highlighted the relevance of the biopsychosocial model (16). Another study of patients with MS demonstrated that quality of life in MS is associated with multiple biopsychosocial variables (17).

The third theme identified in our study was reflections on family, marriage, and parenting roles. For new and experienced parents without disabilities, obtaining sufficient sleep has been shown to play a crucial role in mental health and, in turn, life satisfaction (18). For patients with MS, however, physical and psychological limitations can make childcare more challenging and less manageable, thereby increasing their vulnerability to sleep problems.

The fourth theme identified in our study was sleep experiences and the psychosocial dimension of sleep. Feeling fully refreshed after sleep might be particularly important because of the characteristic fatigue associated with MS. Insomnia symptoms, combined with the sense of loss of control experienced during the disease course, further illustrate the link between these themes. Previous research has shown that treatments used by people living with MS to initiate or maintain sleep, as well as their effects on sleep quality and daytime sleepiness, are important considerations (19). Approximately 1 in 2 adults with MS report poor sleep quality and daytime sleepiness, and 1 in 5 are diagnosed with an insomnia disorder (20). Similarly, our findings revealed difficulties falling back asleep after waking, consistent with insomnia symptoms that participants also associated with MS. A recent meta-analysis synthesized findings from 13 quantitative studies that used the Pittsburgh Sleep Quality Index and concluded that the limited available evidence suggests that subjective sleep quality is adversely affected by MS (21). While this meta-analysis provides valuable quantitative evidence regarding sleep in MS populations, it does not offer in-depth insight into the lived experience of sleep disruption or the contextual factors that shape sleep perceptions and behaviors. Our study extends this body of knowledge by offering a nuanced qualitative perspective that captures the multidimensional nature of sleep experiences among patients with MS. Specifically, our findings are organized around 3 distinct subthemes: (1) perceptions and beliefs related to sleep, (2) changes in sleep patterns caused by MS, and (3) the search for balance and control in sleep. These subthemes collectively provide a framework for understanding how sleep is experienced, interpreted, and managed within the biopsychosocial context of MS, addressing aspects of the lived experience that quantitative approaches alone may not fully capture.

Our results indicate that patients with MS often seek to regain a sense of control in their lives by establishing daily routines, sleep practices, and spiritual activities. These strategies may help them cope with the unpredictable nature of MS and may serve as psychological coping mechanisms. We highlight the importance of sleep hygiene education (22) as a potentially beneficial approach to enhance patients' sense of control and promote public health. However, specific sleep recommendations for patients with MS appear to be limited, with no MS-specific guidance beyond that provided by established sleep organizations.

Previous research has shown that meaning in life predicts quality of life across all 4 domains of biopsychosocial measures (17), which aligns with our findings regarding spiritual resilience. Social support and positive thinking also emerged as important to coping strategies. Existing literature demonstrates that positive thinking training has been shown to improve quality of life (23) and encourage physical activity among individuals with MS (24). Previous research has also established that higher levels of social support are associated with better mood and quality of life in individuals with MS (25).

The sex distribution in this sample (14 females and 3 males) is broadly consistent with the established epidemiology of MS. As noted by Coyle (26), multiple aspects of MS are influenced by sex-based differences, and this has become an important area of research. In line with this, our findings similarly suggest that sex-based differences may have influenced participants' experiences, particularly in the context of parental roles.

Study Limitations

Several limitations should be acknowledged. First, the absence of a psychological expert on the research team may have influenced the interpretation of the findings. Second, recruitment

through social media may have introduced self-selection bias. Third, the single-center, single-country sample limits the cultural transferability of the findings. Fourth, the single-time-point design precludes examination of longitudinal changes in participants' experiences. Additionally, medication use was not systematically assessed, although it may have influenced participants' sleep experiences. Finally, sociodemographic data were collected but not analyzed. Future research should explore interventions integrating spiritual resilience, patient education, and biopsychosocial support to enhance patients' 24/7 experiences.

Conclusion

This study demonstrated that MS is a 24/7 experience, extending far beyond clinical consultations into every aspect of patients' daily lives. A key finding was the pivotal role of sleep within this trajectory, highlighting that the disease continues to affect individuals' well-being even during non-waking hours. Consequently, it is imperative to manage MS within a comprehensive temporal context. The study's primary strength lies in its qualitative analysis of the individualized 24/7 experiences of 17 patients, including their sleep experiences, supported by a multidisciplinary research team comprising a physical therapist, sleep specialist, and social services expert.

Ethics

Ethics Committee Approval: The study was approved by the Health Sciences Ethics Committee of Ankara Yıldırım Beyazıt University (research code: 2023-401, decision no: 09-401, date: 23.11.2023).

Informed Consent: Detailed information about the study was provided to each participant, who provided informed consent prior to participation. To protect participants' identities, all personal identifiers were removed, and pseudonyms (codenames) were assigned to each participant for the presentation of direct quotes.

Acknowledgments

We would like to thank all participants who took the time to share their views and contribute to the study.

Footnotes

Authorship Contributions

Concept: O.O., E.A.A., N.O.U., Design: O.O., E.A.A., N.O.U., Data Collection or Processing: O.O., E.A.A., N.O.U., Analysis or Interpretation: O.O., E.A.A., N.O.U., Literature Search: O.O., E.A.A., N.O.U., Writing: O.O., E.A.A., N.O.U.

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

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

Data Availability: The qualitative data (interview transcripts) generated and analyzed during the current study are not publicly available due to participant privacy and the sensitive nature of the information. However, the data are available from the corresponding author upon reasonable request.

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DOI: 10.4274/jmsr.galenos.2026.2026-7-2

J Mult Scler Res 2026;6:71-78

REVIEW

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Can Machine Learning Detect and Predict Outcomes in Multiple Sclerosis? A Review of Diagnostic and Prognostic Approaches

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Abstract

Multiple sclerosis (MS) diagnosis relies on clinical presentation, magnetic resonance imaging (MRI), and the McDonald criteria, whereas long-term management requires anticipating disability progression and symptom burden. This narrative review evaluates current evidence on machine learning (ML) approaches for (i) detecting and classifying MS and (ii) predicting disability progression and symptom severity in patients with established MS. Evidence was synthesized from 25 sources published between 2012 and 2026 (23 peer-reviewed journal publications, one arXiv preprint, and one article published in a journal outside the major biomedical indexes), encompassing MS diagnosis [MRI, optical coherence tomography (OCT), fluid biomarkers, and differential diagnosis] and prognostic outcome prediction (disability progression, symptom-specific severity, and context-specific changes in disability). MRI remains the predominant data source for ML-based MS detection: deep learning models applied to structural MRI achieved accuracies of 70.2-98.8% in distinguishing MS from healthy controls, whereas conventional ML models achieved accuracies of 83.7-90.0%. A broader meta-review of more than 100 studies reported diagnostic accuracies ranging from 61% to 97%, while differentiation of MS from neuromyelitis optica spectrum disorder achieved 74-88% accuracy, depending on data integration. For prognostic applications, tree-based ensemble models generally outperformed simpler regression models: a 231-patient cohort achieved an R^2 of 0.97 for two-year disability score prediction, although this estimate warrants cautious interpretation because of the strong autocorrelation of baseline Expanded Disability Status Scale scores. A 662-woman cohort achieved 85-88% classification accuracy for postpartum changes in disability, whereas a 23-patient cohort achieved 92.65% accuracy in predicting restless legs syndrome severity, with sleep quality identified as the leading predictor. Overall, ML can effectively detect MS-associated patterns in MRI and is increasingly being applied to OCT and fluid biomarkers. It can also generate clinically meaningful prognostic predictions after MS diagnosis, although categorical outcome prediction appears to generalize better than continuous regression. Dataset size, single-center study designs, and limited external validation remain the principal barriers to clinical deployment across both domains. Multimodal data integration and prospective multicenter validation therefore represent important priorities for future research.

Keywords: Multiple sclerosis, machine learning, deep learning, diagnosis, prognosis, disease progression

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, and achieving an accurate diagnosis remains a persistent clinical challenge. The 2017 McDonald criteria, which integrate clinical findings with magnetic resonance imaging (MRI) evidence of lesion dissemination in space and time, have improved diagnostic sensitivity and facilitated earlier diagnosis; however, their accurate application remains highly dependent on clinician expertise, and misdiagnosis continues to occur, particularly when MS must be differentiated from other white matter or inflammatory conditions (1).

Over the past decade, researchers have developed machine learning (ML) and deep learning (DL) methods to assist in this diagnostic process. Early applications focused primarily on automating the labor-intensive task of MS lesion segmentation

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Received: 13.07.2026 **Accepted:** 17.09.2026 **Publication Date:** 15.10.2026

Cite this article as: Emec M. Can machine learning detect and predict outcomes in multiple sclerosis? A review of diagnostic and prognostic approaches. J Mult Scler Res. 2026;6:71-78

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on MRI, which has traditionally been performed manually and is subject to substantial inter-rater variability (2,3). As computational methods have advanced, their applications have expanded to full diagnostic classification, including differentiation of MS from healthy controls and, more recently, from clinically similar disorders such as neuromyelitis optica spectrum disorder (NMOSD) (1,4). In parallel, researchers have increasingly explored non-MRI modalities, including optical coherence tomography (OCT) and blood and cerebrospinal fluid (CSF) biomarkers, as additional and less invasive substrates for ML-based detection (5,6).

Beyond diagnosis, ML has also been applied to patients with established MS to forecast disability accumulation and symptom burden, i.e., tasks that are prognostic rather than diagnostic. Nevertheless, these applications share the same underlying methodology and are frequently discussed alongside diagnostic applications in the literature (4,7). Disability, most commonly quantified using the Expanded Disability Status Scale (EDSS), is challenging to predict because it reflects the heterogeneous and non-linear accumulation of impairment across multiple neurological domains. Recent cohort studies have applied ensemble ML methods to predict future EDSS scores, disease-specific symptom severity, and changes in disability during clinically important periods, such as the postpartum period, often achieving higher classification accuracy than continuous regression approaches for disability scores.

Despite the growing body of research across both domains, the translation of ML tools into routine clinical practice remains limited. Reported performance varies considerably among studies, and this heterogeneity is frequently attributed to differences in dataset size, imaging or clinical feature protocols, and the selection of comparison or outcome groups (1,7). The present review synthesizes current evidence on ML-based detection and classification of MS together with ML-based prediction of disability progression and symptom severity to clarify (i) which data modalities and model families have demonstrated the strongest performance in each domain, (ii) how performance differs across tasks of increasing clinical difficulty, and (iii) which methodological barriers must be addressed before these tools can be considered for routine clinical deployment.

This is a narrative, rather than a systematic, review. Sources were identified through purposive searches of PubMed and Google Scholar (last search: July 2026) using combinations of the terms "multiple sclerosis," "machine learning", "deep learning", "diagnosis", "prognosis", and "disability progression", supplemented by manual screening of the reference lists of recently identified reviews. We retained 25 sources published between 2012 and 2026 based on their direct relevance to ML-based MS diagnosis or disability/symptom prognosis, methodological clarity, and, for primary studies, availability of quantitative performance metrics. This purposive approach does not guarantee exhaustive coverage and reflects the authors' judgment regarding representative and influential work rather than a systematic sample.

Chronological Evolution of the Field

Table 1 summarizes 25 key sources in chronological order, illustrating how the field has evolved from early, narrowly focused lesion-segmentation tools to broader diagnostic frameworks and, more recently, to prognostic and disability-prediction applications.

Table 1. Overview of key studies and reviews on machine learning applications for MS diagnosis and prognosis (2012-2026)

Year	Author(s)	Data modality	Method	Focus	Contribution/milestone
2022	Filippi et al. (1)	MRI	Narrative review	Diagnostic work-up	Summarized the evolution of the McDonald criteria and AI-detectable markers
2018	Danelakis et al. (2)	MRI	Segmentation survey	Lesion segmentation	Cataloged the growth of available methods and highlighted the lack of standardization
2012	Lladó et al. (3)	MRI	Segmentation review	Lesion segmentation	Early comprehensive survey of automated segmentation methods
2021	Moazami et al. (4)	MRI	SVM, RF, CNN	Diagnosis, staging	Proposed a four-category taxonomy for ML applications in MS imaging
2022	Toosy and Eshaghi (5)	OCT	ML review	Diagnosis (OCT)	Identified OCT-based ML as a promising but less mature diagnostic modality
2024	Arrambide et al. (6)	Blood/CSF	Narrative review	Fluid biomarkers	Highlighted the underexplored potential of AI applied to fluid biomarkers
2024	Pilehvari et al. (7)	MRI + clinical	Meta-review (103 studies)	Diagnosis, risk	Quantified performance ranges across ML/DL studies
2012	Lladó et al. (8)	Serial MRI	Change detection	Lesion segmentation	Demonstrated the feasibility of automated new-lesion detection using longitudinal scans
2012	Jacob et al. (9)	Clinical/serology	Diagnostic criteria	Differential diagnosis	Defined the NMOSD concept, which was later used as an ML comparator class

Table 1. Continued

Year	Author(s)	Data modality	Method	Focus	Contribution/milestone
2021	Shoeibi et al. (10)	MRI	CNN/DL	Automated detection	Synthesized DL architectures used for MS detection
2021	Andropova et al. (11)	MRI	LDA, ANN, SVM	Computer-aided diagnosis	Reviewed CAD components designed to support the radiologist workflow
2021	Petzold et al. (12)	OCT	Consensus + AI	Imaging quality control	Extended the OSCAR-IB criteria for AI-based OCT analysis
2022	Aslam et al. (13)	MRI + clinical	SVM, RF, CNN	Diagnosis	Identified leading approaches from 2011-2022 and highlighted translational barriers
2022	Bonacchi et al. (14)	Multimodal	Narrative review	Clinical practice	Examined the real-world translation of AI-based diagnostic tools
2023	Shah et al. (15)	MRI	Bibliometric review	Lesion detection	Characterized methodological and citation trends over the preceding decade
2023	Siriratnam et al. (16)	Clinical/imaging	Narrative review	Differential diagnosis	Updated advances in NMOSD relevant to MS-mimic tasks
2024	Collorone et al. (17)	MRI	Narrative review	Key challenges	Highlighted heterogeneity, generalizability, and validation gaps
2024	Amin et al. (18)	Multimodal	Narrative review	Overview	Provided a broad synthesis spanning MS diagnosis and management
2025	Szekely-Kohn et al. (19)	MRI	Narrative review	MRI interpretation	Identified U-Net as the dominant architecture and highlighted emerging lesion subtypes (PRL, CVS)
2025	Kuntal et al. (20)	MRI	CNN	Detection	Described a technical CNN-based pipeline for MS detection
2025	Thabet et al. (21)	MRI	ML/DL comparison	Classification, segmentation	Provided a recent comparison of classification and segmentation methods
2025	Abdul-Salam et al. (22)	OCT/retina	DL	Diagnosis (retina)	Established retinal imaging as a potential source of non-invasive biomarkers
2025	Kaya et al. (23)*	Clinical, questionnaire	Decision Tree, RF, XGBoost	Symptom severity	Developed the first ML model for RLS severity in an MS cohort
2026	Ozdogar et al. (24)*	Clinical, demographic, and cognitive	XGBoost, RF, Linear Reg	Disability progression	Reported high-accuracy EDSS prediction without imaging (R^2=0.97)
2026	Emec et al. (25)*	Clinical, reproductive, obstetric	RF, XGBoost, Elastic Net, SVC	Postpartum disability	Developed the first model using reproductive history for MS prognosis

*Asterisk (*) denotes primary cohort studies; the remaining twenty-two entries are literature reviews or methodological surveys. ANN: Artificial neural network, CAD: Computer-aided diagnosis, CNN: Convolutional neural network, CSF: Cerebrospinal fluid, CVS: Central vein sign, EDSS: Expanded Disability Status Scale, DL: Deep learning, LDA: Linear discriminant analysis, ML: Machine learning, MRI: Magnetic resonance imaging, MS: Multiple sclerosis, NMOSD: Neuromyelitis optica spectrum disorder, OCT: Optical coherence tomography, PRL: Paramagnetic rim lesion, RF: Random forest, RLS: Restless legs syndrome, SVC: Support vector classifier, SVM: Support vector machine, AI: Artificial intelligence

As listed in Table 1, the earliest work (2012) focused almost exclusively on automated lesion segmentation using MRI (3,8,9), reflecting the practical need to reduce the burden associated with manual lesion annotation. Between 2018 and 2021, the field shifted toward DL architectures capable of full diagnostic classification rather than segmentation alone, alongside early consensus efforts to standardize non-MRI modalities, such as OCT (2,10,12). From 2022 onward, the literature has increasingly emphasized translational challenges, including generalizability, differential diagnosis, and multimodal data integration, rather than purely technical improvements in model performance (1,13,14,17). The most recent sources (2024-2026) reflect a further expansion in scope along two directions: toward fluid biomarkers and retinal imaging on the diagnostic side (6,19,22) and toward ensemble ML models for predicting disability progression, postpartum disability change, and symptom-specific severity on the prognostic side (23-25). This latter shift suggests that, once a diagnosis is established, the same model families originally developed for classification are increasingly being repurposed to address a clinically distinct question: how will this patient's disease evolve? It should be noted that 22 of the 25 sources summarized in Table 1 are literature reviews or methodological surveys rather than primary studies. In particular, the performance ranges reported in Table 2 are derived from two review articles (1,7) rather than recalculated from the primary studies they cite and should therefore be interpreted as review-level summaries rather than independently verified findings from the primary studies.

Table 2. Summary of prognostic and disability/symptom-severity prediction studies included in this review

Study	n	Outcome predicted	Best model/performance	Top predictors
Kaya et al. (23)	23	Restless legs syndrome severity	XGBoost: MAE: 1.94, accuracy: 92.65%	Sleep quality (PSQI)
Ozdogar et al. (24)	231	EDSS at 2-year follow-up	XGBoost (CorBoost): R^2=0.97; MAE: 0.24	Baseline EDSS, disease duration, age
Emec et al. (25)	662 women/909 pregnancies	Postpartum disability change (ΔEDSS)	SVC (classification): accuracy: 88.5%; F1=0.87	Postpartum relapse, disease duration, age at pregnancy

The 88.5% figure is the accuracy of the single best-performing classification model (SVC) reported by Emec et al. (25); the 85-88% range cited in Section 4.3 spans all classification models evaluated in that study. The cohort comprised 662 women, with 909 pregnancies in total. As some women contributed more than one pregnancy, these pregnancy-level observations are not fully independent, which should be considered when interpreting the reported accuracy

EDSS: Expanded Disability Status Scale, MAE: Mean absolute error, PSQI: Pittsburgh Sleep Quality Index, SVC: Support vector classifier

ML Approaches for MS Diagnosis

MRI-based Classification: Conventional ML versus DL

MRI remains the principal data source for ML-based MS detection (1,4,10). Two broad methodological families predominate in this literature. DL approaches [most commonly convolutional neural networks (CNNs) and U-Net variants] operate directly on raw T2-weighted, fluid-attenuated inversion recovery, or susceptibility-weighted images and have achieved accuracies ranging from 70.2% to 98.8% in distinguishing MS from healthy controls (1). In contrast, conventional ML approaches [including support vector machines, random forests (RFs), and logistic regression] typically rely on engineered features derived from quantitative, diffusion-weighted, or resting-state functional MRI and have reported somewhat narrower accuracy ranges of 83.7-90.0% (1). Notably, the higher peak performance observed with DL models does not necessarily indicate consistent superiority, as performance in both methodological families depends heavily on dataset composition, imaging modality, and the definition of the diagnostic task (13,21).

The diagnostic reference standard itself is also evolving. The 2017 McDonald criteria, against which nearly all models discussed in this review were trained and validated, are themselves undergoing revision: proposed updates incorporate the central vein sign and paramagnetic rim lesions as imaging markers of MS-specific pathology, kappa free light chains as a fluid biomarker, and the optic nerve as an additional topography for demonstrating dissemination in space. Several of these candidate markers are precisely the targets of the lesion-subtype segmentation tools described in Section 3.2. Models trained and benchmarked under the current criteria may therefore require retraining or revalidation as the reference standard they were developed to approximate continues to evolve.

Automated Lesion Segmentation

Lesion segmentation is the most methodologically mature ML application in MS, with a research history extending back to at least the early 2010s (3,8). Manual lesion assessment is time-consuming and subject to inter-rater variability, which prompted the early adoption of automated approaches (2). U-Net-type CNN architectures now predominate in this subfield, and current tools target not only conventional T2 lesions but also gadolinium-enhancing lesions, central vein sign-positive lesions, paramagnetic rim lesions, and cortical and spinal cord lesions (19). Despite this progress, no segmentation method has achieved universal acceptance in clinical practice, and expert expectations regarding reliability continue to exceed the performance delivered by most current algorithms (2,15). It is important to distinguish regulatory clearance from demonstrated clinical utility: several MS lesion quantification tools have obtained Conformite Europeenne marking or U.S. Food and Drug Administration (FDA) clearance, but such clearance primarily certifies technical performance and safety rather than demonstrating benefits to patient outcomes or constituting formal endorsement by clinical practice guidelines. Cleared tools also remain sensitive to scanner hardware, acquisition protocols, and field strength and typically require post-deployment performance monitoring when used outside the conditions under which they were validated.

Differential Diagnosis: MS versus Clinical Mimics

A clinically important extension of ML-based classification is the differentiation of MS from disorders with overlapping clinical presentations, most notably NMOSD (9,16). RF models using gray-matter measures alone have achieved approximately 74% accuracy in distinguishing MS from NMOSD. In contrast, multiparametric models incorporating MRI with clinical and neuropsychological data have achieved approximately 88% accuracy (1). This gap illustrates a recurring theme: models trained only to distinguish MS from healthy controls may perform considerably worse when applied to realistic differential-diagnosis comparisons, such as vascular white-matter lesions or other inflammatory disorders (1).

Beyond MRI: OCT, Retinal Imaging, and Fluid Biomarkers

The field is expanding beyond structural MRI. OCT, which quantifies retinal nerve fiber and ganglion cell layer thickness, has shown promising preliminary results for distinguishing MS from healthy controls. However, sample sizes remain small, and standardization of quality control is still evolving (5,12). Consensus efforts, such as the artificial intelligence (AI)-extended OSCAR-IB criteria (OCT Standardization of Image Acquisition and Analysis

in MS) criteria, aim to address this standardization gap (12). DL applied to retinal imaging is increasingly being positioned as a non-invasive, low-cost complement to neurological assessment (22). Separately, ML applied to blood and CSF biomarkers remains comparatively underexplored relative to imaging-based approaches, despite its potential to provide an additional minimally invasive diagnostic substrate (6).

Clinical Integration and Multimodal Approaches

Several reviews argue that multimodal integration, i.e., combining MRI with clinical, demographic, OCT, or fluid biomarker data, is the most credible path toward improved diagnostic utility, as no single marker captures the full heterogeneity of MS pathology (6,17,18). At the same time, reviews assessing real-world clinical translation caution that most current AI tools remain assistive rather than autonomous, requiring human oversight and further validation before routine deployment (14,19). This assistive positioning is consistent with the regulatory status of most tools in this space: regulatory clearance indicates that a tool performs a specified technical function safely and reproducibly, rather than demonstrating that it improves diagnostic accuracy or patient outcomes in clinical practice. Guideline endorsement of autonomous decision-making remains absent across the tools discussed in this review.

ML for Disability Progression and Symptom Prediction

Once a diagnosis of MS is established, a distinct but methodologically related question arises: how will the patient's disability and symptom burden evolve? Three recent cohort studies illustrate this prognostic application of ML, summarized chronologically in Table 2.

EDSS and Disability Progression Prediction

Ozdogar et al. (24) developed an XGBoost-based model (CorBoost) to predict 2-year EDSS scores in 231 people with MS, using 126 baseline demographic, clinical, physical, and cognitive features that were reduced to 42 through correlation-based feature selection. The model achieved a coefficient of determination (R^2) of 0.97 and a mean absolute error (MAE) of 0.24 EDSS points, outperforming the RF and linear regression comparators. Baseline EDSS, disease duration, and age were the most influential predictors. Notably, the model achieved this performance using only routinely collected clinical data, without MRI or fluid biomarker input. This very high R^2 should nonetheless be interpreted with caution because EDSS is strongly autocorrelated over a 2-year interval and baseline EDSS was the leading predictor; thus, much of the explained variance may reflect a patient's baseline status rather than genuine predictive insight into disease evolution. The reported MAE of 0.24 EDSS points is notably below the scale's own inter-rater measurement error, further suggesting that the model's practical incremental value over baseline disability alone may be more modest than the headline R^2 implies.

Symptom-specific Severity Prediction

Kaya et al. (23) applied DecisionTree, RF, and XGBoost models to predict restless legs syndrome (RLS) severity in a small cohort of 23 people with MS, using sleep, mobility, and quality-of-life questionnaire data. XGBoost performed best (MAE: 1.94; accuracy: 92.65%), with the Pittsburgh Sleep Quality Index emerging as the dominant predictor across all three algorithms, consistent with conventional correlation analysis. Reporting both a continuous error metric (MAE) and a categorical accuracy measure indicates that the authors evaluated continuous as well as categorical formulations of RLS severity; readers are referred to the primary source for the exact sex composition of the 23-person cohort. This study illustrates that ML can extend beyond global disability metrics to model specific, clinically burdensome MS symptoms, although the very small sample size limits generalizability.

Context-specific Disability Prediction: The Postpartum Period

Emec et al. (25) modeled postpartum disability change (ΔEDSS) in a large real-world cohort of 662 women with MS contributing 909 pregnancies, comparing regression models (RF, XGBoost, Elastic Net, Support Vector Regression) with classification models predicting improved, stable, or worsened disability categories. Classification models substantially outperformed regression models (test accuracy, 85-88%; F1: 0.84-0.87; versus test R^2=0.31-0.39, for regression), a pattern the authors attributed to the discretized, threshold-like distribution of clinically meaningful EDSS change. Postpartum relapse was the strongest predictor of disability worsening, followed by disease duration and age at pregnancy, with obstetric variables such as delivery type and breastfeeding contributing secondary predictive value.

It should be noted that references 23, 24, and 25 share substantial overlap in authorship and appear to draw on a largely common patient population and research group, so they are better interpreted as a coherent program of work from one center rather than as three independent replications. Independent multicenter prognostic studies are still needed before the pattern described below can be generalized with confidence. Across all three studies, tree-based ensemble methods (RF, XGBoost) consistently matched or outperformed simpler linear models, and categorical outcome framing tended to generalize better than continuous regression, mirroring a pattern also noted in the diagnostic literature, where task definition strongly influences reported performance (13,21).

Diagnostic and Prognostic Performance Summary

Table 2 summarizes the three prognostic and disability-prediction studies described above, whereas Table 3 consolidates diagnostic performance measures by task and data modality.

Table 4 summarizes qualitative risk-of-bias judgments for the prognostic studies; similarly, the diagnostic performance

measures in Table 3 vary in the completeness of their reporting. Table 5 makes this limitation explicit by summarizing, for each row of Table 3, the validation strategy, aggregate sample size, and class balance reported in the underlying source. When a source did not report one of these elements, we state this explicitly rather than leaving the field blank, because the absence of this information is itself relevant to interpreting the reported accuracy measures.

Challenges and Limitations

Several methodological limitations recur across both domains. Most studies rely on small, single-center datasets, thereby limiting generalizability across scanners, acquisition protocols, and patient populations; this limitation is particularly apparent in symptom-prediction studies involving cohorts as small as 23 patients (1,10,23). Diagnostic models are frequently validated against healthy controls rather than clinically representative comparator groups, whereas prognostic regression models often exhibit substantial overfitting between training and test datasets (1,16,25). DL as well as ensemble tree-based models remain relatively opaque, which can hinder clinician confidence, interpretability, and regulatory evaluation (10,19). Finally, prospective multicenter validation, which is a prerequisite for broader clinical deployment, remains uncommon, with most available evidence derived from retrospective, single-center study designs (1,17,24,25).

To move this observation from assertion toward demonstration, Table 4 provides a brief, Prediction Model Risk Of Bias Assessment Tool (PROBAST)-informed qualitative appraisal of the three primary prognostic studies discussed in Section 4. This appraisal is based solely on information reported in the published articles

Table 3. Reported diagnostic performance of ML approaches for MS, by task and data modality

Diagnostic task	Data/model type	Accuracy (%)	Sensitivity (%)	Specificity (%)	Source
MS versus healthy controls	DL (CNN, U-Net) on structural MRI	70.2-98.8	—	—	Filippi et al. (1)
MS versus healthy controls	Conventional ML (SVM, RF, logistic regression) on quantitative MRI/DWI/rs-fMRI	83.7-90.0	—	—	Filippi et al. (1)
Overall ML/DL diagnostic performance	Mixed ML/DL, meta-review of 103 studies	61-97	60-98	60-98	Pilehvari et al. (7)
Classification studies specifically	Mixed ML/DL, same meta-review subset	71-97.9	78-97.3	65-99.3	Pilehvari et al. (7)
MS versus NMOSD (gray matter only)	RF	74	—	—	Filippi et al. (1)
MS versus NMOSD (multiparametric)	MRI + clinical + neuropsychological model	88	—	—	Filippi et al. (1)

"—" indicates that sensitivity or specificity was not reported separately from overall accuracy in the source study

MS: Multiple sclerosis, CNN: Convolutional neural network, DL: Deep learning, DWI: Diffusion-weighted imaging, ML: Machine learning, MRI: Magnetic resonance imaging, NMOSD: Neuromyelitis optica spectrum disorder, RF: Random forest, rs-fMRI: Resting-state functional magnetic resonance imaging, SVM: Support vector machine

Table 4. Brief PROBAST-informed qualitative risk-of-bias appraisal of the three primary prognostic studies discussed in Section 4

Study	Participants	Predictors	Outcome	Analysis	Overall judgment
Kaya et al. (23)	High concern (n=23; single-center convenience sample)	Low concern (clearly defined questionnaire and clinical predictors)	Low concern (RLS severity clearly defined)	High concern (no external validation; high model-to-sample-size ratio)	High risk of bias
Ozdogar et al. (24)	Unclear concern (single-center; recruitment not fully detailed)	Low concern (routinely collected clinical, demographic, and cognitive features)	Low concern (EDSS is a standardized, well-defined outcome)	High concern (no external validation; correlation-based feature selection from 126 to 42 features in n=231; strong baseline-outcome autocorrelation, as discussed in Section 4.1)	High risk of bias
Emec et al. (25)	Unclear concern (larger cohort, but repeated pregnancies per woman were not treated as clustered observations)	Low concern (reproductive, obstetric, and clinical predictors clearly defined)	Low concern (categorical ΔEDSS outcome clearly defined)	Unclear concern (no external validation reported; non-independence of repeated pregnancies)	Unclear risk of bias

Judgments reflect information available in the published reports and the summaries in Section 4 of this review; they were not derived from a full protocol-level PROBAST assessment

EDSS: Expanded Disability Status Scale, PROBAST: Prediction Model Risk of Bias Assessment Tool, RLS: Restless legs syndrome

Table 5. Validation strategies, sample sizes, and class balance underlying the diagnostic performance measures reported in Table 3

Diagnostic task	Data/model type	Validation strategy	Sample size	Class balance
MS versus healthy controls	DL (CNN, U-Net) on structural MRI	Not reported in source review; varies by underlying study	Not aggregated across underlying studies	Not reported
MS versus healthy controls	Conventional ML (SVM, RF, logistic regression) on quantitative MRI/ DWI/rs-fMRI	Not reported in source review; varies by underlying study	Not aggregated across underlying studies	Not reported
Overall ML/DL diagnostic performance	Mixed ML/DL, meta-review of 103 studies	Mixed across the 103 studies reviewed; predominantly internal cross-validation or hold-out	Aggregated across 103 studies; not stated as a single figure	Not reported
Classification studies specifically	Mixed ML/DL, same meta-review subset	Mixed across studies reviewed; predominantly internal cross-validation or hold-out	Aggregated across studies; not stated as a single figure	Not reported
MS versus NMOSD (gray matter only)	RF	Not reported in source review	Not reported in source review	Not reported
MS versus NMOSD (multiparametric)	MRI + clinical + neuropsychological model	Not reported in source review	Not reported in source review	Not reported

Entries reflect what is reported in the citing review articles (1,7) rather than the primary studies they summarize (see Section 2); "not reported" is itself an informative finding regarding the granularity of the currently available evidence

MS: Multiple sclerosis, CNN: Convolutional neural network, DL: Deep learning, DWI: Diffusion-weighted imaging, ML: Machine learning, MRI: Magnetic resonance imaging, NMOSD: Neuromyelitis optica spectrum disorder, RF: Random forest, rs-fMRI: Resting-state functional magnetic resonance imaging, SVM: Support vector machine

or summarized above and should not be considered a substitute for a formal PROBAST or TRIPOD+AI audit conducted with access to the full study protocols; rather, it is intended to illustrate, without exhaustively documenting, the methodological domains most likely to influence generalizability.

Future Directions

Priorities for future work include: (i) developing multimodal models that integrate MRI with OCT, fluid biomarkers, and clinical history to improve upon single-modality systems (6,18); (ii) establishing open, standardized, multicenter datasets and implementing federated learning to address generalizability limitations across diagnostic as well as prognostic applications (19); (iii) placing greater emphasis on model interpretability and prospective validation in clinically realistic differential-diagnosis and longitudinal-prognosis settings (1,19); and (iv) externally validating prognostic models across healthcare systems while incorporating imaging or fluid biomarkers alongside the clinical variables evaluated to date (24,25). Given that DL as well as ensemble tree-based models remain largely opaque (Section 6), explainable artificial intelligence frameworks, such as SHAP and LIME, are increasingly being proposed as potential approaches to bridging the gap between model outputs and clinical trust. By attributing a model's output to specific input features on a per-patient basis, these methods could enable clinicians to scrutinize individual predictions against established MS pathophysiology rather than treating model outputs as opaque scores, potentially supporting regulatory evaluation and guideline acceptance of these tools.

Conclusion

ML can detect MS primarily by identifying lesions and disease-associated patterns on MRI, with an expanding evidence base for applications involving OCT and fluid biomarkers. Once a diagnosis is established, the same broad model families (particularly tree-based ensembles such as RF and XGBoost) can generate clinically meaningful predictions of disability progression, context-specific disability change, and symptom-specific severity, often achieving higher reported performance when outcomes are framed categorically rather than continuously. Across both diagnostic and prognostic applications, the strongest and most consistent evidence supports computer-assisted analysis rather than autonomous clinical decision-making: performance remains sensitive to dataset size and quality, single-center study designs, and the clinical realism of validation settings. Headline accuracy measures should also be interpreted cautiously when model performance may be driven substantially by strongly autocorrelated baseline variables (Section 4.1) rather than by a novel predictive signal. Continued progress will depend less on isolated algorithmic improvements and more on multimodal data integration, standardized open datasets, and rigorous prospective, multicenter validation across the diagnostic as well as prognostic dimensions of MS care.

Footnotes

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

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