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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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