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REVIEW

Multiple Sclerosis-related Fatigue: An Updated Review of Pathophysiology and Associated Variables Contributing Factors

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Abstract

Multiple sclerosis (MS) is a chronic neurological disorder marked by demyelination and inflammation within the central nervous system. Patients frequently experience present with a range of symptoms, including visual disturbances, ataxia, tremors, motor weakness, fatigue, depression, spasticity, pain, bladder-bowel dysfunction, and cognitive impairment. Among these, fatigue is one of the most commonly reported and disabiling symptoms, affecting approximately 80% of patients and significantly diminishing their quality of life. The pathophysiology of MS realted-fatigue is complex and cannot be explained by a single mechanism. Current evidence indicates the involvement of multiple pathways, including neuroimmune dysfunction (characterized by elevated pro-inflammatory cytokines and decreased anti-inflammatory cytokines), monoaminergic deficits (such as reduced serotonin and dopamine availability in key brain regions), neuroendocrine system abnormalities (notably hyperactivation of the hypothalamic-pituitary-adrenal axis), and structural brain changes (including brain atrophy and increased lesion burden). In addition, secondary factors like depression and sleep disorders may intensify the severity of fatigue. Nevertheless, research into the primary mechanisms underlying fatigue remains limited, with most studies involving small sample sizes. In summary, fatigue in MS is a multifactorial symptom that significantly affects patients' daily lives. Clinical practice should incorporate routine fatigue assessment, and further comprehensive research is necessary to elucidate its underlying mechanisms. Optimizing treatment strategies, including both pharmacological and non-pharmacological interventions, is essential, with personalized approaches playing a pivotal role in effective management.

Keywords: Multiple sclerosis, fatigue, pathophysiology

Introduction

Multiple sclerosis (MS) is a neurological disorder marked by demyelination and inflammation of the central nervous system and is characterized by cycles of exacerbation and remission (1). Classified as an autoimmune illness, MS is among the leading neurological disorders resulting in impairment in young adults (2). MS occurs 2-3 times more frequently in women than in males and presents with a diverse array of symptoms. Commonly seen symptoms include visual abnormalities, ataxia, tremors, motor weakness, exhaustion, depression, spasticity, pain, bladder and bowel problems, and cognitive impairments. Among these, fatigue is one of the most frequently reported and severe symptoms (3,4).

In individuals with MS, fatigue is defined as a reduction in both physical and mental energy that significantly interferes with daily living activities (5). It affects approximately 50-90% of individuals with MS and may occur independently of physical disability (6,7). Fatigue can profoundly impact not only physical functioning but also psychosocial well-being and overall quality of life (5,8). Despite its prevalence, fatigue, being an invisible and difficult to quantify symptom, is frequently overlooked. Diagnosing fatigue is challenging, and its management is equally complex. This is due to the fact that the underlying pathophysiology of fatigue in MS cannot be attributed to a single factor; instead, several mechanisms have been proposed. These include immunological and inflammatory responses, structural and functional brain changes, and neuroendocrine

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system alterations, which are considered primary contributors to fatigue in MS (6,9-12). Additionally, secondary symptoms such as depression, sleep disturbances, pain, and urinary dysfunction also play a role in exacerbating fatigue (13-16). The objective of this review is to elucidate the pathophysiology mechanisms underlying fatigue in MS and to examine associated contributing factors in light of current evidence.

Search Strategy and Inclusion Criteria

A comprehensive literature search was conducted using multiple databases, including Google Scholar, PubMed, Web of Science, Scopus, EBSCO, and Turk Medline, to thoroughly explore the pathophysiology of fatigue in patients with MS. Due to the relatively limited number of studies available on this specific topic, no publication date restrictions were applied. Nonetheless, particular emphasis was placed on research from the past two decades to maintain relevance to the current understanding. The search strategy included a wide range of key terms, such as "MS," "fatigue," "pathophysiology," "neuroimmune dysfunction," "pro-inflammatory cytokines," "hypothalamic-pituitary-adrenal axis," "brain atrophy," "lesion load," "sleep disorder," "depression," and "urinary problems." A variety of study designs, including experimental, quasi-experimental, case-control, and descriptive studies, were reviewed to ensure a broad yet detailed analysis of the existing evidence.

Pathophysiology of Fatigue

Although fatigue is the most commonly reported complaint among patients with MS, its pathogenesis has remained poorly understood for many years. The subjective nature of this symptom, combined with the absence of tools for quantitative assessment, has led to fatigue being categorized as a "invisible" complaint. In the etiology of fatigue in MS, peripheral factors such as muscle disuse and deconditioning, joint abnormalities, and metabolic changes in muscle fibers play a relatively minor role (17). Increasing attention is being given to neuroimmune dysregulation, disruptions in neuroendocrine pathways, and changes in brain structure and function. Moreover, symptoms frequently observed in MS patients, such as sleep disturbances, depression, pain, and other sleep abnormalities, are thought to be closely associated with fatigue.

Neuroimmune Dysregulation

MS is a neurological disorder marked by inflammation, demyelination, axonal injury, and axonal degeneration. Immune system cells and cytokines involved in the pathophysiology of MS as an autoimmune disorder also contribute to the onset of fatigue (11). Several pro-inflammatory [interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-17, IL-35, tumor necrosis factor (TNF)-α, interferon gamma (IFN)-γ] and anti-inflammatory (IL-4, IL-5, IL-10, IL-13) cytokines have been associated with fatigue (18-20) TNF-α is a key pro-inflammatory cytokine that plays a major role in both local and systemic immune responses. In autoimmune diseases such as MS, its prolonged and unregulated release has been shown to increase neuroinflammatory activity, contributing to neurodegeneration (21-23). In a study by Heesen et al. (24), significantly elevated levels of pro-inflammatory cytokines (in blood serum) TNF-α and IFN-γ were reported in the blood serum of fatigued MS patients. Another study investigated the impact of exercise on cytokine levels and fatigue in MS patients, reporting that aerobic exercise led to a reduction in TNF-α levels in blood serum. This reduction in cytokine levels was also associated with an improvement in fatigue (25). In a more recent study, IL-10 levels were measured in the cerebrospinal fluid of MS patients, and the relationship between this cytokine and fatigue was explored. The study found a negative correlation between IL-10 levels and fatigue, suggesting that reduced expression of IL-10, an anti-inflammatory molecule, may exacerbate fatigue (26).

In a study examining the effects of an anti-inflammatory diet on biomarkers and fatigue in MS patients, increased IL-4 levels and no change in IL-17 levels were reported in blood serum. This study also concluded that the diet modulated inflammatory processes and improved fatigue (27). In a research conducted by Malekzadeh et al. (18), the relationship between several pro-inflammatory and anti-inflammatory cytokines and fatigue was examined in blood serum. The study found that only IL-6 was significantly correlated with fatigue, accounting for 21% of the variance in fatigue levels.

A study by Akcali et al. (28) reported significantly higher levels of IL-35 and IL-2 in the blood serum of MS patients compared to a control group. However, no significant difference in cytokine levels was observed between fatigued and non-fatigued MS patients. This finding suggests that although cytokine levels differ between MS patients and healthy individuals, they are not necessarily associated with fatigue severity. Chalah and Ayache (10) comprehensive review, which included studies published up to 2018, investigated the link between inflammation and fatigue in MS patients. According to this review, no significant association was found between T lymphocyte (T-cell) populations (e.g., CD3+CD4+ T-cell, regulatory T-cells) and fatigue. However, although data remain limited, B lymphocytes have been shown to contribute to the pathophysiology of cytokine-mediated fatigue (29,30). Despite the scarcity of studies, a connection between pro-inflammatory cytokines and fatigue has been noted. Based on existing literature, both pro-inflammatory and anti-inflammatory cytokines appear to be associated with fatigue severity in MS, though these studies frequently involve small sample sizes (Table 1). Similarly, Zielinski et al. (31) reported that the pathophysiology of fatigue in autoimmune diseases is multifactorial and requires further investigation for better clarity. This study also emphasized the significant role of cytokines (IL-1 IL-1β, TNF-α, IL-6, IFN-γ) in the pathophysiology of fatigue in autoimmune disorders. Although

Table 1. Studies on neuroimmune changes in the pathophysiology of fatigue in MS patients

Author name	Sample	Results
Heesen et al. (24)	30 patients with MS	√ Fatigued MS patients show significantly elevated TNF-α and IFN-γ levels.
Malekzadeh et al. (18)	35 patients with MS	√ IL-6 levels were significantly correlated with fatigue in MS patients (explaining 21% of variance).
Akcali et al. (28)	54 patients with MS and 26 healthy controls	√ IL-35 and IL-2 levels were significantly elevated in MS patients versus controls. √ Cytokine levels differ between patients with MS and controls but show no association with fatigue.
Mokhtarzade et al. (25)	40 patients with MS (22 experiment group, 18 control group)	√ Aerobic exercise reduces leptin and TNF-α levels in MS patients. √ Reduced cytokine levels are correlated with improved fatigue.
Mousavi-Shirazi-Fard et al. (27)	100 patients with RRMS	√ An anti-inflammatory diet increased IL-4 levels in MS patients. √ Diet can modulate inflammatory processes and improve fatigue.
Gilio et al. (26)	106 patients with RRMS	√ CSF IL-10 levels showed a significant negative correlation with fatigue. √ Higher CSF IL-10 levels are associated with lower fatigue scores. √ Reduced CSF IL-10 expression may contribute to fatigue exacerbation.

MS: Multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis, pwMS: Patients with multiple sclerosis; TNFα: Tumor necrosis factor-alpha, IFNγ: Interferon gamma, CSF: Cerebrospinal fluid, IL: Interleukin

cytokine activity is common across autoimmune diseases, the demyelination-related disruptions of neural conduction in MS may lead to distinct fatigue mechanisms. For instance, while fatigue in rheumatoid arthritis is mainly related to peripheral inflammation, the presence of cortical and subcortical lesions in MS contributes to both physical and cognitive fatigue. Furthermore, sleep disturbances and their impact on fatigue are more prevalent in MS than in other autoimmune conditions such as systemic lupus erythematosus or thyroiditis. This highlights the need for both immunomodulatory and neuroprotective therapies in the management of MS-related fatigue. Additionally, further studies with larger sample sizes are necessary to better clarify the relationship between neuroimmune processes and fatigue.

Neuroendocrine Changes

The neuroendocrine system possesses immunomodulatory potential. Moreover, bidirectional communication between the neuroendocrine and immune systems is mediated by messenger molecules such as hormones, neurotransmitters, and cytokines. Consequently, an imbalance within this system or its pathways can impact other physiological systems (32). In MS, a disease characterized by multifactorial etiopathogenesis, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis is frequently addressed (33). Although the precise cause of altered HPA axis activity in MS patients remain unclear, it is believed to result from hypothalamic damage or a generalized stress response triggered by such damage (34). Heesen et al. (35) investigated whether HPA axis dysregulation occurs in MS patients and whether this dysregulation correlates with disability levels and cognitive impairment. Although no significant differences were found between patients with relapsing-remitting MS (RRMS) and a control group, elevated HPA axis activity was reported in patients with progressive MS. Furthermore, the study found a significant association between increased HPA activity and levels of fatigue, cognitive impairment, and depression. In a separate study, HPA axis regulation was assessed using the combined dexamethasone/corticotropin-releasing hormone test RRMS patients. Gottschalk et al. (36) reported significantly higher concentrations of adrenocorticotropic hormone (ACTH) and evidence of HPA axis hyperactivation in MS patients experiencing fatigue. In a study involving patients with four different types of MS, primary progressive MS, secondary progressive MS, RRMS, and RRMS during an exacerbation, Ysrraelit et al. (37) observed that ACTH and cortisol levels were significantly elevated in all MS subgroups compared to control group. These findings further confirmed the presence of HPA axis hyperactivation in MS patients.

Akcali et al. (28) also reported generally higher HPA axis activity in MS patients than in controls. However, their findings indicated no significant difference in HPA parameters between fatigued and nonfatigued patients. Similarly, Heesen et al. (24) found that while HPA axis activity was significantly associated with cognitive dysfunction, it was not linked to fatigue. A recent cohort study with rigorous methodology found no association between primary fatigue, defined by the exclusion of secondary fatigue-induced conditions and daily cortisol levels, suggesting that different mechanisms may contribute to primary fatigue in MS patients (38).

When these studies are evaluated collectively, a relationship between fatigue and neuroendocrine dysregulation in MS patients is suggested. However, given the existence of studies reporting no association between fatigue and the HPA axis, further research with larger sample sizes and robust methodologies is necessary (Table 2).

Dysregulation of Monoaminergic Pathways

In MS, pro-inflammatory cytokines (TNF-α, IL-6, IFN-γ), which are activated by neuroinflammation, can disrupt both serotonin and dopamine systems, thereby contributing to fatigue. These cytokines redirect tryptophan metabolism toward the kynurenine pathway through the activation of the enzyme indoleamine 2,3-dioxygenase, which reduces serotonin synthesis. Additionally, they deplete tetrahydrobiopterin, a critical cofactor required for dopamine production. Moreover, pro-inflammatory cytokines suppress monoamine release and increase reuptake within the mesocorticolimbic pathways, leading to reduced synaptic monoamine levels. These alterations impair communication between the prefrontal cortex and basal ganglia, which in turn contributes to physical and cognitive fatigue, as well as to motivational deficits and anhedonia. Therefore, dysregulation of serotonergic and dopaminergic systems play a central role in the pathophysiology of fatigue in MS (13,15,39,40). A study by Hesse et al. (41) reported lower levels of the serotonin transporter (SERT) in the cingulate cortex, thalamus, and insula regions of the brain in MS patients compared to healthy controls (41). Furthermore, decreased SERT levels in the insular cortex were found to be associated with fatigue. In another recent study, abnormalities in dopamine, serotonin, and noradrenaline levels were identified in MS patients compared to healthy individuals (42). These monoaminergic disruptions were reflected in altered resting-state functional connectivity (RSFC): there was decreased RSFC in frontal and subcortical regions such as the cerebellum and thalamus, and increased RSFC in temporo-parieto-occipital cortical areas, including the bilateral precuneus. In conclusion, the study emphasized widespread dysregulation of monoaminergic networks in MS patients and highlighted that specific alterations within these networks contribute to the development of symptoms such as fatigue and depression.

Structural and Functional Changes in the Brain

Neuroimaging data indicate that both structural changes (such as brain atrophy and lesion load) and functional impairments in the brain are associated with primary fatigue in patients with MS. Although various studies have identified different brain regions involved, a consistent finding is the significant association between fatigue and both brain atrophy and lesion load.

A recent study by Eren et al. (43) examined the relationship between the morphometric structure of the pituitary gland and fatigue in MS patients. This study found that pituitary gland dimensions were significantly larger in MS patients compared

Table 2. Neuroendocrine changes in the pathophysiology of fatigue in patients with MS

Author name	Sample	Results
Heesen et al. (35)	40 patients with MS and 11 healthy controls.	√ The DEX/CRH test revealed HPA axis hyperactivation in progressive MS. √ Relapsing-remitting MS patients show normal HPA axis activity versus controls. √ HPA axis activation correlates with fatigue in MS patients.
Gottschalk et al. (36)	31 patients diagnosed with RRMS who did not receive disease-modifying therapy for MS.	√ This study evaluated HPA axis regulation using DEX/CRH testing. √ The current study reported elevated ACTH levels and HPA axis hyperactivation in fatigued patients with MS.
Heesen et al. (24)	15 MS patients with fatigue and 15 MS patients without fatigue.	√ HPA axis dysfunction shows no significant correlation with fatigue pathogenesis in MS. √ HPA axis dysfunction is associated with cognitive impairment in MS.
Ysrraelit et al. (37)	173 patients with MS and 60 healthy controls.	√ Cortisol, ACTH, and DHEAS plasma concentrations and urinary cortisol levels are significantly elevated in MS patients compared to healthy controls. √ HPA axis hyperactivation is present in MS patients.
Akcali et al. (28)	54 patients with MS diagnosed with RRMS and 26 healthy controls.	√ HPA axis hyperactivity is observed in MS patients versus controls. √ No significant differences in HPA were observed between fatigued and non-fatigued MS patients. √ Patients with MS showed elevated ACTH/cortisol levels but reduced CLIP levels compared to controls.
Malekzadeh et al. (38)	223 patients with MS diagnosed with multiple sclerosis who experienced fatigue.	√ Daily cortisol secretion was not correlated with MS-related fatigue.

MS: Multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis, HPA: Hypothalamus-pituitary-adrenal axis, ACTH: Adrenocorticotropic hormone, DHEAS: Dehydropianrosterone sulfate, CLIP: Corticotropin-like intermediate lobe peptide, DEX/CRH: Dexamethasone-corticotropin-releasing hormone

to a control group. Furthermore, structural differences in the pituitary gland were also observed between fatigued and non-fatigued patients. A long-term cohort study further demonstrated a relationship between fatigue and brain atrophy, independent of disability level (44). Similarly, a study involving patients with RRMS and low disability levels found that those experiencing high fatigue had significantly greater brain atrophy and lesion load compared to those without fatigue (45).

In contrast, Andreasen et al. (46) reported no significant difference in lesion load between fatigued and non-fatigued RRMS patients. However, the same study did identify regional brain atrophy in fatigued individuals. Several other studies have likewise reported regional brain atrophy in MS patients with fatigue (47-49).

Another recent study found that fatigue accompanied by anxiety and depression was associated with cerebellar atrophy, while fatigue accompanied by cognitive impairment was linked to global cortical and deep gray matter atrophy (50). Numerous studies have also emphasized strong associations between fatigue and both structural and neurochemical changes in white matter (51-57).

A study by Gilio et al. (26) reported a correlation between T2 lesion load and fatigue levels. Similarly, another study highlighted that the structural abnormality most strongly linked to fatigue was atrophy of the posterior parietal cortex (58).

Additional studies have associated fatigue in MS patients with various forms of brain atrophy (59), including gray matter atrophy, reductions in total brain volume, cerebral gray matter, and thalamic volumes (60), corpus callosum atrophy (61), cerebellar lobular atrophy (62), atrophy in the temporal lobe and insula (63), as well as overall gray matter volume reductions (64). However, one study found no significant relationship between structural changes and fatigue in early-stage MS (65). According to a recent systematic review, structural and functional brain changes are more pronounced in fatigued patients than in those without fatigue. In particular, abnormalities in thalamic activation and atrophy, as well as alterations in regions of the sensorimotor network, have been linked to fatigue (66-68).

Overall, research indicates that both structural and functional brain impairments are correlated with fatigue in MS. These structural changes are not confined to a single brain region, suggesting that involvement of multiple areas may contribute to the experience of fatigue. Nevertheless, the existing literature remains limited by small sample sizes and study numbers, highlighting the need for further research (Table 3).

Secondary Factors Associated with Fatigue

Although many factors and symptoms contribute to fatigue in patients with MS, depression remains one of the most prominent. Like fatigue, depression is an invisible symptom and is more prevalent in MS patients than in the general population (69). In individuals with MS, depression is among the strongest predictors of fatigue, influencing this symptom both directly and indirectly (8). Numerous recent studies have demonstrated a positive correlation between depression and fatigue (70-79). The strong association between these symptoms may be attributed to a shared pathophysiology mechanism (13,42,80,81). In this context, depression is often considered a predictor of fatigue. While fatigue does not necessarily indicate the presence of depression, patients with depression are highly likely to experience fatigue. Thus, it can be concluded that depression tends to precede and intensify fatigue (8). Consequently, patients presenting with fatigue should always be screened for depression, and improvements in depression symptoms is likely to positively impact fatigue levels.

Following depression, sleep disturbances are among the most commonly investigated symptoms associated with fatigue and are also recognized contributors (82). In MS patients, sleep problems are frequently overlooked, as clinical attention is focused on neurological symptoms, and sleep disturbances are often misattributed. As a result, unless reported by the patient, these issues may go unnoticed. The most frequently reported sleep disorders in MS include insomnia, movement-related sleep disturbances, respiratory-related sleep problems, and circadian rhythm disruptions (83). These conditions lead to poor-quality sleep, resulting in inadequate rest and exacerbation of both physical and mental fatigue (73,84). Additionally, insomnia may contribute to fatigue through heightened activation of the central nervous system (85). Recent studies further confirms that sleep disturbances slightly aggravate fatigue symptoms (8,86,87).

Urinary problems also represent a commonly examined factor in the context of fatigue among MS patients. MS can cause a wide range of urinary symptoms related to both bladder storage and emptying functioning (88-90). Notably, frequent urges due to overactive bladder, urgency, and urinary incontinence can disrupt sleep cycles, thereby worsening daytime fatigue (91,92). Some patients may reduce fluid intake in response to frequent urination, which can lead to dehydration and further aggravate fatigue (93). Thus, urinary dysfunctions is a meaningful contributor to fatigue, and its effective management should be prioritized. It addition to depression, sleep disturbances, and urinary issues, other MS-related symptoms also contribute to fatigue. These include pain (94), spasticity (95), and bowel dysfunction (91), are of which are closely associated with increased fatigue levels. Furthermore, as overall symptom burden tend to rise with increasing disability (96), fatigue severity also tend to escalate in more disability patients. While these symptoms may not be the primary cause of fatigue, they are considered secondary contributors.

Table 3. Studies on structural and functional brain changes in the pathophysiology of fatigue in MS patients

Author name	Sample	Results
Marrie et al. (44)	134 patients with MS	√ Early fatigue progression in MS predicts long-term brain atrophy independent of disability, mood, or other MRI changes. √ The association remained significant even after adjusting for clinical and imaging confounders.
Tedeschi et al. (45)	222 patients with RRMS	√ Fatigued patients with MS exhibited significantly higher abnormal white matter fraction. √ Increased T1 and T2 lesion burden is also associated with fatigue.
Andreasen et al. (46)	17 RRMS patients with fatigue and 17 RRMS patients without fatigue.	√ Fatigue is not associated with total lesion load in MS. √ Fatigued patients exhibit regional brain atrophy.
Pellicano et al. (58)	24 patients with MS and 24 healthy controls	√ Parietal cortex thinning is a structural correlate of fatigue in MS.
Yaldizli et al. (61)	70 patients with MS	√ Corpus callosum atrophy is significantly correlated with fatigue severity in MS.
Cruz Gómez et al. (47)	60 RRMS and 15 healthy controls	√ Patients with MS exhibit significant sensorimotor cortex atrophy with reduced gray/white matter volume in motor areas, correlated with motor dysfunction.
Papadopoulou et al. (52)	91 patients with MS	√ WM lesion volume was not correlated with depression and cognitive fatigue but was significantly correlated with motor fatigue.
Rocca et al. (48)	63 patients with MS and healthy controls	√ Microstructural abnormalities and regional WM/GM damage correlate with fatigue. √ Focal T2 lesion burden shows stronger association than global measures. √ No link was found between fatigue and total WM/GM lesion load or atrophy.
Filippi et al. (68)	64 patients with MS and 60 healthy controls	√ Fatigue in MS is related to functional disruption of the thalamic connector.
Sander et al. (49)	46 patients with MS and 14 healthy controls	√ Regional atrophy is linked to cognitive fatigue. √ No association was found between total lesion load and cognitive fatigue.
Nourbakhsh et al. (65)	43 patients with MS	√ Thalamic and cortical atrophy, but not global brain atrophy, significantly predicts fatigue in MS.
Bisecco et al. (53)	60 patients with RRMS and 29 healthy controls	√ Fatigue is associated with white matter damage, particularly in the frontal lobe region.
Hidalgo de la Cruz et al. (67)	122 patients with MS and 94 healthy controls	√ Regional thalamic abnormalities in different cortical regions, including the frontal lobe, sensorimotor network, precuneus, insular cortices, and cerebellum, contribute to fatigue in MS.
Novo et al. (51)	60 patients with MS and 60 healthy controls	√ Fatigue is linked to white matter damage in MS patients. √ No significant association with total lesion load or gray matter damage.
Palotai et al. (59)	98 patients with MS	√ Gray matter and hippocampal atrophy are associated with fatigue in patients with MS.
Yarraguntla et al. (54)	48 patients with RRMS	√ Neurochemical alterations in the bilateral frontal white matter were found to be associated with high fatigue levels.
Lazzarotto et al. (62)	61 patients with RRMS and 50 healthy controls	√ Cerebellar lobular atrophy is associated with fatigue in patients with MS.
Khedr et al. (60)	43 patients with RRMS	√ Thalamus and brainstem atrophy is associated with fatigue in MS.
Ziccardi et al. (63)	69 patients with MS	√ Temporal lobe and insula volume reduction is associated with fatigue in MS.
Gilio et al. (26)	106 patients with RRMS	√ T2 lesion load correlates with fatigue scores in MS patients.
Eren et al. (43)	85 patients with MS and 45 healthy controls	√ The pituitary gland dimensions are increased in patients with MS. √ The pituitary gland structure differs between fatigued and non-fatigued MS patients.
Peño et al. (64)	41 patients with MS	√ T2 lesion load is strongly associated with fatigue in MS patients.

Table 3. Continued

Author name	Sample	Results
Ezzeldin et al. (55)	63 patients with RRMS	√ Whole brain volume total and regional WM lesion load (juxtacortical, periventricular and infratentorial lesion volumes) were significantly correlated with fatigue severity.
Rimkus et al. (50)	102 RRMS patients and 98 healthy controls	√ Cerebellar atrophy is most strongly associated with fatigue, anxiety, and depression in MS. √ Global cortical and deep gray matter atrophy is linked to cognitive impairment, fatigue, anxiety, and depression in MS.
Danciut et al. (56)	71 patients with RRMS	√ Poorer white matter structure, lower interoceptive insight, and the worse the fatigue.
Figueroa-Vargas et al. (57)	32 people with RRMS and 29 healthy controls	√ Reduced white matter volume and impaired microstructural integrity in specific brain regions are significantly associated with fatigue severity.

T1: T1-weighted magnetic resonance imaging, T2: T2-weighted magnetic resonance imaging, RRMS: Relapsing-remitting multiple sclerosis; MS: Multiple sclerosis, WM: White matter, GM: Gray matter, MRI: Magnetic resonance imaging

In conclusion, although the pathophysiology of primary fatigue in MS patients remains unclear, abnormalities in neuroimmune function, neuroendocrine dysregulation, and structural and functional brain changes appear to be central mechanisms. Additionally, numerous secondary symptoms, particularly depression, sleep disturbances, and urinary problems further exacerbate fatigue. Fatigue is among the most debilitating symptoms experienced by MS patients. It is subjective and invisible, arises from multifactorial mechanism, and poses significant diagnostic and treatment challenges. Therefore, clinical assessments of MS patients should include fatigue evaluation. Methodologically robust research is necessary to uncover the underlying pathophysiological mechanisms and contributing secondary factors so that targeted treatment strategies can be implemented.

Footnotes

Authorship Contributions

Concept: K.Y., M.T., Design: K.Y., M.T., Literature Search: K.Y., Writing: K.Y., M.T.

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REVIEW

Knowledge Mapping of Balance Rehabilitation in Multiple Sclerosis: A Bibliometric Analysis

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Abstract

Multiple sclerosis (MS) is a complex neurological disorder that leads to multifactorial disability, with balance impairments being among the most prevalent and debilitating symptoms. These impairments may impede mobility and contribute to secondary complications such as increased fall risk. Using bibliometric methods, this study aimed to systematically assess the global research landscape on balance rehabilitation in MS patients. To conduct a comprehensive bibliometric analysis of global research trends, contributors, and thematic focuses related to balance rehabilitation in individuals with MS. A bibliometric analysis was conducted utilizing data retrieved from the Web of Science database on November 5, 2024. Using the search keyword "MS and balance rehabilitation," we identified 1,400 initial records. After applying the inclusion criteria, 895 original research articles published between 1995 and 2024 were included in the final analysis. Bibliometric indicators examined included publication trends, geographic and institutional distributions, research categories, article types, leading authors, citation metrics, and keyword frequencies. Few publications were recorded before 2010, after which there was a sharp increase between 2020 and 2022, peaking at 95 publications in 2022. The observed decline in 2023-2024 may represent the lasting impact of the coronavirus disease 2019 pandemic. The United States led with 265 publications, followed by Italy (149) and Turkiye (77). The University of Illinois emerged as the top institution (40), followed by Hacettepe University (27) and Oregon Health & Science University (20). Elsevier was the leading publisher (262), ahead of Taylor & Francis (95) and Sage (83). Davide Cattaneo was the leading contributor with 48 publications and 2,060 citations. His 2002 study, "risks of falls in subjects with MS," was the most cited, with 202 citations. Common keywords included "MS" (552), "balance" (186), and "walking" (109). This bibliometric study presents an in-depth assessment of the evolution and current state of balance rehabilitation research in MS. The findings highlight the significance of enhanced global collaboration and continued research efforts to foster innovation and advance evidence-based interventions in neurorehabilitation.

Keywords: Multiple sclerosis, bibliometrics, Web of Science, visualization of similarities, balance rehabilitation

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disorder of the central nervous system (1). With disease progression, gait and balance impairments develop (2,3). Approximately 50-80% of MS patients experience balance dysfunction (4,5), which hinders mobility and increases the risk of falls (4,6).

Balance control is a complex motor skill that depends on the interaction of motor, sensory, and cognitive systems (7). Neural lesions and degeneration in MS impair axonal transmission and integration, affecting peripheral nerves (8,9), the spinal cord, and the cerebral cortex (10). The degeneration of neural pathways disrupts the integration of sensory inputs and impedes the execution of rapid, adequate motor responses, leading to balance control deficits (11,12). Moreover, the cognitive aspects of sensory processing are also affected, influenced by factors such as limbic activity, fatigue, expectation, and divided attention.

Balance training refers to exercises aimed at controlling the center of mass relative to the support base during various challenging activities (13). The beneficial effects of balance

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training are attributed to neuroplasticity, which refers to "the central nervous system's ability to adapt in response to environmental changes or lesions" (14). The effort to enhance performance quality during challenging motor tasks promotes neural network reorganization, thereby improving balance (15). A recent systematic review conducted by Wallin et al. (16) revealed improvements in balance scores and mobility because of MS balance rehabilitation training. Another meta-analysis performed in 2022 indicated that while all forms of exercise are beneficial for balance rehabilitation, yoga, virtual reality training, and aerobic training were particularly effective in improving balance function in MS patients (17).

Bibliometric analysis employs statistical methods that quantitatively evaluate publications, interpublication relationships, author impact, and citation rates, as well as monitor emerging academic trends within any field, region, or timeframe. The aim of a bibliometric approach is to generate measurable data and quantitative indicators for assessing research performance (18). This analysis is crucial for understanding advances in rehabilitation studies.

Few bibliometric studies have specifically focused on MS and balance rehabilitation (19,20). Scanning and categorizing a large volume of publications across multiple dimensions (including country, journal, authors, categories, institutions, and keywords) enables tracking of citation relationships and research trends in the field of MS and balance rehabilitation. This study conducted a bibliometric analysis of global research on MS and balance rehabilitation published between 1995 and 2024 using the Web of Science (WoS) database, aiming to evaluate the existing studies and summarize the characteristics of the obtained publications.

Materials and Methods

All analyses were primarily based on citation metrics. We analyzed the distribution of publications across countries, institutions, authors, journals, articles, and keywords. To facilitate the readability of the analysis results, tables and figures were used. All tables and figures were generated using WoS and the visualization of similarities (VOSviewer) software version 1.6.20 (Leiden University, the Netherlands) and the WoS database. In the keyword analysis, only keywords with a minimum of two occurrences were included. Additionally, terms reflecting study design, such as "clinical research" or "retrospective study", as well as noninformative descriptors like "case-control", "human", "male", "female" and "adult" were excluded (18).

Article Selection

The article search was performed on November 5, 2024. Studies on balance rehabilitation in the context of MS, indexed in Science Citation Index Expanded (SCIE) within the WoS, were included in the analysis. The search employed the keywords "MS and balance rehabilitation", without applying any time constraints. The research included studies published between 1995 and 2024. As the study used publicly available data and posed no ethical concerns, ethical approval was not required.

Inclusion and Exclusion Criteria

This study included research articles published between 1995 and 2024 in journals indexed in the SCIE that focused on balance rehabilitation methods and clinical treatment for MS. Only original research articles were considered for analysis, while other publication types-such as abstracts, notes, letters, discussions, and book chapters-were excluded. This selection prioritized peer-reviewed, full-text studies offering comprehensive data and methodological details.

Data Analysis

The search conducted on November 5, 2024, using the keyword "MS and balance rehabilitation" across all fields retrieved 1,400 results. After applying the inclusion criteria, 895 studies were retained for analysis. This study utilized content indexed in the WoS database as its data source.

The articles included in the study were examined using WoS and the VOSviewer software version 1.6.20. VOSviewer, a tool for visualizing similarities between objects, was used to analyze co-occurrence patterns of author keywords in the imported article data (18).

To reveal publication trends in MS balance rehabilitation research, analyses were performed on the distribution of countries, institutions, and the twenty most cited articles over the last 29 years. Additionally, data mining, mapping, and clustering were conducted on the included articles using VOSviewer software. The VOSviewer analysis generated outputs in distinct colors and shapes. The size of the labels and circles for each item was determined by its assigned weight in the analysis. Items with greater weight were represented by proportionally larger labels and circles.

Results

According to WoS data, a total of 895 publications related to MS and balance rehabilitation were published worldwide between 1995 and 2024. Publication trends over the years were analyzed and are shown in Figure 1. The first publication on MS and balance rehabilitation indexed in WoS dates back to 1995. From 1995 to 2010, studies on MS and balance rehabilitation were quite limited. However, a considerable increase in the number of publications was observed after 2010. Notably, the publication rates peaked between 2020 and 2022. In 2022, the highest annual output of publications was recorded, with 95 publications (Figure 1). In the last two years (2023-2024), the number of publications has shown a declining trend.

Country Distribution Analysis

Over the past 29 years, 34 countries have published articles on MS balance rehabilitation. The analysis results for the top 25 contributing countries are presented in Figure 2. Research on MS balance rehabilitation demonstrated that the United States of America (USA) ranks first in terms of the number of published articles (265), followed by Italy (149) and Turkiye (77) (Figure 2). An analysis of yearly publication trends reveals that the USA led in 2016, Italy in 2017, and Turkiye in 2018 (Figure 3).

Notably, due to the official change of the country name from "Turkey" to "Türkiye" in 2021, the visual representations in Figures 2-4 display them as separate circles. The VOSviewer software could not merge these entries, although they refer to the same country.

The coauthorship relationship network among countries was analyzed and visualized using the VOSviewer software. Countries with at least three citations and three publications were included in this study, resulting in 34 countries meeting the threshold. As illustrated in Figure 4, the USA serves as the central hub for research on MS balance rehabilitation and has strong collaborative links with countries such as Australia, Canada, and Italy. Significant research collaborations are also observed between countries like Belgium, Italy, the United Kingdom, and the USA (Figure 4).

Analysis of Publications by Institution

A bibliometric network analysis of publications by institution was performed, with the results presented in Figure 5. Between 1995 and 2024, a total of 74 institutions or organizations published articles related to MS and balance rehabilitation, with USA institutions leading in publication activity. The University of Illinois was the leading contributor with 40 publications, while Hacettepe University and Oregon Health & Science University followed with 27 and 20 publications, respectively. In this analysis, the thickness of the lines between countries represents the frequency of coauthorship collaborations between institutions or organizations (Figure 5).

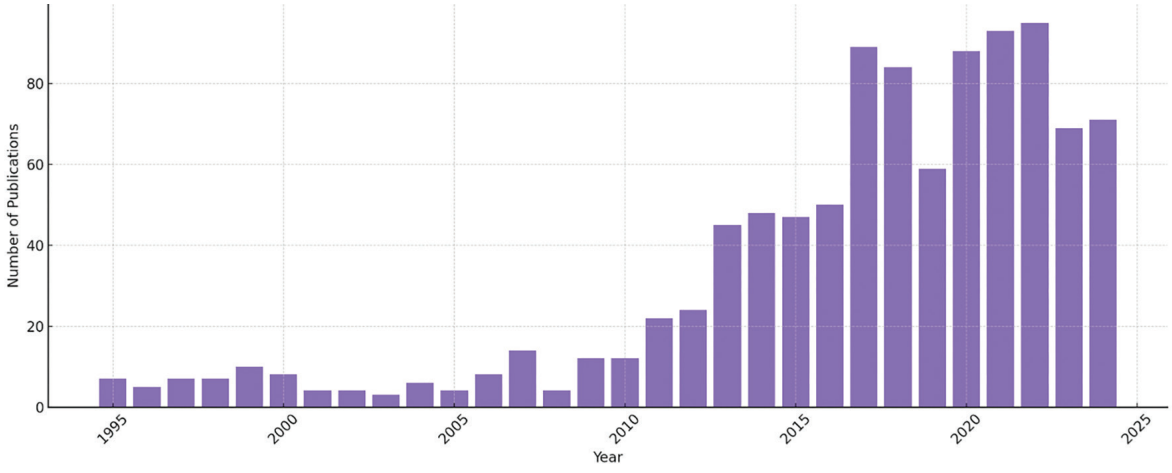

Figure 1. Yearly analysis of publications on MS and balance rehabilitation (1995-2024)
MS: Multiple sclerosis

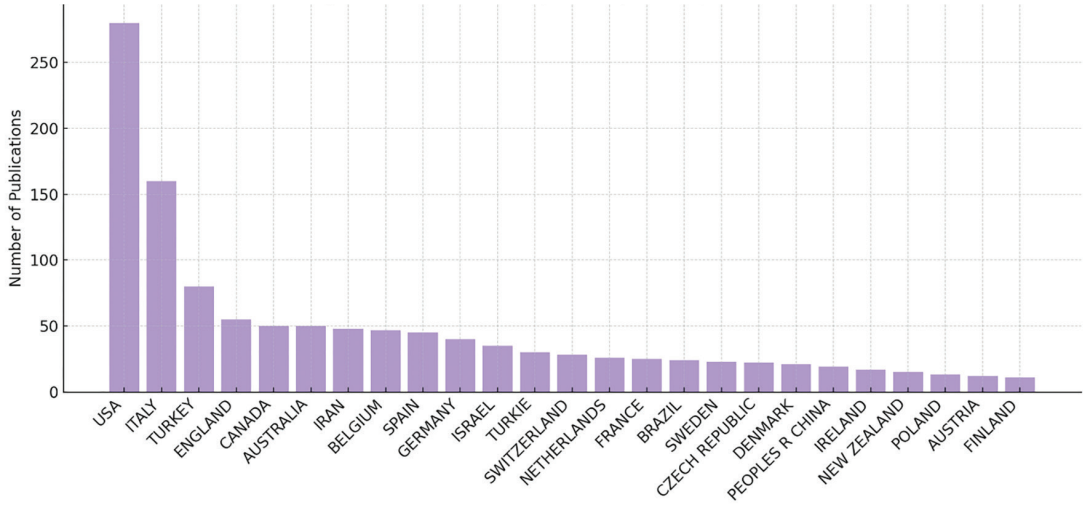

Figure 2. Distribution of publications by the top 25 contributing countries
USA: United States of America

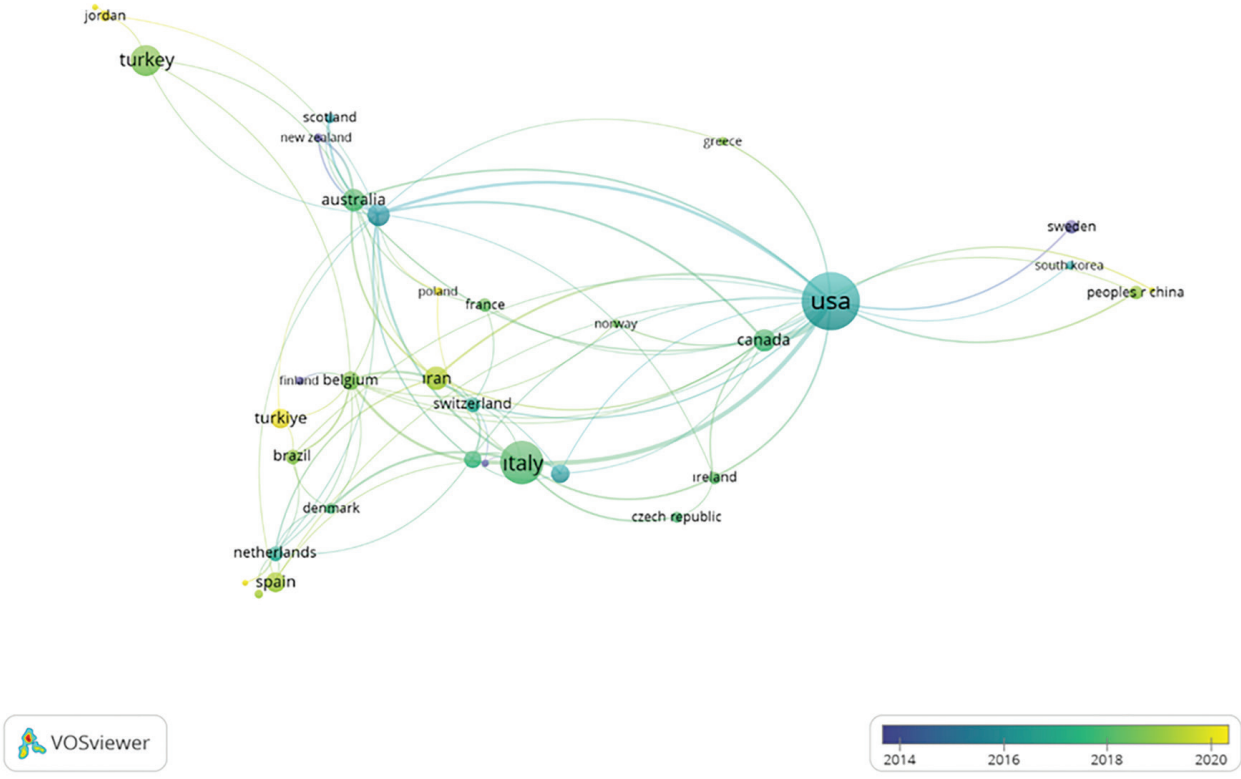

Figure 3. Bibliometric analysis of publications across countries
USA: United States of America

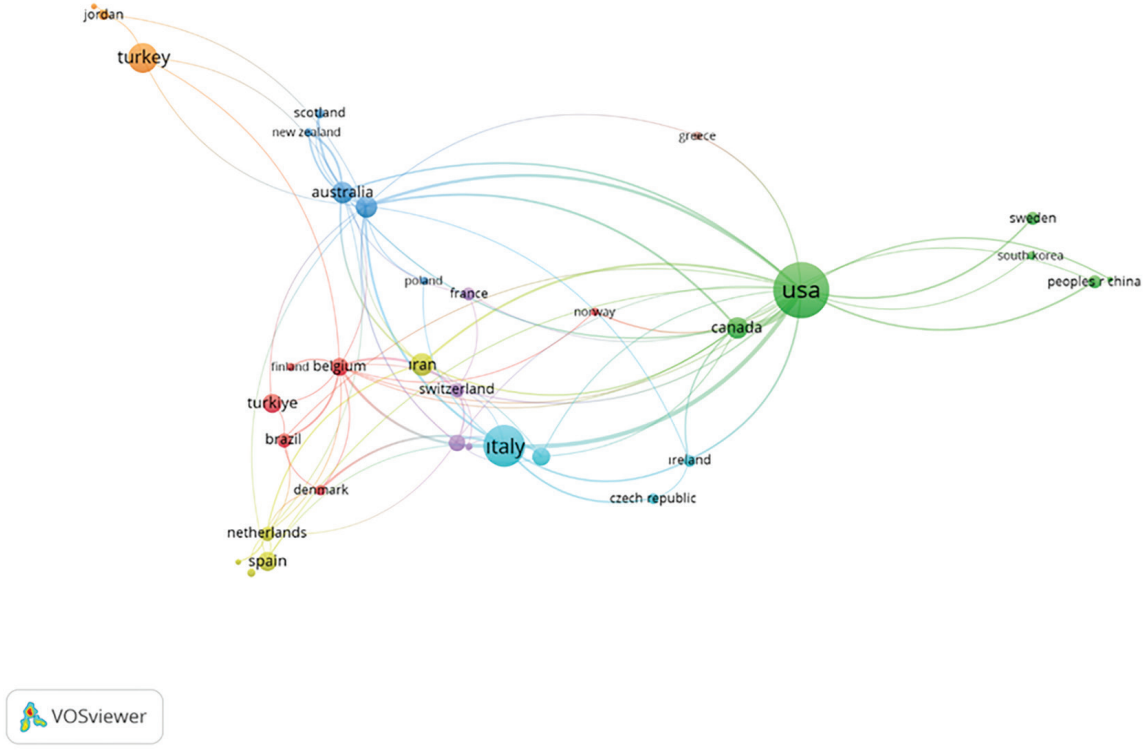

Figure 4. Country-level bibliometric network analysis of publications
USA: United States of America

Research Categories and Article Types

In total, 74 journal categories were identified for articles on MS and balance rehabilitation, with the most represented being rehabilitation (351), clinical neurology (287), and neuroscience (209). The distribution of publications across journal categories is displayed in Figure 6. Elsevier published the most articles in the field of MS balance rehabilitation (262), with Taylor & Francis (95) and Sage (83) following (Figure 7).

Top 3 Active Authors and Most Cited Articles

The most productive authors in the fields of MS and balance rehabilitation were identified through the WoS database, and a network analysis of their publications was performed. Figure 8 illustrates the analysis results. The analysis identified Davide Cattaneo (Italy) as the leading contributor to the literature, with 48 publications and 2,060 citations. He is followed by Motl et al. (10) (USA), who has contributed 28 publications with 997 citations, and Peter Feys (Belgium), with 24 publications and 670 citations. Together, they are central to MS and balance rehabilitation research, with frequent collaborations and significant scholarly influence. An analysis of the citation counts revealed that Cattaneo's 2002 study as the most cited publication, with 202 citations to date (Figure 9). This highlights the enduring impact of foundational work in the field and highlights the signficance of early contributions to the scientific discourse on MS rehabilitation.

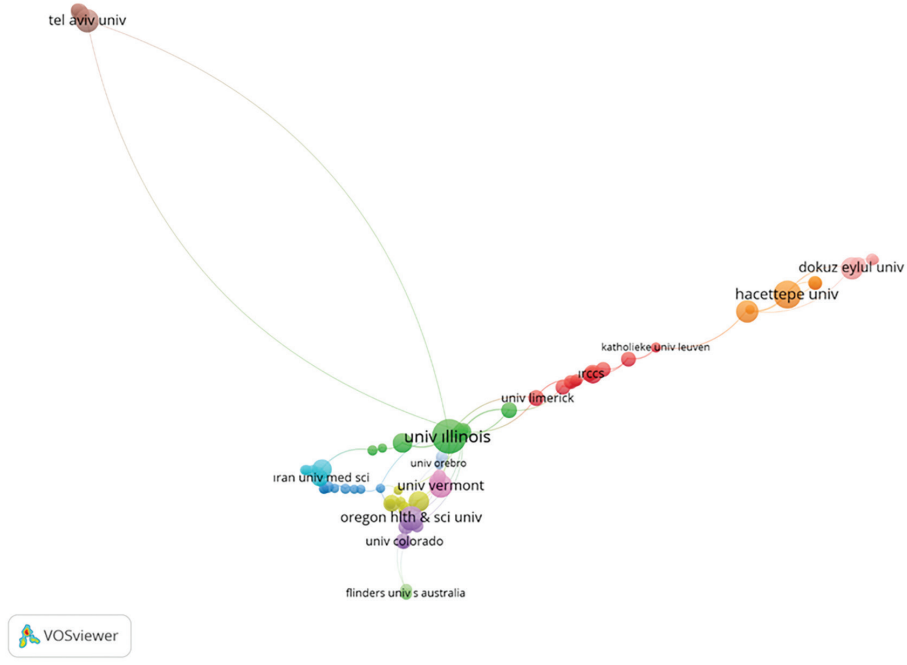

Figure 5. Bibliometric network visualization of publications by institution

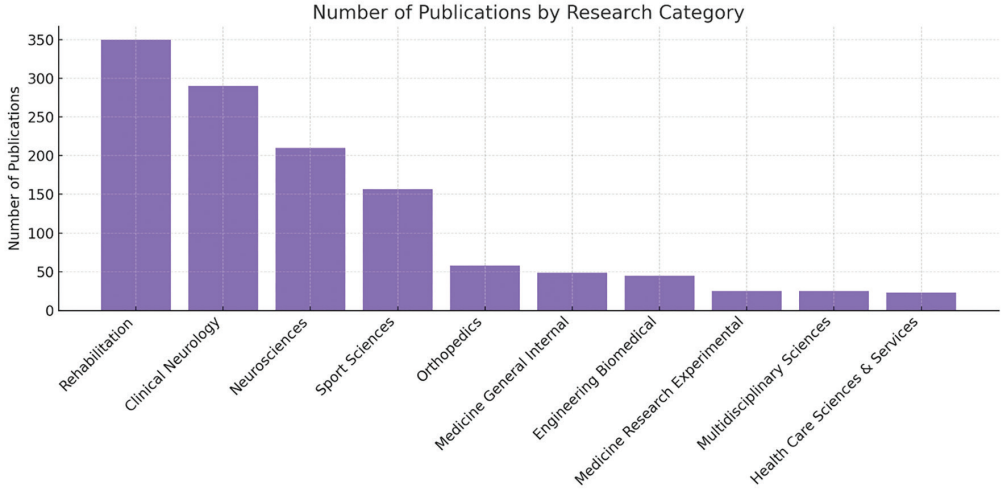

Figure 6. Distribution of publications across journal categories

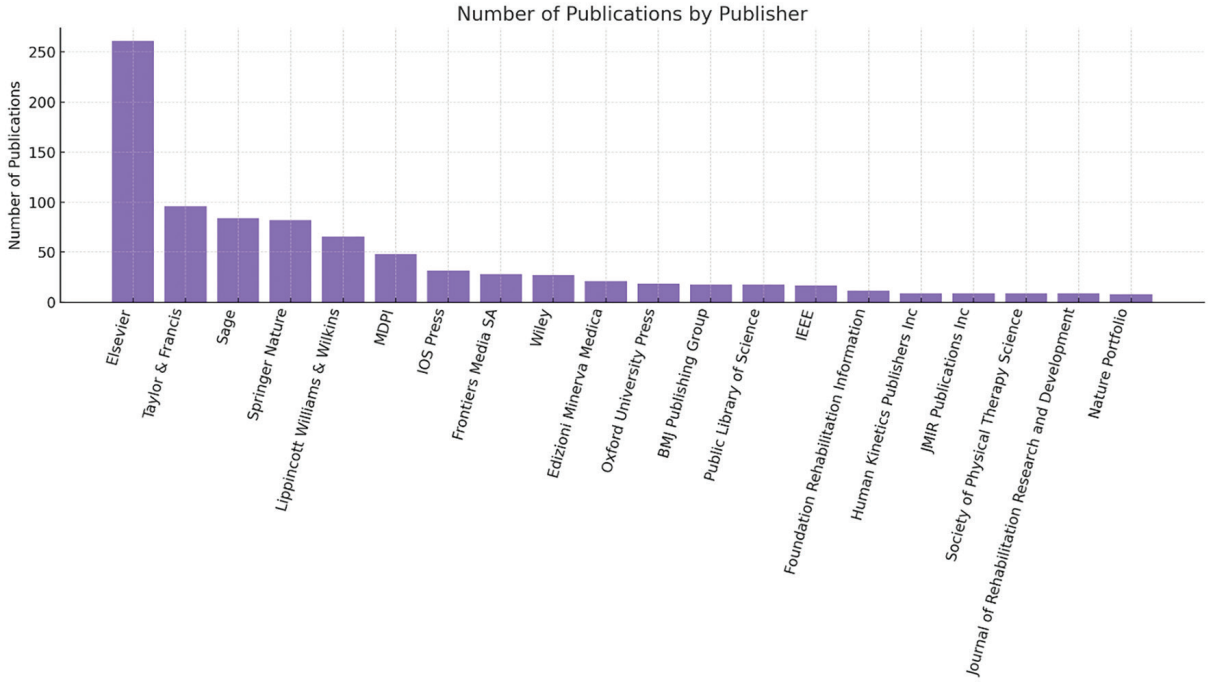

Figure 7. Distribution of publications across to the top 20 journals in MS balance rehabilitation research
MDPI: Multidisciplinary Digital Publishing Institute, IEEE: Institute of Electrical and Electronics Engineers, MS: Multiple sclerosis

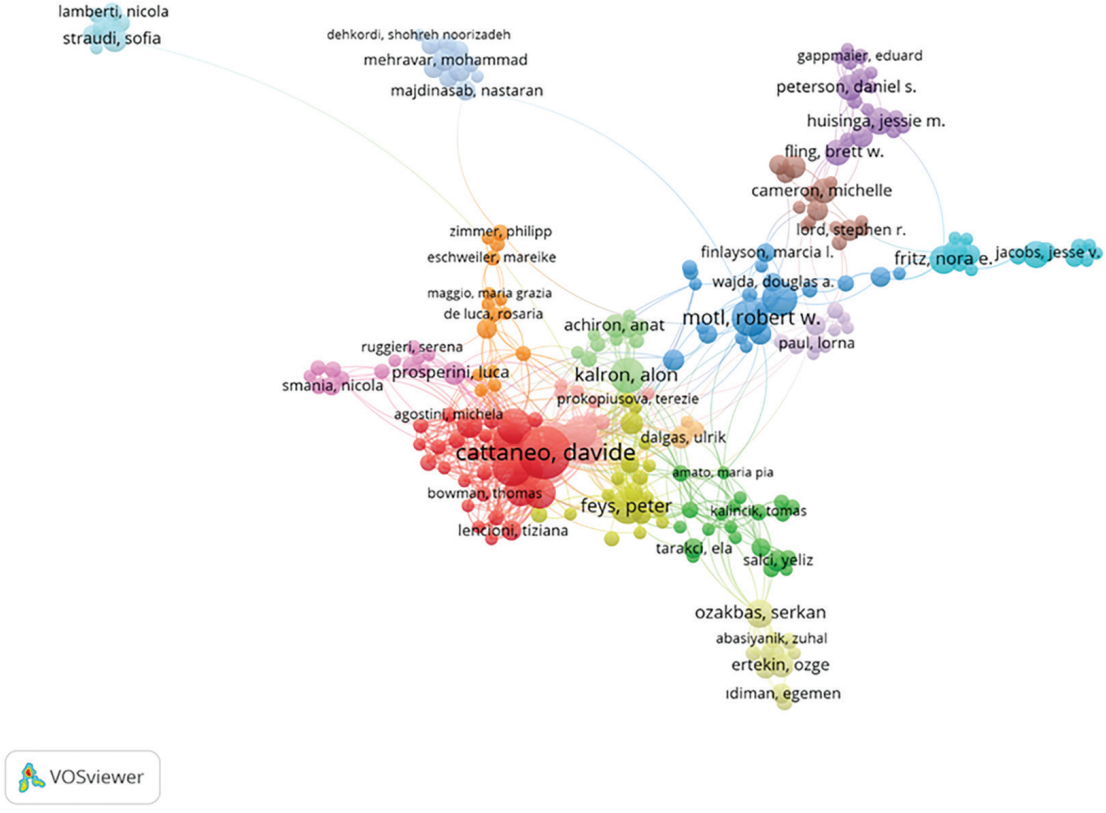

Figure 8. Researcher-based network analysis of publications

Keyword Analysis

Keywords associated with MS and balance rehabilitation in the literature were analyzed using VOSviewer software. For all the 1,526 keywords, the total strength of their connections with other keywords was calculated. The findings revealed that "MS," "balance", and "gait" were the most frequently utilized keywords. The keyword "MS" appeared in 552 articles, "balance" in 186 articles, and "gait" in 109 articles. In total, 199 frequently used keywords were identified across the 29-year period (Figure 10).

Conclusion

This bibliometric study charts the evolution and current research trends in balance rehabilitation in MS patients over the last 29 years. Using WoS and VOSviewer, 895 studies published between 1995 and 2024 were analyzed. The findings indicate a limited number of studies until 2010, followed by substantial growth-particularly between 2020 and 2022, when publication activity reached its peak. This upward trend can be attributed to increasing awareness of balance impairments in MS patients, advances in rehabilitation strategies, and greater international collaborations (16,17).

However, a marginal decline in publication numbers was observed during 2023-2024, which may be attributed to the residual impact of the coronavirus disease 2019 pandemic, disruptions in research funding, and delays in data collection and dissemination (12,20).

In terms of country-based contribution, the USA, Italy, and Turkiye emerged as the top three. The dominance of USA-based institutions and their frequent collaborations with European partners such as Italy and Ireland were evident in co-authorship network visualizations. Despite Turkiye's high publication volume, the analysis revealed relatively limited international research collaboration. This could be attributed to language barriers, rising costs of international research due to currency fluctuations, and limited funding opportunities-factors that may impede participation in multicenter trials or cross-border projects (18).

From an author-level perspective, Davide Cattaneo (Italy), Robert W. Motl (USA), and Peter Feys (Belgium) emerged as the most influential contributors to this field. Cattaneo, with 48 publications and 2,060 citations, has played a pivotal role in shaping the field of MS balance rehabilitation. Motl and Feys followed with 997 and 670 citations, respectively. Cattaneo et al.'s (21) 2002 publication, "risks of falls in subjects with MS," emerged as the most cited work in the dataset, garnering 202 citations.

The most frequent keywords "MS," "balance," and "gait" suggest an ongoing focus on core motor impairments in MS. Yet, terms related to cognitive rehabilitation, psychological factors, or virtual reality-based interventions remain underrepresented, suggesting potential areas for future exploration (19).

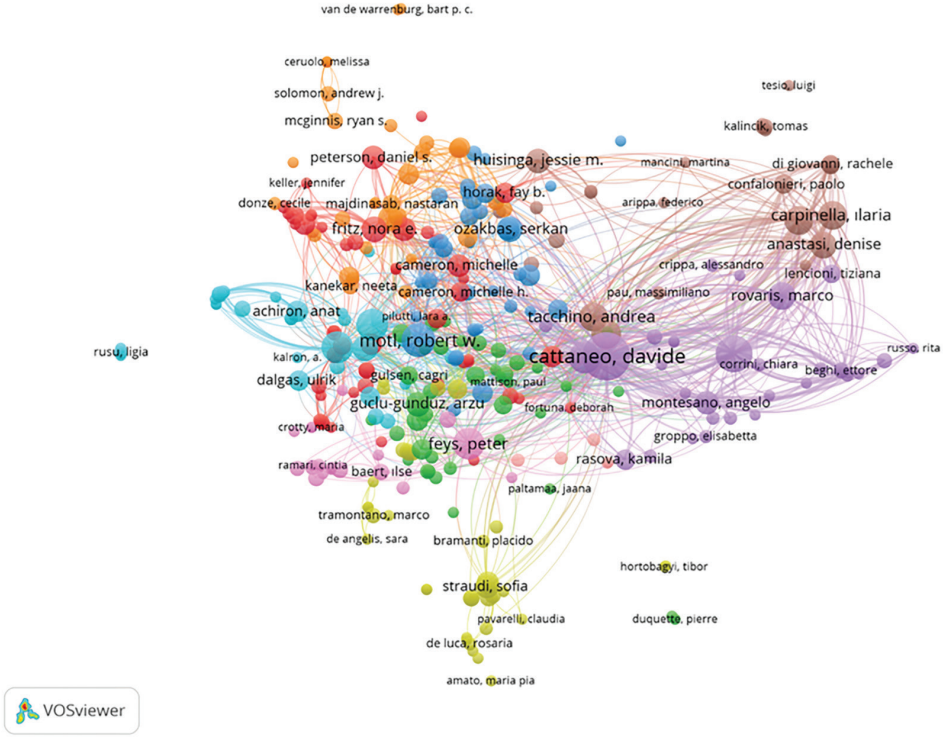

Figure 9. Network analysis of publications by citation counts

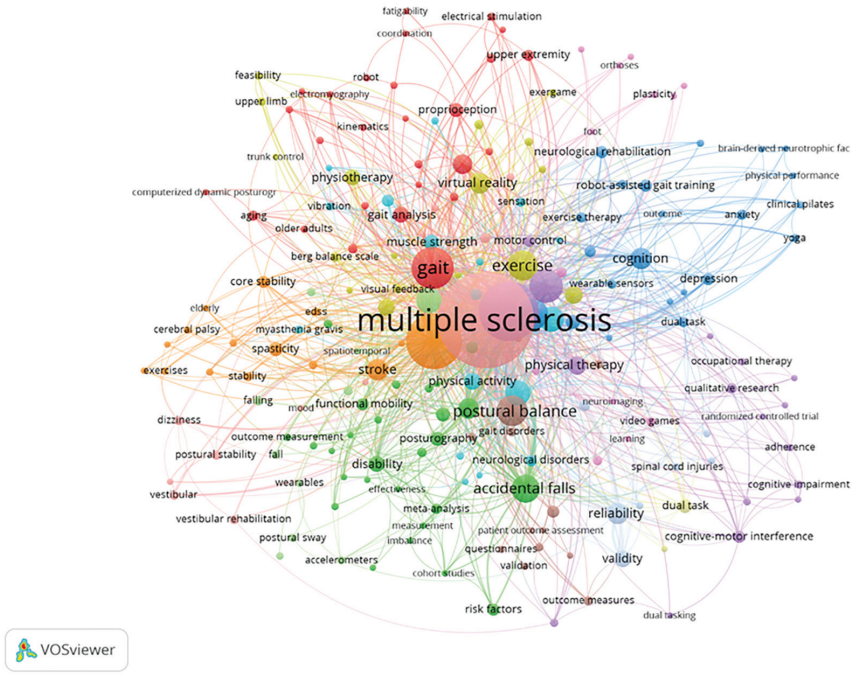

Figure 10. Network analysis of publications by keywords

Clinical Recommendations

The findings of this study offer valuable clinical insights for advancing rehabilitation strategies in MS patients. Given the multifactorial nature of balance impairment in MS, future interventions should extend beyond purely motor-based strategies to also incorporate sensory and cognitive components (10). Clinicians are encouraged to adopt technology-assisted rehabilitation approaches-such as virtual reality, wearable sensors, and exergaming-which have shown promise in enhancing engagement and personalization of treatment (11). Additionally, advancing the development of low-cost, scalable, and home-based rehabilitation programs is crucial, especially in low- and middle-income settings where access to specialized care may be limited. Rehabilitation outcomes should address physical improvements as well as psychosocial dimensions such as fall-related self-efficacy, quality of life, and participation in daily activities. Finally, there is an urgent need for strong international and interdisciplinary collaboration to establish clinical guidelines and funding strategies that ensure equitable access to high-quality MS rehabilitation across diverse socioeconomic contexts (7).

In conclusion, this bibliometric analysis provides detailed analysis of trends in MS and balance rehabilitation research, highlights key contributors and collaborative patterns, and identifies critical gaps and emerging opportunities to guide future studies. It offers valuable guidance to emerging researchers and emphasizes the importance of sustained support and innovation to meet the complex rehabilitation needs of MS patients.

A key limitation of this study is its reliance on a single database (WoS), which may not capture all relevant publications indexed in other databases such as Scopus, PubMed, or Embase. Additionally, only original research articles were included, while reviews, editorials, and conference proceedings were excluded. This may have resulted in the omission of valuable insights from the literature. The data were also analyzed using VOSviewer, which, although effective for network visualization, may have limitations in addressing inconsistencies in author or institution naming conventions.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.C., Concept: N.C., I.C., Design: N.C., Data Collection or Processing: N.C., S.K., Analysis or Interpretation: N.C., E.C.M., I.C., Literature Search: N.C., E.C.M., B.K., Writing: N.C.

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

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RESEARCH ARTICLE

Pediatric-onset Multiple Sclerosis in Families: A Distinct Phenotype

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Abstract

Objective: Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system. Pediatric-onset MS (POMS) represents a distinct subgroup with unique clinical and immunological features. Although familial predisposition contributes to MS pathogenesis, data on familial POMS remain limited. To investigate the demographic and clinical characteristics of familial POMS and compare them with those of the broader MS patient cohort.

Materials and Methods: We performed a retrospective descriptive analysis of 3,411 patients diagnosed with MS at a university hospital MS center. Of these, 523 had a family history of MS, and 251 were identified as having POMS, defined as disease onset before age 18. Data on demographic and clinical characteristics, cerebrospinal fluid (CSF) findings, treatment history, and disability scores were analyzed using IBM SPSS version 25.

Results: Among 3,411 MS patients, 251 (7.36%) had POMS. Of these, 177 (70.5%) were female and 74 (29.5%) were male. Most had a relapsing-remitting course (236 patients, 94%), while 15 (6%) developed secondary progressive MS; no cases of primary progressive MS were identified. Within the 523 familial MS cases, 51 (9.75%) had POMS. CSF analysis was available for 31 patients, 24 (77.4%) of whom showed MS-specific abnormalities; 13 (41.9%) had an elevated IgG index. Regarding treatment history, 59 patients (23.5%) received first-line therapies, 123 (49%) second-line therapies, and 69 (27.5%) third-line therapies. The mean Expanded Disability Status Scale score was 1.3.

Conclusion: This study adds to the literature on POMS by providing detailed demographic, clinical, and familial data. The findings underscore the importance of considering familial predisposition when evaluating pediatric MS and highlight the need for further research into the genetic and immunological mechanisms underlying POMS. Long-term follow-up and genetic studies are warranted to deepen understanding of this uncommon yet clinically important MS subtype.

Keywords: Familial MS, multiple sclerosis, onset multiple sclerosis, pediatric-onset multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system characterized by a complex interplay of genetic and environmental factors (1). Although most cases occur in adults, a subgroup arising in children-referred to as pediatric-onset MS (POMS)-has distinct biological and clinical features (2,3). The International Pediatric Multiple Sclerosis Study Group defines pediatric MS as disease onset before the age of 18 and highlights the importance of age-specific diagnostic criteria and management strategies (4,5). Globally, epidemiological data on POMS remain limited; according to 2013 estimates from the MS International Federation, the worldwide prevalence was 0.63 per 100,000 people (6).

The primary distinction between POMS and adult-onset MS (AoMS) lies in the clinical course. Most POMS cases follow a relapsing-remitting pattern (RRMS), characterized by episodes of neurological dysfunction followed by remission.

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Immunologically, POMS differs in cerebrospinal fluid (CSF) profiles, particularly in lower rates of oligoclonal band (OCB) positivity compared with adults. These differences suggest distinct disease pathophysiology, potentially reflecting more robust immune responses in younger patients or unique genetic predispositions.

Familial predisposition plays a significant role in MS pathogenesis. Familial pediatric MS refers to cases in which patients have a first- or second-degree relative diagnosed with the disease. Genetic susceptibility-particularly associations with the HLA-DRB1*1501 allele-along with environmental triggers such as Epstein-Barr virus infection, has been implicated in familial MS (7,8). However, studies focusing specifically on the familial aspect of POMS remain scarce, limiting our understanding of its genetic and environmental determinants. This study therefore aimed to investigate the demographic and clinical characteristics of familial POMS and to compare them with non-pediatric familial MS, thereby contributing to the existing knowledge base.

Materials and Methods

The study was approved by the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 2014/125, date: 25.02.2015). We conducted a retrospective descriptive study of 3,411 patients diagnosed with MS at the MS center of a university hospital. POMS was defined as disease onset before 18 years of age, in accordance with the 2017 revised McDonald criteria. Familial MS cases were identified by the presence of a first- or second-degree relative with an MS diagnosis. Within the familial MS subgroup, patients were further categorized as having POMS or AoMS based on their age at disease onset.

Statistical Analysis

Demographic and clinical data were extracted from patient records and included age at onset, gender, MS subtype, disease duration, Expanded Disability Status Scale (EDSS) score, CSF findings (OCBs and IgG index status), and treatment history. Descriptive statistics were used to summarize the data. Categorical variables (gender, MS subtype, family history, CSF profile, and treatment category) were reported as frequencies and percentages, while continuous variables (age at onset, disease duration, and EDSS score) were expressed as means and ranges. Comparisons between POMS and AoMS, as well as between familial and nonfamilial cases, were performed using appropriate statistical tests. A p-value <0.05 was considered statistically significant.

All analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 3,411 MS patients were evaluated, of whom 251 were identified as having POMS, defined as disease onset before the age of 18. This corresponded to a pediatric-onset rate of 7.36% within the overall cohort (Figure 1).

Demographic analysis showed that most POMS patients were female (n=177, 70.5%) compared with male patients (n=74, 29.5%). The predominant MS subtype was RRMS (n=236, 94%), while 15 patients (6%) had secondary progressive MS (SPMS). No cases of primary progressive MS (PPMS) were observed (Table 1).

The mean age at disease onset was 15.7 years (range, 4-18), and the mean disease duration was 16.0 years (range, 1-55). The mean EDSS score was 1.3, reflecting generally mild disability at the time of evaluation.

CSF analysis was available for 31 POMS patients. Of these, 24 (77.4%) were positive for OCBs (Type 2 or Type 3), consistent with intrathecal IgG synthesis. An elevated IgG index was detected in 13 patients (41.9%).

Among 440 patients with available CSF data, an elevated IgG index was observed in 13 POMS patients (41.9%) and 259 AoMS patients (58.9%). A normal IgG index was found in 18 POMS patients (58.1%) and 181 AoMS patients (41.1%). Although

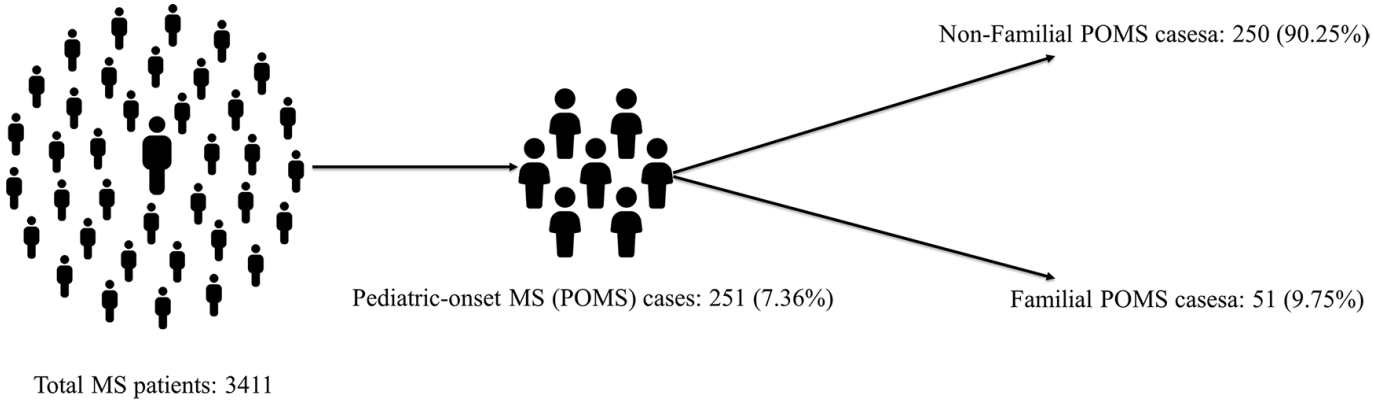

Figure 1. Distribution of familial and nonfamilial POMS cases within the total MS cohort
MS: Multiple sclerosis, POMS: Pediatric-onset MS

Table 1. Demographic and clinical characteristics of pediatric-onset MS (POMS) patients (n=251)		
Category	**Subcategory**	**n (%) or mean (range)**
Gender distribution	Female	177 (70.5%)
	Male	74 (29.5%)
MS subtypes	Relapsing-remitting MS (RRMS)	236 (94.0%)
	Secondary progressive MS (SPMS)	15 (6.0%)
CSF analysis (n=31)	OCB-positive (Type 2 or Type 3)	24 (77.4%)
IgG	Elevated IgG index (among those with abnormal CSF)	13 (41.9%)
Treatment history	First-line treatment	59 (23.5%)
	Second-line treatment	123 (49.0%)
	Third-line treatment	69 (27.5%)
Disability status	Mean EDSS score	1.3
Age at onset	Mean (range)	15.7 years (4-18)
Disease duration	Mean (range)	16.0 years (1-55)

This table summarizes the demographic and clinical characteristics of 251 POMS cases, identified among a total of 3,411 MS patients (7.36%)
MS: Multiple sclerosis, CSF: Cerebrospinal fluid, OCB: Oligoclonal band

the proportion of elevated IgG index was lower in the POMS group, the difference between groups did not reach statistical significance (p=0.065).

Similarly, the difference in OCB positivity between the POMS and AoMS groups was not statistically significant (p=0.863).

Discussion

POMS is a rare subtype of MS that occurs in individuals younger than 18 years and accounts for approximately 3%-10% of all cases. Compared with AoMS, POMS demonstrates distinct clinical features and disease courses (6,9,10). Epidemiological studies report that the incidence of POMS varies globally from 0.05 to 2.85 per 100,000 children (11,12). This variability is likely influenced by genetic predisposition, environmental exposures, and differences in diagnostic awareness and criteria across populations.

In our study, POMS represented 7.36% of the total MS cohort, consistent with previously reported prevalence rates. The increasing detection of POMS in recent years may be explained by advances in diagnostic techniques, heightened clinical awareness, and the adoption of the 2017 revised McDonald criteria. In agreement with earlier studies, most POMS patients in our cohort were female (70.5%), reflecting the well-documented female predominance in MS (2). This gender imbalance, also observed in adult MS, has been attributed to hormonal factors, genetic susceptibility, and immunological differences (10). While our findings confirm this female predominance, we were unable to assess whether the pattern varied before and after menarche, which could influence hormonal susceptibility and immune responses.

One of the most important findings of our study is the predominance of RRMS subtype in pediatric patients, accounting for 94% of cases. This observation is consistent with previous research showing that nearly all pediatric MS patients initially present with RRMS and are less likely to develop PPMS at an early stage (11,13). Although progressive forms of MS are rare in pediatric populations, the risk of transition to SPMS increases with disease duration. In our study, SPMS was observed in 6% of patients-lower than the rate reported in AoMS-supporting the view that POMS typically follows a more favorable early disease course (14). Despite higher relapse rates in the early stages, pediatric patients generally demonstrate better recovery, as reflected by the low mean EDSS score of 1.3 in our cohort. This finding aligns with prior reports suggesting that disability accumulation is slower in POMS than in AoMS (15).

CSF analysis remains an important diagnostic tool in MS, with OCBs serving as key biomarkers. Previous studies have reported lower OCB positivity rates in POMS compared with AoMS, with frequencies ranging from 40% to 80% (2,16,17). In our cohort, OCB positivity was observed in 77.4% of POMS patients and 76.1% of AoMS patients, a difference that was not statistically significant (p=0.863). These comparable OCB rates suggest that OCBs alone may not adequately reflect age-related differences in intrathecal immune responses. Although earlier reports have described lower OCB frequencies in pediatric cases, our findings underscore the potential heterogeneity of immunological profiles within both POMS and AoMS populations. Variability in diagnostic timing, assay sensitivity, and population characteristics may contribute to these discrepancies. Nonetheless, our results add to the current understanding of OCB distribution in MS and highlight the need for further research to clarify its age-dependent immunopathological relevance.

The primary focus of our study was familial MS in the pediatric population. The prevalence of familial MS varies widely, with reported rates ranging from 10% to 21% (18). In our cohort, 20.3% of POMS patients had a family history of MS, further supporting the role of genetic factors in disease susceptibility. Previous studies have identified specific genetic variants-particularly the HLA-DRB1*1501 allele-as risk factors for familial MS (7). Familial clustering suggests that POMS cases with a family history may exhibit distinct clinical and immunological profiles compared with sporadic cases. However, additional research incorporating genetic analyses is needed to clarify the exact contribution of hereditary factors to disease pathogenesis.

Despite providing insights, our study has several limitations. First, a larger dataset is required to draw more definitive conclusions. Second, the absence of genetic analyses restricts our ability to identify specific hereditary risk factors associated with POMS. Future studies utilizing genome-wide association studies and familial linkage analyses could offer a more comprehensive understanding of the genetic basis of POMS. Additionally, the lack of long-term follow-up data limits our evaluation of disease progression and treatment effectiveness in pediatric patients. Longitudinal cohort studies are needed to assess transition rates to progressive MS and to identify prognostic factors that influence outcomes in POMS.

In conclusion, our study contributes to the growing body of literature on POMS by providing insights into its demographic, clinical, and familial characteristics. The findings underscore the importance of considering familial predisposition when evaluating pediatric MS patients and highlight the need for further research into the genetic and immunological mechanisms underlying POMS. Future studies incorporating long-term follow-up and genetic analyses will enhance our understanding of this rare yet clinically significant MS subtype.

Study Limitations

Several limitations should be considered when interpreting our findings. First, the retrospective design limits the ability to establish causal relationships and relies on the accuracy and completeness of medical records. Second, the relatively small number of patients with available CSF data restricts the generalizability of immunological findings, including OCB and IgG index results. Third, the absence of genetic analyses precludes identification of specific hereditary markers underlying familial POMS. Additionally, the lack of longitudinal follow-up prevented assessment of long-term disease progression, cognitive outcomes, or sustained treatment efficacy. Finally, the single-center nature of the study may introduce selection bias and limit the generalizability of the results. Future multicenter, prospective studies incorporating genetic profiling and long-term clinical monitoring are needed to validate and expand upon these findings.

Conclusion

In summary, our study adds to the growing body of evidence on POMS, with a particular focus on familial cases. We found that POMS accounts for a substantial proportion of MS diagnoses and is predominantly characterized by an RRMS and mild early disability. Familial cases were relatively common, highlighting the potential role of genetic predisposition in disease development. Although no significant differences were observed in CSF biomarkers between pediatric and AoMS, our findings emphasize the need for further immunological and genetic investigations. Recognizing familial MS in pediatric population may enable earlier diagnosis and more tailored monitoring strategies. Continued research with larger cohorts, long-term follow-up, and integrative approaches is essential to advance understanding of the pathophysiology and clinical trajectory of familial POMS.

Ethics

Ethics Committee Approval: The study was approved by the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 2014/125, date: 25.02.2015).

Informed Consent: We conducted a retrospective descriptive study of 3,411 patients diagnosed with MS at the MS center of a university hospital.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., E.S.Z., Concept: S.A., C.C., E.S.Z., Y.S., Design: S.A., C.C., E.S.Z., Y.S., Data Collection or Processing: S.A., C.C., Y.S., Analysis or Interpretation: S.A., C.C., Y.S., Literature Search: S.A., C.C., E.S.Z., Y.S., Writing: S.A., C.C., E.S.Z.

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

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