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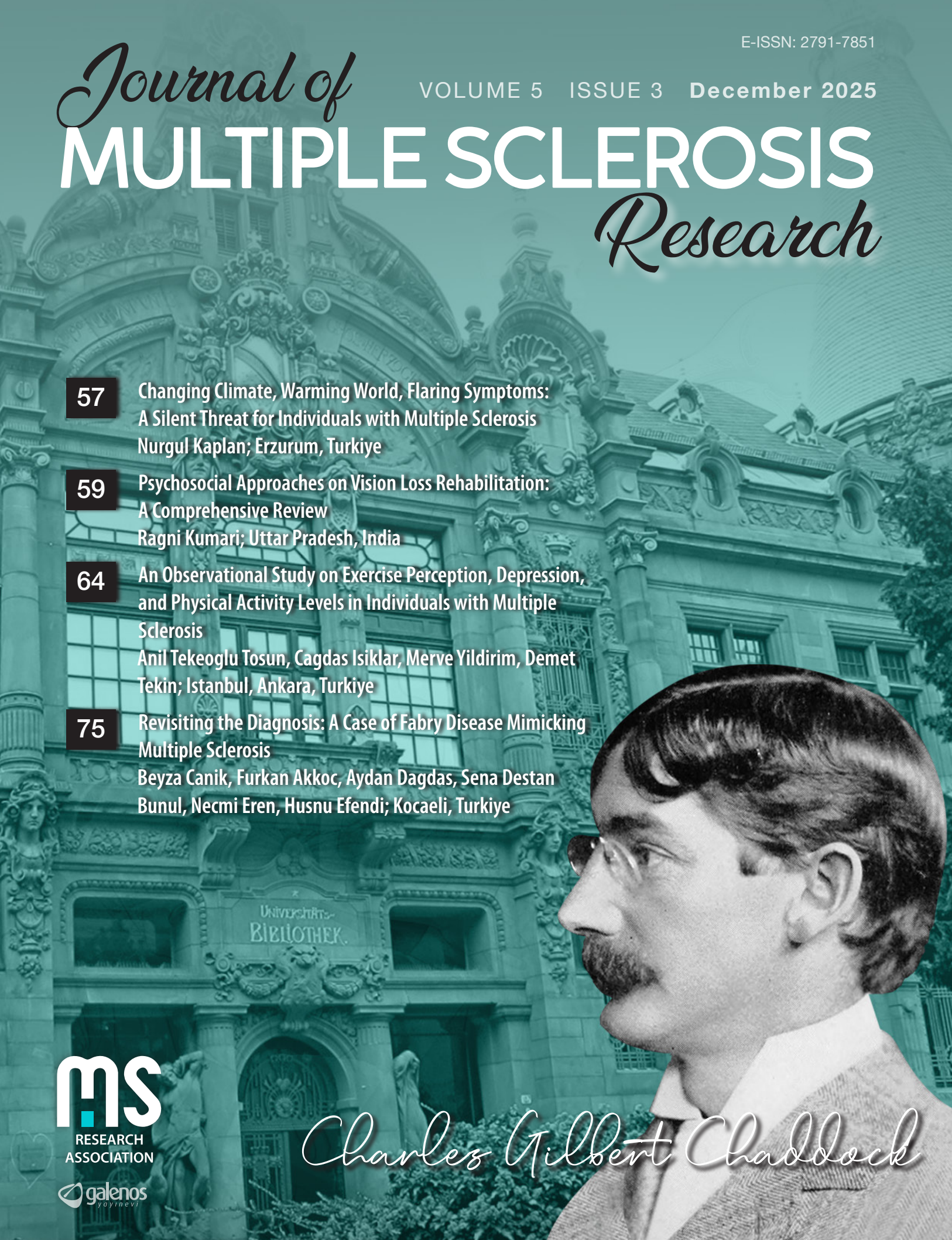

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LETTER to the EDITOR

Changing Climate, Warming World, Flaring Symptoms: A Silent Threat for Individuals with Multiple Sclerosis

Nurgul Kaplan

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Keywords: Climate change, multiple sclerosis, symptom exacerbation

Dear Editor,

Climate change represents one of the most pressing global challenges of the modern era, adversely affecting quality of life through rising ambient temperatures, altered precipitation patterns, and an increasing frequency of extreme weather events linked with glacial melting. These environmental changes not only compromise physical health but also exert profound effects on mental well-being and public health by exacerbating both acute and chronic disease conditions (1).

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that primarily affects young adults (2). Growing evidence suggests that climate-related environmental stressors may amplify neuroinflammatory activity and disrupt immune homeostasis in individuals with MS, thereby contributing to symptom exacerbations (3). Although some inconsistencies exist across studies, the majority of available data indicate that rising temperatures and extreme environmental conditions are associated with worsening MS symptoms and an increased risk of hospitalization (4).

Heat sensitivity, commonly referred to as the Uhthoff phenomenon, is characterized by a transient worsening of neurological function following exposure to elevated temperatures and is frequently observed in individuals with MS (5). Increased ambient temperatures are strongly associated with heightened fatigue, impaired gait performance, and an elevated risk of falls in this population (6). Furthermore, mobility limitations related to climate-induced symptom aggravation may hinder timely access to essential resources during emergencies, further increasing vulnerability among individuals with MS (3).

Recent evidence indicates that exposure to elevated environmental temperatures significantly increases symptom severity in individuals with MS, with each 1 °C rise in temperature associated with a measurable worsening of pre-existing neurological manifestations (7). Short-term heat exposure has also been shown to transiently impair physical performance, elevate core body temperature, and reduce mobility in heat-sensitive patients with MS (8). Furthermore, hot weather has been associated with an increased susceptibility to MS relapses, a risk expected to escalate with the progression of global climate change (9).

An investigation into healthcare utilization patterns revealed that individuals with MS are more likely to seek acute medical care during periods of extreme heat, reflecting a growing strain on healthcare systems under climate-related stress (10). Climate change-related disasters further jeopardize the health and safety of vulnerable populations, including individuals with MS. In disaster contexts, adequate preparedness among MS patients and proactive identification of their specific needs by healthcare professionals are essential to ensure continuity of care and reduce morbidity both during and after such events (11).

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In conclusion, substantial gaps remain in understanding the full extent of climate change effects-a major ongoing global challenge-on individuals with MS and the progression of their symptoms. Targeted strategies must be developed to mitigate these adverse effects. Systematic documentation of symptom exacerbation and climate-related environmental stressors using robust scientific data is crucial, as is timely communication with healthcare authorities and continuous education of healthcare professionals regarding climate-sensitive neurological conditions. The implementation of evidence-based regulatory frameworks will support policy development aimed at improving the quality of life of individuals with MS and provide a solid scientific foundation for future interdisciplinary research. Given this emerging silent threat, coordinated action by healthcare providers and policymakers is urgently required. A global, systematic assessment of the climate-related risks faced by individuals with MS is essential to ensure the delivery of high-quality, holistic care.

Footnotes

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J Mult Scler Res 2025;5(3):59-63

REVIEW

Psychosocial Approaches on Vision Loss Rehabilitation: A Comprehensive Review

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Abstract

Vision impairment (VI) affects more than 2.2 billion people worldwide, profoundly influencing their quality of life, social participation, and access to rehabilitation services. This narrative review examines key methodological strategies employed in social research on VI and rehabilitation, encompassing qualitative, quantitative, mixed-methods, and participatory approaches. It evaluates the strengths and limitations of these methodologies in capturing the diverse lived experiences of individuals with VI and in assessing rehabilitation outcomes. The review identifies several persistent challenges in the field, including the need to ensure accessibility in research instruments, achieve representative sampling across diverse populations, and address ethical considerations such as informed consent and confidentiality. It also discusses measurement difficulties, particularly in evaluating complex constructs like quality of life, social inclusion, and rehabilitation success, with special attention to cultural and contextual influences. Furthermore, the review emphasizes the importance of culturally sensitive and inclusive research designs, especially in settings constrained by limited resources and technological infrastructure. It highlights the impact of the digital divide and the barriers associated with assistive technology use, which may affect both data collection and participant engagement. The review advocates for participatory research models in which individuals with VI are actively engaged as co-researchers, ensuring that their perspectives directly inform research design and interpretation. Finally, the review calls for future research that prioritizes adaptive, inclusive, and culturally responsive methodologies to promote equitable and effective rehabilitation interventions. Such approaches are essential for advancing the quality of life and social well-being of individuals with VI globally.

Keywords: Vision impairment, rehabilitation, social research, methodological strategies, qualitative methods, quantitative methods, participatory research

Introduction

Vision impairment (VI) is a major global health concern, affecting more than 2.2 billion people worldwide and profoundly influencing functional capacity, psychosocial well-being, and social participation (1). Social research in this field seeks to understand the lived experiences of individuals with VI, identify barriers to inclusion, and evaluate the effectiveness of rehabilitation services and assistive technologies (2). The social dimensions of VI—encompassing stigma, social isolation, and accessibility—require methodological approaches that account for the specific needs and circumstances of this population (3).

Conducting research with individuals who have VI poses several methodological challenges, including ensuring accessibility of research instruments, achieving representative sampling across diverse populations, and addressing ethical considerations such as informed consent and confidentiality (4). Moreover, assessing complex constructs such as quality of life, social inclusion, and rehabilitation success demands methodological sensitivity to cultural, psychological, and environmental contexts. This review synthesizes the principal methodological strategies in social research on VI and rehabilitation, evaluates their respective strengths and limitations, and identifies key areas for further inquiry.

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Transparency and Openness

In accordance with the Transparency and Openness Promotion guidelines, this narrative review incorporates several measures to ensure clarity and integrity throughout the review process:

- **Literature Search and Selection Criteria:** The literature search was conducted using clearly defined inclusion and exclusion criteria to achieve comprehensive and unbiased coverage of relevant studies. Details of the search strategy, including the databases consulted and specific search terms used, are detailed in the supplementary materials.
- **Data Availability:** As a narrative review synthesizing previously published studies, no new data were generated. However, all cited sources are publicly accessible, and complete references are provided to facilitate verification and replication of the review process.
- **Preregistration:** This review was not preregistered, as preregistration is typically not applicable to narrative reviews. Nevertheless, the methodology, including the review protocol, was designed to minimize potential bias by adhering best practices for systematic searching and study inclusion.
- **Conflict of Interest and Funding:** A declaration of potential conflicts of interest and funding sources is included in the manuscript to maintain transparency and ethical accountability in the research process.
- **Open Access:** The manuscript will be published in an open-access journal to promote broad dissemination and accessibility.

Methodological Strategies in Social Research on VI and Rehabilitation

Research on VI and rehabilitation employs a range of methodological strategies, each offering distinct advantages and limitations depending on the study objectives, population, and context. The primary approaches include qualitative, quantitative, mixed-methods, and participatory research designs. This section critically evaluates the advantages and challenges of each methodology and emphasizes the importance of context-specific application in VI research.

Qualitative Methods

- Qualitative approaches are fundamental for understanding the subjective experiences, psychosocial processes, and meaning-making associated with living with VI. These methods are particularly valuable in community-based or resource-limited settings where capturing localized realities and social dynamics is essential.
- **In-depth Interviews:** These allow for flexible, open-ended exploration of personal narratives, including psychological adjustment to VI. For example, Nakade et al. (5) used interviews to examine identity transformation and emotional adaptation following late-onset VI. Interview methods can be adapted using accessible formats, such as audio-recorded consent procedures or screen reader-compatible materials.
- **Focus Groups:** Group discussions facilitate shared experiences and peer dynamics, particularly regarding stigma, social support, and rehabilitation participation. Williams (6) demonstrated that focus groups with individuals with VI generated valuable insights into the role of peer support networks (7). However, this method may inadvertently exclude participants who experience social anxiety or require individualized communication accommodations.
- **Case Studies and Ethnography:** These methods provide in-depth contextual understanding, making them useful for examining long-term rehabilitation processes or challenges related to navigating public spaces and workplace environments (8). Although these methods provide rich, nuanced data, these are limited in generalizability due to small sample sizes and context-specific findings.

Critical Insight: Qualitative methods excel at capturing emotional, cultural, and lived-experience perspectives. These approaches are most effective in exploratory research phases or when informing program design, service design, and policy development.

Quantitative Methods

Quantitative designs provide measurable, comparable, and generalizable data on VI prevalence, intervention outcomes, and psychosocial indicators. These approaches are particularly well suited to clinical research, policy evaluation, and longitudinal analysis, where statistical rigor is essential.

- **Surveys and Standardized Instruments:** Instruments such as National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) and VI offer structured metrics of vision-related quality of life and functional impairment (9). While these tools are essential for assessing large-scale interventions, they may overlook subjective perceptions and culturally specific nuances.
- **Longitudinal Studies:** Tracking participants over extended periods enables the identification of rehabilitation trajectories and key adjustment factors (10). However, attrition, mobility limitations, and evolving support needs can compromise retention and the validity of data within VI populations.
- **Experimental and Quasi-Experimental Designs:** Randomized controlled trials (RCTs) remain the gold standard for determining intervention efficacy. Nevertheless, RCTs are often challenging in VI research due to limited sample

sizes, ethical constraints, or difficulties in standardizing interventions. Quasi-experimental designs, which allow naturalistic group comparisons, therefore provide a more adaptable alternative (11).

Critical Insight: Quantitative methods generate robust evidence for policy and program validation, yet they depend on accessible and inclusive instruments and may insufficiently capture the emotional or social complexity of rehabilitation experiences.

Mixed-methods Approaches

Mixed-methods research integrates qualitative and quantitative techniques to encompass both the breadth and depth of rehabilitation experiences. This design is especially valuable when evaluating multifaceted programs that combine clinical care, psychological support, and assistive technology training.

For example, Stone (12) applied a mixed-methods framework to investigate the impact of assistive technology on social inclusion in low-income communities. Quantitative data measured device usage and satisfaction, while qualitative interviews revealed underlying barriers such as stigma and digital illiteracy.

Critical Insight: Mixed-methods designs effectively bridge gaps, but they require methodological alignment and advanced skills in data integration. They are particularly advantageous in program evaluation, where both stakeholder perspectives and quantifiable outcomes must both be addressed.

Participatory Research

Participatory research actively involves individuals with VI as co-researchers rather than passive participants. Grounded in principles of equity, empowerment, and inclusion, it hols particular relevance for disability research.

Veraart et al. (13) showed that participatory design enhanced the relevance and accessibility of survey instruments. Participants provided feedback on questionnaire layout, terminology, and dissemination strategies, ensuring cultural and contextual appropriateness.

Critical Insight: Participatory methods strengthens research legitimacy and foster community trust, particularly among marginalized groups. However, they require considerable time, training, and relationship-building, and may not always be feasible within institutional or funding constraints.

Comparative Evaluation of Methodologies

Each methodological approach serves distinct purposes depending on the research context:

- Clinical settings benefit most from quantitative and mixed-methods designs, where standardized data support clinical decision-making and service optimization.
- Community-based and culturally diverse contexts are best served by qualitative or participatory approaches that capture localized realties and enhance research relevance.
- Policy-driven studies frequently depend on quantitative evidence, yet integrating qualitative insights strengthens advocacy for inclusive services.

Although no single approach is universally optimal, effective research aligns the chosen methodology with the study context, adapt instruments for accessibility, and ensures meaningful participant engagement. Trade-offs between depth and generalizability, feasibility and rigor, or standardization and flexibility should be weighed carefully during study design.

To complement this analysis, Table 1 (added below) summarizes the principal characteristics, applications, and limitations of each methodological approach.

Key Methodological Issues and Challenges

- **Accessibility and Inclusion:** Ensuring accessibility in research instruments is essential. Standard printed questionnaires are inadequate for individuals with VI.

Table 1. Comparative summary of methodologies in VI research

Methodology	Strengths	Limitations	Ideal use cases	Common pitfalls
Qualitative (e.g., interviews, ethnography)	Rich insights into lived experiences; flexible and adaptive	Small samples; subjective interpretation	Community-based research, stigma exploration, identity reconstruction	Lack of generalizability; interviewer bias
Quantitative (e.g., surveys, RCTs)	Standardized measures; generalizable results	Requires large, representative samples; less contextual depth	Clinical trials; policy evaluation; outcome metrics	Accessibility issues; underrepresentation of marginalized groups
Mixed-methods	Combines depth and breadth; triangulation of data	Complex to design and analyze; resource-intensive	Evaluating both outcomes and user satisfaction	Methodological inconsistency; integration challenges
Participatory research	Promotes empowerment and relevance; improves accessibility	Time-consuming; requires sustained engagement	Tool development; program co-design; research with underserved groups	Tokenism risk; need for careful facilitation

VI: Vision impairment, RCTs: Randomized controlled trials

Instruments must be available in alternative formats such as Braille, large print, or audio, and digital platforms should be compatible with screen readers and other assistive technologies (14). Failure to provide accessible materials can results in biased samples and the exclusion of certain participant groups (15).

- **Sampling Difficulties:** Recruitment challenges are substantial in VI research due to the geographic dispersion and diversity of the population. Convenience sampling is frequently employed, but this approach can introduce bias, particularly when specific subgroups, such as younger adults or urban residents, are overrepresented (16). Although purposive and snowball sampling techniques are useful for reaching specialized populations, they may also limit the generalizability of findings (12).
- **Thical Considerations:** Ensuring informed consent is critical in VI research. Consent forms should be available in accessible formats, and oral consent may be required for participants with limited literacy. Ethical considerations also extend to maintaining participant confidentiality, especially within smaller communities where individuals may be easily identifiable (17).
- **Measurement Challenges:** Measuring constructs such as quality of life and social inclusion presents significant methodological challenges. These constructs are inherently subjective and influenced by cultural and environmental factors (18). Standardized instruments, such as the NEI VFQ-25, may not fully capture the psychosocial and emotional dimensions of VI, highlighting the need for more sensitive and context-specific measures (10).
- **Cultural and Contextual Sensitivity:** The experience of VI varies across cultures, shaping perceptions of disability, rehabilitation, and social inclusion (19). Cross-cultural research must therefore consider language diversity, cultural variations in health perceptions, and local rehabilitation infrastructures. Studies conducted in low- and middle-income countries face additional challenges, including limited infrastructure, lower literacy levels, and greater technological constraints (20,21).

Future Directions and Recommendations

To enhance inclusivity and methodological rigor in VI research, future studies should prioritize the following areas:

- **Innovative Digital Tools:** Continued development of accessible digital platforms is essential to promote broad participation, particularly among individuals with limited access to technology (14).
- **Long-term Research:** Longitudinal studies should be emphasized to evaluate the sustained effectiveness of rehabilitation interventions over time (10).
- **Comprehensive Measurement:** Future research should aim to develop more sensitive and culturally relevant measurement instruments that integrate qualitative and quantitative data, enabling a more nuanced understanding of the impact of VI on quality of life and rehabilitation success (12).
- **Global Representation:** Greater efforts are needed to ensure that research samples reflect the diversity of the VI population, including participants from rural areas, older age groups, and culturally varied backgrounds (11).

Conclusion

Research on VI and rehabilitation requires an integrated application of qualitative, quantitative, and mixed-methods approaches to address the diverse needs of this marginalized population. While qualitative methods yield deep insights into personal experiences, quantitative approaches provide generalizable evidence on prevalence and intervention efficacy. Key challenges, including accessibility, achieving representative sampling, ethical consent, and bias reduction, must be addressed through culturally sensitive research designs and precise measurement strategies. Future studies should emphasize methodological rigor in conjugation with the active participation of individuals with VI, ensuring the development of more effective, equitable, and inclusive rehabilitation services that enhance quality of life and social participation globally.

Footnotes

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RESEARCH ARTICLE

An Observational Study on Exercise Perception, Depression, and Physical Activity Levels in Individuals with Multiple Sclerosis

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Abstract

Objective: Individuals with multiple sclerosis (MS) often exhibit reduced levels of physical activity (PA), which are influenced by psychological factors, including depression and perceptions of exercise. Accordingly, this study aimed to assess PA levels among individuals with MS and to examine the associations between depression, exercise perception, and PA levels.

Materials and Methods: A total of 80 individuals with MS (mean age: 32.71±9.22 years) participated in this cross-sectional study. Depression was evaluated using the Beck Depression Inventory, exercise perception was measured with the Exercise Benefits/Barriers Scale, and PA levels was determined through the International Physical Activity Questionnaire-Short Form.

Results: The majority of participants were classified as minimally active (72.5%), whereas 8.8% were inactive and 18.8% were very active. A weak but positive correlation was identified between depression and exercise barriers ($r=0.443$, $p<0.001$), as well as between depression and body mass index ($r=0.314$, $p=0.005$). No significant correlation was observed between depression and total PA level. Participants most frequently cited physical effort and environmental limitations as major barriers to exercise.

Conclusion: Although most individuals with MS acknowledge the advantages of exercise, depression, and perceived barriers can impede their participation in PA. Addressing both psychological and environmental factors may enhance exercise adherence and overall disease management in this population.

Keywords: Multiple sclerosis, physical activity, depression, exercise perception, IPAQ, EBBS

Introduction

Multiple sclerosis (MS) is a progressive, chronic, demyelinating disease that affects the white matter and subcortical structures of the central nervous system (CNS). Individuals with MS experience symptoms such as balance disorders, fatigue, muscle weakness, and sensory disturbances in the early stages, and widespread disability resulting from spasticity, bladder dysfunction, depression, pain, and cognitive impairment in the later stages (1,2). Nearly 2.5 million people worldwide are affected by this disease (3). MS causes progressive damage to the CNS, leading to symptoms including pain, fatigue, depression, mobility limitations, and reduced quality of life (QOL) (4-6). The neurodegenerative process associated with axonal and neuronal loss contributes to disease progression and various forms of CNS damage (6). Such CNS damage can result in pain, fatigue, depression, ambulatory and cognitive dysfunction, deconditioning, and diminished QOL (4).

Over the past decade, increasing evidence has shown that engaging in physical activity (PA) alleviates the aforementioned problems in individuals with MS and

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enhances their QOL. However, compared with the general population, individuals with MS engage in insufficient PA (1,7). PA has been demonstrated to reduce fatigue, depression, impairment, cognitive and walking difficulties, and to improve cardiorespiratory fitness, muscle strength, balance, endurance, and QOL (8,9). Recent studies published in 2025 have further highlighted these associations, examining internet-based PA promotion programs, aerobic exercise interventions, and perceived benefits and barriers among MS populations (10-12). Consequently, PA has been recognized as one of the most effective therapeutic strategies for comprehensive MS care (7), and guidelines have been established to promote PA within this population (13). Depression is one of the most common comorbidities in MS and is known to decrease motivation and adherence to PA. Moreover, patient's perceptions of the benefits and barriers of exercise strongly influence their willingness to engage in regular activity. Because both psychological and perceptual factors can determine exercise behavior, examining their interaction offers clinically relevant insights that can inform the design of more effective rehabilitation strategies aimed at increasing participation in PA and improving QOL in individuals with MS. The present study aimed to determine the PA levels of individuals with MS and to investigate the relationship between depression, exercise perception, and PA levels. We hypothesized that higher depression levels would be associated with greater perceived barriers to exercise and lower PA levels in individuals with MS.

Materials and Methods

Study Design

The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (Supplementary Table 1). A descriptive study design was employed.

Participants

The inclusion criteria for the study were a diagnosis of MS, literacy, and the absence of hearing or vision problems. The exclusion criteria included cognitive impairment and being in the active attack phase. The demographic information collected at registration included age, height, weight, and sex, along with self-reported data on marital status, education level, active employment status, and regular exercise habits. In addition, disease type and disability level [Expended Disability Status score (EDSS)] were determined by a neurologist. Ethical approval for the study was obtained from the Ethics Committee of Fenerbahce University (decision no: 6, date: 01.09.2021). Participant recruitment occurred between September 3, 2021 and March 3, 2022, following ethics approval granted on September 1, 2021. Questionnaires created using Google Forms were distributed to a total of 189 individuals with MS. Based on the inclusion criteria, 80 participants with MS (57 women and 23 men) were included in the study (Figure 1). A power analysis determined that a minimum of 78 participants was required to detect correlations among Beck Depression Inventory (BDI), Exercise Benefits/Barriers Scale (EBBS), and International Physical Activity Questionnaire (IPAQ) scores with a medium effect size (p=0.30), power of 0.80, and α=0.05 (14). Similar sample sizes have been reported in previous MS studies investigating PA, psychological factors, and exercise perception [Stroud et al. (15), n=84; Husu et al. (16), n=62]. Therefore, our final sample of 80 participants met the calculated requirement and was consistent with previous literature. Written informed consent for the use of data in research was obtained from all participants at enrollment.

Outcome Measures

The EBBS was used to assess exercise perception (17,18). The BDI (19) was used to evaluate depression levels, and the IPAQ was used to measure PA levels (20).

Expended Disability Status Score

The EDSS is widely used worldwide to evaluate and monitor neurological examinations in patients with demyelinating diseases such as MS and neuromyelitis optica. It assesses functional status on a scale from 0 to 10, where 0 indicates normal function and 10 indicates death due to MS. Lower scores represent less disability (21).

International Physical Activity Questionnaire

The IPAQ is available in long and short forms. The short form, introduced in 1996 by Michael Booth MD, was designed to determine the relationship between health and PA levels in adults. Saglam et al. (20) confirmed the validity and reliability of the Turkish version, with a Cronbach's alpha coefficient of 0.75. The short form includes seven items that collect information on time

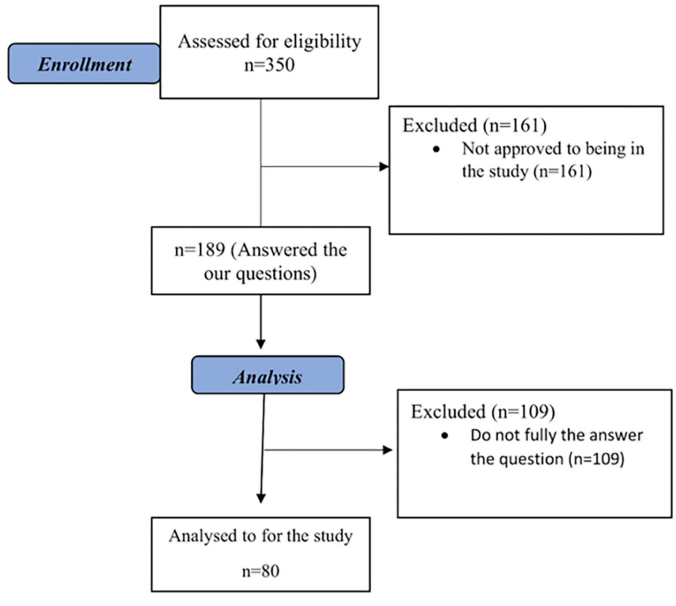

Figure 1. Flow chart of the study

spent walking, and engaging in moderate-to-vigorous or intense activities. Participants report the number of days and duration of vigorous PA, moderate-intensity PA, and walking during the previous week. The time spent in sedentary behavior (sitting, lying down) is also recorded. PA level is expressed in metabolic equivalent task (MET)-minutes. One MET is defined as 3.5 mL/kg per min, representing the amount of oxygen consumed per kilogram of body weight per minute at rest. Standard MET values in the IPAQ are 8.0 for vigorous activity, 4.0 for moderate activity, and 3.3 for walking. Total MET values are calculated based on the number of days and duration of PA performed during the past week (22). PA levels are categorized into three groups (23):

Inactive (category 1): The lowest level of PA; activities not meeting the criteria for categories 2 and 3.

Minimally Active (category 2): Individuals who meet one of the following criteria: a) vigorous activity for at least 20 minutes on 3 or more days, b) moderate-intensity activity or walking for at least 30 minutes per day on 5 or more days, c) moderate-intensity activity and walking totaling to at least 600 MET-min/week across 5 or more days.

Very Active (category 3): Equivalent to about one hour or more of moderate-intensity activity per day, sufficient for health benefits. a) vigorous activity on at least 3 days, yielding a minimum of 1500 MET-min/week, or b) a combination of 7 or more days of walking, moderate, or vigorous activity totaling at least 3000 MET-min/week.

The following MET values were used for IPAQ data analysis:

Walking=3.3 METs

Moderate PA=4.0 METs

Intense PA=8.0 METs

Exercise Benefits/Barriers Scale

The EBBS, developed by Sechrist et al. (17), assesses individuals' perceptions of the benefits and barriers associated with exercise. Higher total EBBS scores indicate greater recognition of exercise benefits. The Turkish version of the scale was validated by Ortabag et al. (18), with a Cronbach's alpha coefficient of 0.95. The scale consists of 43 Likert-type items rated as "1: strongly disagree, 2: disagree, 3: agree, 4: strongly agree." The total score range for the benefits scale is 29-116, and for the barriers scale, 14-56. Higher Benefit scores reflect greater perceived exercise benefits, whereas higher barriers scores indicate stronger perceived exercise Barriers (Table 1) (18).

Table 1. Subscales of the Exercise Benefits/Barriers Scale

Exercise Benefits Scale subdimensions (29 items)	
Life enhancement	(25,26,29,32,34,35,36,41)
Physical performance	(7,15,17,18,22,23,31,43)
Psychological view	(1,2,3,8,10,20)
Social interaction	(11,30,38,39)
Preventive health	(5,13,27)
Exercise Barriers Scale subdimensions (14 items)	
Exercise environment	(9,12,14,16,28,42)
Spending time	(4,24,37)
Physical effort	(6,19,40)
Family barrier	(21,33)

Beck Depression Inventory

The BDI was developed by Beck in 1961 to measure depression risk and the severity and progression of depressive symptoms in adults. The Turkish version's reliability and validity were confirmed by Hisli (24), with a Cronbach's alpha coefficient of 0.80 and validity coefficient of 0.74. It is a one-dimensional, 4-point Likert-type scale consisting of 21 items, each scored from 0 and 3 according to symptom severity. The pathological cut-off point is 17, with total scores ranging from 0 to 63. Score ranges are defined as follows: 0-9, no depression; 10-16, mild depression; 17-24, moderate depression; 25 and above, severe depressive symptoms (24). The BDI has been translated into multiple languages and shown strong cross-cultural reliability and validity. It has been used in Turkiye by Hisli (24) and Aktürk et al. (19) in various research and clinical settings, with Cronbach's alpha values of 0.80 and 0.85, respectively.

Statistical Analysis

Data analysis was performed using SPSS 22.0. Sample size was determined by power analysis. Descriptive characteristics of the participants were analyzed using percentage and frequency distributions. Mean and standard deviation (SD) values were calculated for scale analyses. Effect size was determined using Cohen's (d) and eta-squared (η^2) coefficients. Comparisons by demographic variables (sex, marital status, education) were exploratory and analyzed using frequency/percentage distributions and chi-square tests where applicable. No formal correction for multiple testing was applied.

Results

Key Characteristics of the Patients

The study initially included 189 individuals with MS and an EDSS score between 1 and 5. However, based on the exclusion criteria, data from 80 patients who completed the survey were analyzed. The participants' ages ranged from 18 to 63 years, with a mean of 32.71±9.22 years. The mean disease duration ranged from 1 to 40 years, with an average of 3.81±5.46 years. Detailed information on key characteristics is provided in Table 2.

The mean ± SD, minimum, and maximum scores of participants for the EBBS, IPAQ, and BDI are presented in Table 3. As shown in Table 3, the total IPAQ scores demonstrated high variability (mean ± SD=2116±1825 MET-min/week), indicating a skewed distribution of self-reported PA.

The frequency and percentage distribution of participants' PA

Table 2. Characteristics of the patients		
Groups	**Frequency (n)**	**Percentage (%)**
Sex		
Male	23	28.7
Female	57	71.2
Marital status		
Single	46	57.5
Married	34	42.5
Education status		
High school or lower	18	22.5
University	48	60.0
Post-graduate	14	17.5
Active working status		
Yes	35	43.8
No	45	56.2
Regular exercise status		
Yes	23	28.7
No	57	71.2
	Mean	**SD**
Age (year)	32.710	9.222
Weight (kg)	67.800	17.390
Height (cm)	168.340	8.999
BMI	23.749	4.784
EDSS	2.210	1.187
Disease duration (year)	3.810	5.468

EDSS: Expended Disability Status Score, BMI: Body mass index, SD: Standard deviation

levels are shown in Figure 2. Based on the PA classification, 7 participants (8.8%) were inactive, 58 (72.5%) were minimally active, and 15 (18.8%) were very active.

The parameters examined and the results of the correlation analyses are presented in Table 4.

The correlation between age, body mass index (BMI), EDSS, disease duration, total benefits, total barriers, total EBBS, depression, and IPAQ scores revealed the following: a positive weak correlation between EDSS and age ($r=0.433$, $p<0.001$); a positive moderate correlation between disease duration and age ($r=0.537$, $p<0.001$); a positive moderate correlation between disease duration and EDSS ($r=0.535$, $p<0.001$); a positive weak correlation between total barriers and BMI ($r=0.347$, $p=0.002$); a positive very high correlation between EBBS total and total benefits ($r=0.949$, $p<0.001$); a positive weak correlation between depression and BMI ($r=0.314$, $p=0.005$); and a positive weak correlation between depression and total barriers ($r=0.443$, $p<0.001$). No other correlations were statistically significant ($p>0.05$).

The results of all analyses comparing scale scores according to descriptive characteristics are provided in Table 5. Total benefits, barriers, EBBS total, depression, and PA scores did not differ significantly by sex ($p>0.05$). Total benefits, EBBS total, and depression scores showed no significant differences by marital status ($p>0.05$). Similarly, total benefits, barriers, EBBS total, depression, and PA scores did not differ significantly by education level ($p>0.05$). Benefits, barriers, EBBS total, depression, and PA scores were also not significantly different according to active employment status ($p>0.05$). Finally, EBBS total and depression scores showed no significant difference according to regular exercise status ($p>0.05$).

Table 3. Mean scores of the EBBS, IPAQ and depression					
	n	**Mean**	**SD**	**Min**	**Max**
Life enhancement	80	24.225	5.313	8.000	32.000
Physical performance	80	26.575	5.334	8.000	32.000
Psychological view	80	18.838	4.232	6.000	24.000
Social interaction	80	10.550	2.599	4.000	16.000
Preventive health	80	9.200	2.113	3.000	12.000
Total benefits	80	89.388	17.765	32.000	116.000
Exercise environment	80	11.413	2.745	6.000	21.000
Spending time	80	5.788	1.429	3.000	10.000
Physical effort	80	7.588	2.353	3.000	12.000
Family barrier	80	3.638	1.478	2.000	8.000
Total barriers	80	28.425	5.708	14.000	44.000
EBBS total	80	117.813	17.898	59.000	145.000
Depression	80	15.600	9.853	1.000	51.000
IPAQ physical activity	80	2116.181	1825.311	450.000	9513.000

EBBS: Exercise Benefits and Barriers Scale, IPAQ: International Physical Activity Questionnaire, SD: Standard deviation

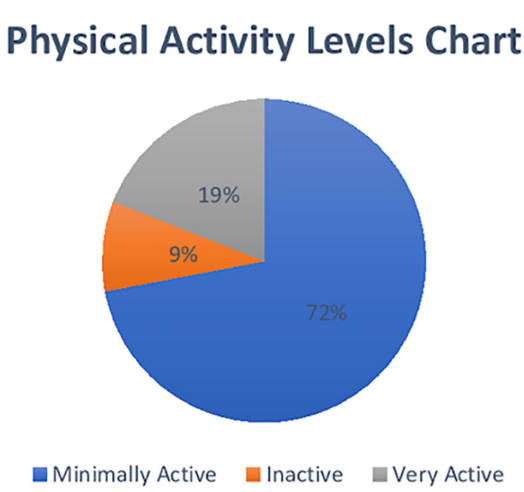

Figure 2. Physical activity levels chart

Discussion

The main finding of this study is that individuals with MS recognize the benefits of exercise; however, they consider depression, lack of physical effort, and environmental factors as major barriers to participation. Although participants believed that depression negatively affected their PA levels, this relationship was not statistically significant.

The present study aimed to determine whether depression influences exercise perception and PA levels in individuals with MS. The mean age of the 80 participants was 32.71 years, and most were university graduates. The mean EDSS score of 2.21 indicates that participants had mild disability. Studies in the literature using this scale have shown a positive correlation between EDSS score and age (25). The positive correlations observed in our study between EDSS, age, and disease duration are consistent with these findings.

MS is a chronic neurodegenerative disease with diverse symptoms and an unpredictable course that can severely affect patient's QOL. Among these symptoms, depression is the prevalent psychiatric disorder (28). Although it is generally mild, the proportion of patients with moderate and severe depression is quite high (8,29). In our study, the mean BDI of 15.60 supports previous findings that MS patients commonly experience mild depression symptoms. Depression negatively affects QOL and is influenced by various factors, including socio-economic status, education level, and physical condition.

Sebastião and Motl (30) reported that a high BMI is associated with increased disease risk and longer disease duration in individuals with MS. They also identified links between elevated BMI and comorbidities such as cardiovascular diseases, musculoskeletal pain, arthritis, and hypertension (30). Cambil-Martín et al. (31) found that overweight MS patients had higher levels of depression, reduced functional capacity, and poorer health compared to those of normal weight. In our study, a

Table 4. Correlation analysis of the data

		Age	BMI	EDSS	Disease duration	Total benefit	Total barriers	EBBS total	Depression	IPAQ physical activity
Age	r	1.000								
	p	0.000								
BMI	r	-0.059	1.000							
	p	0.603	0.000							
EDSS	r	0.433**	-0.013	1.000						
	p	0.000	0.908	0.000						
Disease duration	r	0.537**	0.048	0.535**	1.000					
	p	0.000	0.672	0.000	0.000					
Total benefits	r	-0.076	-0.127	-0.204	-0.023	1.000				
	p	0.503	0.262	0.069	0.840	0.000				
Total barriers	r	0.115	0.347**	0.156	0.065	-0.137	1.000			
	p	0.309	0.002	0.166	0.568	0.224	0.000			
EBBS total	r	-0.039	-0.015	-0.153	-0.002	0.949**	0.183	1.000		
	p	0.733	0.892	0.176	0.986	0.000	0.105	0.000		
Depression	r	-0.019	0.314**	0.092	0.089	-0.123	0.443**	0.020	1.000	
	p	0.867	0.005	0.418	0.432	0.279	0.000	0.863	0.000	
IPAQ physical activity	r	0.123	0.091	-0.072	0.151	0.148	-0.142	0.102	-0.195	1.000
	p	0.277	0.421	0.524	0.182	0.190	0.208	0.370	0.083	0.000

*: <0.05, **: <0.01, pearson correlation analysis, EDSS: Expended Disability Status Score, EBBS: Exercise Benefits and Barriers Scale, IPAQ: International Physical Activity Questionnaire, BMI: Body mass index

Table 5. Differentiation of scale scores according to descriptive characteristics

Demographic characteristics	n	Total benefits	Total barriers	EBBS total	Depression	IPAQ physical activity
Sex		**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
Male	23	89.478±17.835	27.609±5.868	117.087±16.790	16.261±10.082	2623.804±2243.637
Female	57	89.351±17.896	28.754±5.661	118.105±18.462	15.333±9.837	1911.351±1604.374
t		0.029	-0.811	-0.229	0.379	1.595
p		0.977	0.420	0.820	0.706	0.115
Marital status		**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
Single	46	92.478±16.408	27.370±5.975	119.848±16.101	14.739±8.755	2520.011±2008.784
Married	34	85.206±18.897	29.853±5.064	115.059±19.994	16.765±11.201	1569.824±1392.334
t		1.837	-1.958	1.186	-0.908	2.368
p		0.070	0.054	0.239	0.367	0.020
Education status		**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
High school or lower	18	85.389±24.222	28.889±5.132	114.278±25.584	18.000±12.291	1822.417±1635.941
University	48	89.938±16.614	28.625±5.945	118.563±16.066	15.396±9.165	2227.844±1863.068
Post-graduate	14	92.643±10.867	27.143±5.789	119.786±11.570	13.214±8.631	2111.036±2008.090
F		0.709	0.436	0.472	0.954	0.317
p		0.495	0.648	0.626	0.390	0.729
Active working status		**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
Yes	35	90.229±16.863	28.314±5.285	118.543±17.631	13.371±7.963	2177.000±1930.418
No	45	88.733±18.599	28.511±6.074	117.244±18.281	17.333±10.875	2068.878±1759.890
t		0.371	–0.152	0.320	-1.810	0.261
p		0.711	0.880	0.750	0.064	0.795
Regular exercise status		**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
Yes	23	97.087±12.894	25.130±5.463	122.217±14.164	12.304±7.289	3216.696±2511.862
No	57	86.281±18.594	29.754±5.289	116.035±19.023	16.930±10.479	1672.114±1234.221
t		2.546	-3.506	1.407	-1.933	3.689
p		0.013	0.001	0.163	0.057	0.009

EBBS: Exercise Benefits and Barriers Scale, IPAQ: International Physical Activity Questionnaire, F: Analysis of variance test; t: Independent groups t-test , post-hoc: Tukey, least significant difference

positive correlation was observed between BMI and BDI scores, indicating that higher BMI was associated with higher levels of depression. Furthermore, individuals with higher depression scores demonstrated lower perceptions of exercise benefits and reported greater barriers to exercise.

Because effective strategies for preventing MS remain unclear, current research increasingly focuses on managing the disease and alleviating its symptoms. PA has been shown to yield both general and specific benefits for individuals with MS (9). Numerous studies have demonstrated that PA lays a crucial role in managing MS and meeting its physical challenges (9,15). Despite these benefits, individuals with MS tend to lead more sedentary lifestyles compared with the general populations (3,32,33). Multiple studies have confirmed that individuals with MS engage in less PA than healthy controls and fail to achieve sufficient PA levels despite increased efforts to promote its (3,9). In the present study, the IPAQ results showed that most participants were inactive or minimally active, consistent with previous findings. However, the extent to which this inactivity is associated with depression remains inadequately understood. Psychological distress in individuals with MS may contribute to inactivity, yet it remains uncertain whether this stems from limited awareness of PA benefits and reduced physical energy. Only a few studies using the EBBS scale have examined these parameters together in MS populations (15,29).

The EBBS, with includes benefit and barrier subdimensions, is a comprehensive tool assessing adults' perceptions of exercise benefits and barriers (18-88) (34). By identifying perceived deficiencies, this scale an help enhance motivation and improve attitudes toward exercise participation. In a study conducted to

examine perspective on PA and exercise using the EBBS, it was found that individuals' awareness was insufficient to promote exercise participation, and that the most significant barrier was related to physical effort (15). Zunft et al. (32) reported that one of the key parameters preventing exercise participation is time. In our study, lack of physical effort and environmental limitations were identified as the main factors preventing exercise. Participants stated that exercising caused physical fatigue, was difficult to perform, and that lacked the appropriate environment and financial resources to overcome these challenges. They also reported that family- and time-related problems were lower-level barriers to exercise. In addition, our study revealed that depression levels constitute a major obstacle to engaging in exercise. Plow et al. (33) investigated factors limiting PA by interviewing 13 individuals with MS and found that physical factors (such as access to facilities and weather conditions), social factors (including lack of support from family and friends), and health factors (such as fatigue or depression) were influential, findings consistent with those of the present study. Likewise, our results align with those of Kayes et al. (35) who surveyed 282 individuals with MS and found that the primary barriers to PA were self-efficacy and mental fatigue. In line with these findings, Ozden et al. (12) also emphasized that individuals with MS encounter significant barriers to PA, including environmental limitations, fatigue, and depressive symptoms. Their research confirmed the predictive role of exercise perception and kinesiophobia in physical inactivity, highlighting the multidimensional nature of exercise avoidance in this population. These findings further validate the importance of assessing both physical and psychological barriers when designing rehabilitation strategies for individuals with MS.

Many factors have been cited in the literature as contributing to PA deficiencies. These factors were also observed in our study, which demonstrated the relationship between depression and scores on the exercise barrier/benefit questionnaire. The most significant determinants were internal, particularly an individual's mental perception, sense of self-efficacy, and motivation level. Fifolt et al. (36) examined the relationship between exercise and self-efficacy in individuals with MS and reported that, although individuals believe in their own abilities, this perception may fluctuate over time. Enhancing self-efficacy and demonstrating individual's capacity for success may be an effective approach to increase PA levels among individuals with MS.

Strengthening self-efficacy and reinforcing individuals' confidence in their ability to succeed may thus represent an effective strategy for enhancing PA participation in MS. Furthermore, exercises with family members and friends may increase motivation and help make PA a sustainable part of daily life. Our findings contribute significantly to this field by showing that participants with low PA levels identified both perceived benefits and barriers to exercise. Specifically, on the exercise benefits scale, the highest mean score was observed for the physical performance subscale, while the lowest was recorded for the social interaction subscale. Participants emphasized improvements in muscle strength, physical fitness, flexibility, cardiovascular function, and endurance as the most important exercise-related benefits. Consistent with our findings, a study conducted among university students also reported the highest values for the physical performance subscale and the lowest for the social interaction subscale (37). Dalibaltaa and Davison (38) likewise found the same pattern for these subscales. Other results reported in the literature are consistent with our findings, and our study is particularly significant as it is the first to classify the EBBS according to subscales in individuals with MS. In recent years, studies have increasingly emphasizing the importance of identifying behavioral patterns and providing interventions to address deficiencies in order to increase PA levels and promote activity among individuals with MS (39). In this context, it is crucial to define depression and PA levels in MS patients and to explore their perspectives on exercise, as demonstrated in the present study. It is recommended that professionals working with individuals with MS conduct evaluations prior to implementing programs that include exercise and PA, taking into account the depression status of participants, and design interventions accordingly.

Study Limitations

Due to the length of the questionnaires, individuals with MS experienced difficulty completing them. A larger number of participants could potentially have been included through the use of shorter forms. Given the high variability observed in IPAQ scores, reporting both the mean ± SD and the median (interquartile range) would provide a more comprehensive description of the data. Although only mean ± SD values were available in the present study, this consideration should be addressed in future research. Another limitation of the study is the absence of detailed information regarding MS subtypes (RRMS, PPMS, SPMS). Since MS types may influence depression and PA levels, future studies should report and analyze subtype-specific outcomes. Additionally, because multiple subgroup comparisons were conducted without adjustments for multiple testing, the potential for type I error should be acknowledged, and these findings interpreted with caution. All outcome measures in this study were based on self-report questionnaires, which may be affected by recall and response bias. Furthermore, the cross-sectional design precludes drawing causal inferences between depression, exercise perception, and PA levels. Although the sample size met the calculated requirement, it remains relatively small and may limit the generalizability of the findings.

Conclusions

Depression influences PA levels and exercise perception in individuals with MS, highlighting the need for targeted interventions. Psychological problems may negatively affect exercise perception, leading to reduced participation in PA. Further studies are warranted in this area, as early interventions may positively influence disease prognosis. Future research should employ longitudinal designs to clarify causal relationships between depression, exercise perception, and PA. Moreover, intervention studies addressing both psychological (e.g., self-efficacy, depressive symptoms) and environmental (e.g., accessibility, social support) barriers could yield valuable insights for developing more effective rehabilitation strategies.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of Fenerbahce University (decision no: 6, date: 01.09.2021).

Informed consent: Was obtained from all individual participants included in the study. Participants completed electronic informed consent forms prior to enrollment.

Footnotes

Authorship Contributions

Concept: A.T.T., C.I., Data Collection or Processing: M.Y., Writing: A.T.T., C.I., D.T.

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

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Supplamentary Table 1. STROBE statement-checklist of items that should be included in reports of observational studies

	Item no	Recommendation	Page no	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Title page
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	3	End of the third page
Methods				
Study design	4	Present key elements of study design early in the paper	4	Participants part
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	Participants part
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	4	Participants part
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4	Outcome measures part
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5-6-7	Outcome measure part to end of the sixth page
Bias	9	Describe any efforts to address potential sources of bias	N/A	
Study size	10	Explain how the study size was arrived at	7	Data analysis

Supplamentary Table 1. Continued				
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Data analysis
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7	Data analysis
		(b) Describe any methods used to examine subgroups and interactions	N/A	
		(c) Explain how missing data were addressed	N/A	
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(e) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Key charecteristics of the patients
		(b) Give reasons for non-participation at each stage	8	Key charecteristics of the patients
		(c) Consider use of a flow diagram	4	Participants part/Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg., demographic, clinical, social) and information on exposures and potential confounders	Table 1 and Table 2	
		(b) Indicate number of participants with missing data for each variable of interest	8	Key charecteristics of the patients
		(c) Cohort study—Summarise follow-up time (eg., average and total amount)	N/A	
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A	
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9 and Tables of the study	
		(b) Report category boundaries when continuous variables were categorized	Table 2	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg., analyses of subgroups and interactions, and sensitivity analyses	N/A	

Supplamentary Table 1. Continued				
Discussion				
Key results	18	Summarise key results with reference to study objectives	9	First part of nineth page
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10-11-12-13	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10-11-12-13	
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10-11-12-13	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14	

*: Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies, STROBE: Strengthening the Reporting of Observational studies in Epidemiology, N/A: Not applicable

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org

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CASE REPORT

Revisiting the Diagnosis: A Case of Fabry Disease Mimicking Multiple Sclerosis

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Abstract

Fabry disease (FD) is a rare, X-linked lysosomal storage disorder that may mimic multiple sclerosis (MS) due to overlapping neurological symptoms and similar magnetic resonance imaging findings. We report a young man who was initially diagnosed with MS based on sensory symptoms and the presence of white matter lesions. However, the atypical lesion pattern, together with systemic signs including hearing loss and proteinuria, prompted a reevaluation of the diagnosis. Genetic testing confirmed FD, and subsequent family screening identified ten affected relatives, including the patient's mother. This case highlights the importance to recognizing red flags in atypical MS to ensure an accurate diagnosis and the early initaiation of disease-specific treatment.

Keywords: Multiple sclerosis, differential diagnosis, magnetic resonance imaging, Fabry disease

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system. Its clinical features and demyelinating lesions frequently overlap with the radiological and clinical presentations of several other diseases, thereby considerably broadening the differential diagnosis (1).

Metabolic disorders, such as Fabry disease (FD), are rare and often overlooked in the differential diagnosis of MS (2). FD is an X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, which result in alpha-galactosidase A deficiency.

This enzymatic deficiency leads to the systemic accumulation of globotriaosylceramide (Gb3) and its derivatives, causing progressive multiorgan dysfunction (3). Endothelial vascular involvement represents the primary pathology, with common manifestations affecting the nervous system, kidneys, heart, eyes, and skin (e.g., cerebrovascular diseases, angiokeratomas, cornea verticillata, proteinuria, and left ventricular hypertrophy). Males are typically more severely affected, whereas heterozygous females may also be symptomatic due to random X inactivation. It is the most common lysosomal storage disorder and has an estimated incidence of 1 in 40,000 (4). Its prevalence is reported as 0.31% in Turkiye among patients receiving renal replacement therapy (5).

White matter lesions resulting from cerebrovascular involvement may mimic demyelinating lesions and consequently lead to misdiagnosis (2). In this case report, we highlight the risk of FD being misdignosed as MS and emphasize the importance of thorough history and rigorous clinical, radiologic, and genetic evaluation to establish the correct diagnosis.

Case Report

A 32-year-old right-handed man presented for a second opinion regarding his diagnosis of MS. His neurological symptoms began at the age of 13 with recurrent, painful, self-limited paresthesias.

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At the age of 20, following the new onset hypoesthesia in the right upper and lower limbs accompanied by diplopia, brain magnetic resonance imaging (MRI) was performed. The MRI revealed T2 hyperintense cortical/juxtacortical and periventricular lesions suggestive of demyelination. Intravenous (IV) corticosteroids were administered with a diagnosis of MS. Cerebrospinal fluid (CSF) examination revealed no oligoclonal bands (OCBs).

Over subsequent years, he experienced similar relapses. Each relapse was treated with IV steroids, resulting in complete recovery, and no disease-modifying therapy was initiated. At the age of 23, when he was admitted to our hospital, neurological examination revealed brisk deep tendon reflexes in the right upper and lower extremities with preserved strength and coordination. Babinski's sign was absent. Distal lower limb paresthesias were present. His past medical history included bilateral hearing loss, and the family history revealed ischemic stroke in his mother.

Spinal MRI revealed no lesions, whereas brain MRI demonstrated stable cortical/juxtacortical and periventricular T2 hyperintense lesions (Figure 1 A-C), with accompanying T1 hypointensity in one lesion and no gadolinium enhancement (Figure 1D). Nerve conduction studies were normal, with no evidence of large fiber neuropathy. Transthoracic echocardiography was unremarkable. Urinalysis revealed proteinuria, which was confirmed by a 24-hour urine protein excretion of 894.6 mg/day. There were no evidence of angiokeratoma, cornea verticillata, or gastrointestinal/autonomic involvement.

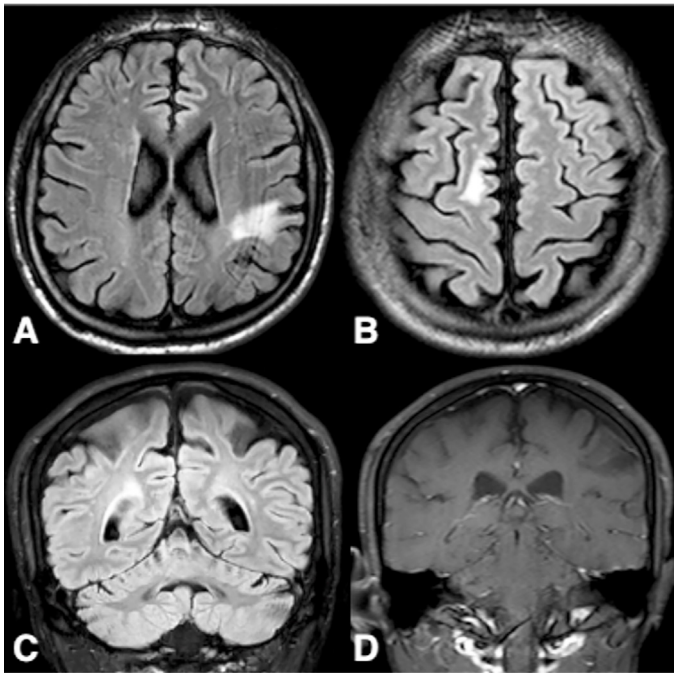

Figure 1. Brain MRI (A,B). Axial T2-FLAIR demonstrate hyperintense lesions in the left frontoparietal cortical/juxtacortical region (A) and the right posterior frontal cortical/juxtacortical region (B). (C) Coronal T2-FLAIR image demonstrates a right periventricular hyperintensity. (D) Coronal postcontrast T1-weighted image demonstrates T1 hypointensity without gadolinium enhancement in the left frontoparietal lesion

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

Genetic analysis identified a hemizygous c.680G>A (p.R227Q; p.Arg227Gln) pathogenic variant in the *GLA* gene. Plasma lyso-globotriaosylsphingosine (lyso-Gb3) level were also elevated at 6.4 ng/mL. Together with the systemic findings, these results supported the diagnosis of FD. Subsequent family screening identified FD in ten relatives, including the patient's mother, who carried the same pathogenic variant.

Enzyme replacement therapy (ERT) with agalsidase beta was initiated, and clopidogrel was started for secondary prevention of cerebrovascular events. During follow-up, the patient has remained clinically stable, with preserved cardiac and renal function, absence of recurrent cerebrovascular events, and a marked reduction in painful paresthesias while receiving ERT.

Written informed consent was obtained from the patient.

Discussion

FD frequently presents with neurological involvement, including painful distal paresthesias, small fiber neuropathy, early-onset ischemic stroke, and autonomic dysfunction (3). Typical brain MRI findings in FD include T2 hyperintense lesions located in the subcortical and deep white matter, consistent with an underlying small-vessel vasculopathy. Cerebral microbleeds are commonly observed, whereas haemorrhagic stroke remains rare (6). Additional reported imaging markers include vertebrobasilar dolichoectasia. The pulvinar sign was once considered pathognomonic; however, due to its low incidence and limited diagnostic specificity, it should no longer be regarded as a diagnostic marker (7,8).

From a radiological perspective, FD can closely mimic MS; however, several distinguishing features may assist in differentiation (Table 1). MS typically demonstrates optic nerve, periventricular, juxtacortical, and infratentorial lesions, frequently associated with gadolinium enhancement and common spinal cord involvement. In contrast, Fabry-related lesions are generally diffuse and patchy, exhibit a non-specific distribution, are typically non-enhancing, and usually spare the spinal cord (7,9). More recent studies have further shown that the absence of corpus callosum and infratentorial lesions may aid in differentiating FD from MS (8-10). Furthermore, the central vein sign (CVS), which is characteristic of MS lesions, is absent in FD; in one study, CVS was identified in 78.1% of relapsing-remitting MS lesions (57/73), whereas it was absent in Fabry lesions (0/36) (11). Beyond neuroimaging, CSF-specific OCBs are typically absent in FD. However, as spinal cord imaging and lumbar puncture are not routinely performed during the

Table 1. MRI characteristics to differentiate Fabry disease and multiple sclerosis

Feature	MS	Fabry disease
Lesion distribution	Optic nerve, periventricular, juxtacortical/cortical, infratentorial	Diffuse/patchy, non-specific distribution, supratentorial
Enhancement pattern	Frequent gadolinium enhancement in active lesions	Usually non-enhancing
Corpus callosum involvement	Common	Generally spared
Spinal cord involvement	Common	Generally spared
Central vein sign	Characteristic; present in many lesions	Absent

MS: Multiple sclerosis

diagnostic work up in many centers, the available comparative data remain limited.

Several case reports further illustrate this important diagnostic overlap. In a large Italian family, Russo et al. (12) described the presence of FD and MS in different members, emphasizing the critical role of meticulous neuroimaging review and detailed family history in establishing the correct diagnosis. Saip et al. (13) reported a woman initially misdiagnosed as MS who later developed typical dermatological findings (angiokeratomas) and proteinuria; leading to a confirmed diagnosis of FD through enzyme assay.

Our patient represented the index case of FD within his family. The combination of recurrent diplopia and sensory symptoms, together with periventricular, juxtacortical, and deep white matter lesions, appeared to satisfy dissemination in space and time according to the McDonald criteria, thereby leading to an initial misdiagnosis of MS. However, a definitive diagnosis should only be established after the careful exclusion of alternative causes. In this case, several red flags were already present, including the absence of corpus callosum and spinal cord involvement, a patchy lesion distribution, and the lack of gadolinium enhancement. Furthermore, childhood-onset painful paresthesias—consistent with small fiber neuropathy—together with the absence of CSF-specific OCBs and the presence of systemic features such as bilateral hearing loss and significant proteinuria, collectively argued strongly against a diagnosis of MS. Subsequent genetic analysis confirmed a the presence of pathogenic *GLA* variant.

Although misdiagnosis as MS has been reported more frequently in heterozygous women, adolescent-onset classical FD in a male patient who received multiple high-dose corticosteroid treatments is far less commonly described. This case further demonstrates that, once an index diagnosis is established, cascade family screening can identify multiple previously unrecognized affected relatives, thereby enabling earlier diagnosis and timely initiation of disease-specific therapy, with important public health implications.

This report has several limitations. Small fiber neuropathy was not specifically evaluated, as neither a skin biopsy for the assessment of intraepidermal nerve fiber density nor quantitative sensory testing was performed. This limitation restricts our ability to accurately quantify neuropathic involvement, which is common and frequently an early manifestation of FD, and which cannot be reliably detected by nerve conduction studies alone. Future evaluations incorporating skin biopsy, quantitative sensory testing, or corneal confocal microscopy would allow more precise characterization of small fiber dysfunction and its response to ERT.

Renal involvement was inferred on the basis of proteinuria, and a renal biopsy was not undertaken. In the absence of histopathological confirmation, we were unable to stage renal involvement or document characteristic Gb3/lyso-Gb3 deposition. Although renal biopsy is not always indicated in the presence of a pathogenic *GLA* variant, elevated lyso-Gb3, and stable kidney function, longitudinal monitoring of estimated glomerular filtration rate and proteinuria—and consideration of biopsy in the event of disease progression—would enhance disease staging and prognostic evaluation.

The OCB status was derived solely from patient-reported historical testing and was reported negative; however, the original lumbar puncture report and band count were unavailable, and repeat CSF analysis was not performed.

Conclusion

In conclusion, FD may satisfy the McDonald criteria at an early stage if alternative diagnoses are not actively considered and excluded. Prompt recognition is crucial, as early initiation of disease-specific treatment may improve long-term outcomes and prevent irreversible organ damage. Clinicians should therefore maintain a high index of suspicion for FD in patients presenting with atypical demyelinating features, particularly when systemic findings such as proteinuria or hearing loss are present. The implementation of a simple, low-cost diagnostic pathway may minimize diagnostic delay, facilitate appropriate therapy, and enable timely family counseling.

Ethics

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

Footnotes

Authorship Contributions

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

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

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