Review

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Association of multiple sclerosis with chronic fatigue syndrome, restless legs syndrome, and various sleep disorders, along with the recent updates

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Abstract

Multiple sclerosis (MS) and myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) share the symptom of fatigue, and might even coexist together. Specifically focusing on genetics, pathophysiology, and neuroimaging data, the authors discuss an overview of the parallels, correlation, and differences in fatigue between MS and ME/CFS along with ME/CFS presence in MS. Studies have revealed that the prefrontal cortex and basal ganglia regions, which are involved in fatigue regulation, have similar neuroimaging findings in the brains of people with both MS and ME/CFS. Additionally, in both conditions, genetic factors have been implicated, with particular genes known to enhance susceptibility to MS and CFS. Management approaches for fatigue in MS and ME/CFS differ based on the underlying factors contributing to fatigue. The authors also focus on the recent updates and the relationship between MS and sleep disorders, including restless legs syndrome, focusing on pathophysiology and therapeutic approaches. Latest therapeutic approaches like supervised physical activity and moderate-intensity exercises have shown better outcomes.

Keywords: chronic fatigue syndrome, multiple sclerosis, myalgic encephalomyelitis, restless leg syndrome, sleep disorders

Introduction

Multiple sclerosis (MS) and myalgic encephalomyelitis (ME), or chronic fatigue syndrome (CFS), are two conditions that share several overlapping symptoms and might even coexist, including fatigue, cognitive difficulties, and pain. Although they have distinct clinical presentations and diagnostic criteria, researchers are searching for a correlation between CFS and MS to better understand the fundamental mechanisms and potential treatment options for these conditions. Currently, some scientists attribute ME/CFS to a mental or stress-related origin[1]. This has led to the emergence of several trials studying the effects of psychological illness in relation to this entity[1,2].

Sleep disorders (SDs) tend to occur at a higher prevalence in patients with MS (PwMS); this significantly affects their

HIGHLIGHTS

- The manuscript discusses the parallels, correlation, and differences in fatigue between multiple sclerosis (MS) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), with a specific focus on genetics, pathophysiology, and neuroimaging data.
- Neuroimaging studies have revealed that the prefrontal cortex and basal ganglia regions, which are involved in fatigue regulation, have similar findings in the brains of people with both MS and ME/CFS.
- Genetic factors have been implicated in both MS and CFS, with specific genes known to enhance susceptibility to both conditions.
- Management approaches for fatigue in MS and ME/CFS differ based on the underlying factors contributing to fatigue.
- The manuscript also discusses the relationship between MS and sleep disorders, restless legs syndrome, and recent therapeutic approaches like supervised physical activity and moderate-intensity exercises.

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well-being and quality of life. However, these issues are often neglected. Obstructive sleep apnea (OSA), snoring, central sleep apnea (CSA), insomnia, as well as restless legs syndrome (RLS) are the major sleep disturbances in MS. It has been suggested that SDs were greater in patients suffering from MS than in the general population. Women are more likely to be diagnosed with MS than men, even though disturbances to one's sleep do not differ significantly across different phenotypes of MS. SD in MS can either be a secondary symptom or a primary issue, and they are linked to multiple debilitating MS symptoms, this includes, fatigue, depression, and abnormalities in cognition, impacting the way these patients lifestyle. Despite the link between CFS and MS not being fully understood, exploring the similarities and differences between these two conditions may help in understanding their underlying mechanisms and potential treatment options[2].

This paper aims to review the most recent studies addressing the relationship between CFS and MS and the SD associated with MS, with a focus on the most recent updates in research related to both conditions. By exploring the similarities and differences between these conditions and their underlying mechanisms, this study seeks to better understand their potential treatment options and their effects on patients' lives.

Multiple sclerosis and chronic fatigue syndrome

Background

ME/CFS and MS are similar in that they can both severely impair a person's standard of living. While these conditions may have distinct clinical presentations and diagnostic criteria, they share overlapping symptoms and might coexist, including fatigue, cognitive difficulties, and pain. This has led some researchers to search for a correlation between CFS and MS to better comprehend the fundamental mechanisms and potential treatment options for these conditions.

Some researchers currently believe ME/CFS are stress-linked or psychiatrically derived[1,2], like the original explanations for MS symptoms. Many people with ME and CFS have trouble accessing medical care, diagnosis, and treatment because of the widespread perception that their condition is psychological in origin. One research indicated that 71% of patients with ME/CFS consulted more than four doctors before getting an accurate diagnosis, and 63% of patients searched for a diagnosis for more than 2 years[3]. Ninety-five percent of women who sought medical help for CFS also reported feeling lonely[4]. Another study indicated that 609 CFS patients assessed experienced 66% more physician-caused illness than the overall medical patient group[5]. A recent study on ME/CFS and its impact on life showed that individuals with ME/CFS experienced significant impairment in their overall health status, with a mean score of 33.8 on a Visual Analogue Scale (0 = worst, 100 = best). Standard activity performance, pain, mobility, and self-care were the most impacted areas, whereas anxiety was the least affected[6].

Recent research has shed some light on the relationship between CFS and MS. For example, in one study, fatigue was frequent in MS patients, which was reported as a significant problem in 80% of individuals[7]. However, the study also found that fatigue in MS is different from CFS, with different patterns of onset, severity, and response to treatment.

Numerous efforts have been undertaken by researchers to identify biological markers for ME/CFS that might be utilized to distinguish it from MS. The proinflammatory cytokine interleukin-8 (IL-8), for instance, is overexpressed in people with CFS and MS[8]. Recent studies have looked at stimulated and unstimulated blood cells from individuals with CFS, MS, and healthy controls[8]. Global immunologic activation in CFS patients was different from that in MS patients and healthy controls. By comparing the correlations between unstimulated and stimulated peripheral blood mononuclear cells from control and MS samples, differential neighborhood connection exposes the differences between MS and CFS.

Despite these results, further studies are needed to determine the precise nature of the connection between CFS and MS. This part of the paper aims to review the available literature on the relationship between CFS and MS, with a focus on the most recent updates in research related to both conditions. We can better understand their underlying mechanisms and potential treatment options by exploring the similarities and differences between these two conditions.

Phenomenological correlation between MS and CFS

Phenomenological convergence between the diseases of MS and CFS refers to the subjective similarities reported by individuals who have both disorders. MS and CFS are both chronic, debilitating conditions that can significantly impact the lifestyle of patients. The most notable symptom of both conditions is fatigue, which is frequently the most debilitating and persistent symptom patients experience. The fatigue associated with MS and CFS may differ in terms of severity, quality, and treatment response (Table 1).

Numerous MS patients exhibit symptoms that are typical of ME/CFS. ME/CFS patients may experience a diverse array of symptoms[9]. Chronic fatigue, migraine-like headaches, insomnia, and even a reversal of the normal sleep–wake cycle are among the symptoms that may occur. Patients also report symptoms that fit the profile of a persistent flu-like condition. These symptoms feature incapacitating degrees of muscular fatigability, in addition to severe, persistent, physical, and mental fatigue. Difficulties in recalling information and forming new memories are also common. Patients often struggle to find the right words, leaving them unable to finish their sentences. Increases in mental or physical exertion bring on all these symptoms.

The inability to manage even slight increases in either mental as well as physical activity above individual standards is what characterizes ME/CFS[5]. This intolerance manifests itself as a flare-up of the disease, which can last for a brief time or an extended period[10,11]. Parasympathetic and sympathetic nervous system activity measures are aberrant in ME/CFS patients[12,13]. Common cardiovascular problems include neurally mediated hypotension and orthostatic intolerance[14]. Another prevalent observation is Postural Orthostatic Tachycardia Syndrome (POTS). There have been reports of increased sympathetic activity and exaggerated postural tachycardia[12,15]. In addition, intolerance for extreme temperature changes and severely compromised thermostatic stability are also observed autonomic symptoms.

It has also been shown that the heart has a reduced response to exercise[16]. Replicable findings in ME/CFS include increased sympathetic activity at rest and decreased vagal modulation[17,18]. Attenuated cardiac sympathetic reactivity was also indicated by diminished heart rate (HR) responses in another investigation.

Table 1

Key differences in fatigue and other findings in MS and CFS.

Fatigue	Multiple sclerosis	Chronic fatigue syndrome
Characteristic	Common symptoms; related to physical disability, depression, and other psychosocial factors	Core symptom; not relieved by rest
Onset	Often coexists with other MS symptoms, such as pain, spasticity, or depression	Sudden onset, often triggered by a viral illness or other stressors
Severity	May be mild to moderate in some individuals, but can be severe and debilitating in others	Often severe and debilitating
Duration	May be intermittent or chronic	Chronic, with symptoms lasting for at least 6 months
Daily life impaction	Can significantly impact daily life, particularly in individuals with more severe MS-related disability	Can significantly impact daily life, often resulting in significant functional impairment
Cognitive impairment	Common in later stages of the disease; may include difficulties paying attention, processing information, as well as recalling details	Core symptom; may include difficulty with attention, information processing, and memory
Muscle pain	May be present, particularly in individuals with spasticity or muscle spasms	Core symptom
Sleep disturbances	May be present, particularly in individuals with other symptoms such as pain or spasticity	Core symptom

CFS, chronic fatigue syndrome; MS, multiple sclerosis.

These lower HR responses could not be explained by patient deconditioning or prolonged inactivity[19]. According to those authors, there was a considerable hemodynamic response reduction in individuals with ME/CFS as compared to healthy individuals. Autonomic dysregulation in ME/CFS has been described by many researchers[20–22]. Pacing and other energy conservation measures are commonly used by ME/CFS patients to lessen the impact of fatigue on their daily lives. Women with CFS were studied to see if an activity-pacing self-management (APSM) intervention enhanced their capacity to perform daily activities. The outcomes demonstrated that APSM was successful in maximizing the engagement of women with CFS in their preferred activities of daily living[23].

Disabling fatigue affects between 53 and 92% of MS patients[24]. Chronic, debilitating fatigue[25,26] is a common complaint from MS patients. MS patients often experience daytime drowsiness and an overwhelming desire to nap due to this fatigue. Clinical manifestations of fatigue include tiredness, lack of energy, daytime somnolence, and symptoms that deteriorate. In MS, activity seems to exacerbate fatigue[27]. Thus, exacerbations resulting from total loss of energy following physical or cognitive effort exacerbate the sensation of chronic weariness. Disabling fatigue and drastically diminished exercise tolerance are major factors in the impaired functioning of MS patients[28].

Many MS patients also report a severe intolerance for even very little exercise[29]. PwMS typically struggle to focus or finish mental activities[29]. Patients frequently report malaise[29]. Autonomic dysfunction manifests most often in MS patients with impotence, digestive tract problems, sleep difficulties, micturition disorders, and orthostatic intolerance[30].

Patients with underlying autonomic dysfunction are at risk of developing POTS[31]. Orthostatic dysregulation, neurocardiogenic syncope, and cardiac dysrhythmias have been described by many research groups[32,33]. Pacing methods are also used by PwMS to reduce the effect of fatigue in their daily activities. These methods include organizing one's schedule such that one's busiest times are in the morning and one's rest and sleep times are placed between those times[23]. Several studies have enrolled patients in a course where they were instructed in different pacing methods and empirically tested the effectiveness of pacing. There was a notable drop in fatigue after taking these classes[34,35].

Pathophysiological and neuro-immunological similarities and differences between MS and CFS

Researchers have shown that cerebrospinal fluid (CSF) and blood plasma samples from individuals suffering from MS contain higher levels of the inflammatory cytokines IL-1[36], tumor necrosis factor-alpha (TNF-α)[37], and IL-6[38]. Further, as relapsing–remitting MS progresses, so does the cytokine pattern in the CSF of affected individuals. IL-1β plays an important role, with new reports on its cellular sources and actions. During experimental autoimmune encephalomyelitis (EAE), a variety of immune cell types release IL-1β, with the potential for IL-1 blockade as an MS therapy[36]. Increased levels of Th1-like cytokines are observed during disease activity. These include IL-2, interferon (IFN), and IL-12. An increase in IL-10, transforming growth factor β (TGF-β), and IL-4 production all characterizes remission, all of which belong to the Th2 cytokine family[39].

CSF and the lesions contain Th1 and Th2 cytokines[40] throughout both relapse and remission. Evidence from higher serum and CSF levels of TNF-α and IL-10 during an MS episode suggests that Th1 and Th2 cytokines are being produced together, rather with Th1 cytokines being expressed first, then Th2 cytokines[41]. Multiple investigations on ME/CFS have revealed elevated levels of the key proinflammatory cytokines TNF and IL-1[42]. The long-held belief that people with ME/CFS have an overactive Th2 immune system has been called into question by recent findings[43]. Some people with ME/CFS have a balance of proinflammatory and anti-inflammatory cytokines; however, this is not the case for the majority of patients[42,44].

Methodological discrepancies, such as differences in patient selection, may contribute to the conflicting results found in studies of Th cytokine profiles in persons with ME/CFS. Cyclooxygenase 2 (COX2) is highly upregulated in MS lesions, and it is hypothesized that this is because COX2 couples with inducible nitric oxide synthase (iNOS) to enhance excitotoxic death and destruction of oligodendrocytes[45]. In one study, histological methods were used to verify COX2's role in oligodendrocyte death[46]. Nuclear factor-kappa B (NFκB) increased adhesion molecules and proinflammatory cytokine production as a result of overexpression in macrophages at sites of inflammation. Microglia from active lesions contain considerable amounts of activated NFκB[47].

It is thus hypothesized that elevated levels of NFκB may account for the very low rate of oligodendrocyte death in MS.

Activation of NFκB in microglia, on the other hand, has been shown to promote neuronal degeneration[48], despite the fact that overexpression of NFκB in neurons appears to be protective. NFκB upregulation in lesion-based macrophages increases adhesion molecule and proinflammatory cytokine production, therefore amplifying the inflammatory response. Significant quantities of active NFκB can be seen in microglia from active lesions[47].

Neuroimaging and biomarker similarities and differences in MS and CFS

Upon conducting an investigation into cerebral perfusion through the employment of single photon emission computed tomography (SPECT), it was observed that regions of cortical gray and white matter exhibited notable reductions in blood flow among individuals diagnosed with MS[49,50]. Individuals diagnosed with MS exhibit a reduced volume of blood flow to the thalamus and caudate nuclei in comparison to a healthy control group. This phenomenon holds true for both the outer layer of the brain and the deeper regions of gray matter. Cognitive impairment is associated with a systemic decrease in white and gray matter oxygen consumption and blood flow[51]. Patients with primary and secondary progressive MS have been shown to have decreased perfusion, especially in gray matter. There was a significant reduction in the flow of blood in the gray and white matter of the cortex upon assessment of cerebral perfusion using SPECT, resulting in decreases in volume in both subcortical and cortical regions, and these results have indicated either a reduction in the metabolic activity of neurons or possible neuronal death[52].

On the other hand, CFS patients have decreased perfusion throughout the brain, especially in the brainstem[53]. It is well-established that SPECT abnormalities are more likely to be seen in patients with ME/CFS compared to magnetic resonance imaging (MRI) abnormalities[53]. Eighty percent of ME/CFS patients have decreased brain blood flow as measured by SPECT[54]. Also, it has been observed that there was a significant reduction in brainstem hypoperfusion in individuals diagnosed with ME/CFS in comparison to their healthy counterparts.

Thus, a notable and positive correlation between neurocognitive impairments and reduced frontal blood flow was observed[55]. The positive correlation between cerebral glucose metabolism and the clinical development of MS has been established through the utilization of positron emission tomography (PET) with a labeled natural glucose analog, fludeoxyglucose (FDG), 18F[56]. A study has revealed that individuals diagnosed with MS who reported experiencing severe fatigue concurrently exhibited compromised glucose metabolism in their basal ganglia and prefrontal cortex[56].

Using FDG-PET, researchers have shown widespread hypometabolism of glucose in the brain in CSF patients[57]. White matter disease progression in PwMS has traditionally been monitored using T1-weighted, T2-weighted, non-contrast, or gadolinium MRI imaging[57]. MRI has shown atrophy and abnormalities in the cerebral cortex as well as the deep gray matter areas. Hypo-intensity in areas of gray matter is associated with brain atrophy in MS patients[58]. While traditional MRI techniques may detect white matter lesions, their sensitivity is limited when it comes to gray matter abnormalities. Pure cortical MS lesions cannot be detected by current MRI methods due to a lack of sensitivity[59]. Increasing the field strength or employing voxel-based morphometry are two ways to boost this sensitivity[60]. Gray matter volume loss has been found in individuals with ME/CFS using voxel-based morphometry MRI[60].

These declines appear to have a minimal connection with the severity of the disease or the patient's age being evaluated. Hyperintensities in the subcortical white matter have been documented on multiple occasions in ME/CFS[61]. Proton magnetic resonance spectroscopy (MRS) has been used to identify elevated levels of cerebral lactate among individuals with MS[62,63]. High choline levels in the basal ganglia were detected using choline MRS[64]. MRS was used to show that choline, lactate, and lipid concentrations were all much higher than average. A dramatic reduction in the levels of *N*-acetyl aspartate in the hippocampus of patients diagnosed with MS was discovered using MRS. An increase in lactate has been linked to anaerobic glycolysis in disease-fighting leukocytes[65].

MRI and nuclear MRS were used to study a group of people with ME/CFS. Proton MRS found considerably lower *N*-acetyl aspartate levels in the hippocampus regions of patients with CFS. Using the same method, a study showed that ME/CFS patients' basal ganglia had higher choline signaling activity[66]. It was noted that gliosis increased the level of turnover in the cellular membrane, and this was thought of as the probable cause for choline peak values in the basal ganglia[66]. Patients with ME/CFS also showed a significant signal of choline/creatine in the occipital brain.

As for biomarkers in MS, parameters such as neurofilament light chain (NfL) and oligoclonal bands (OCBs) are commonly used to monitor disease activity and progression. NfL is released into the CSF and blood when axons are damaged, making it a useful biomarker for activity and disease progression in MS[67]. OCBs are present in up to 90% of MS patients[68,69].

In CFS, the search for biomarkers has been more challenging due to the lack of objective diagnostic criteria for the condition. However, recent studies have identified potential biomarkers such as cytokines and chemokines. In particular, the blood of CFS patients revealed that the levels of proinflammatory cytokines such as IL-1 and IL-6, as well as TNF-α, have been elevated; this indicated an inflammatory role in the pathophysiology of the condition[70]. Additionally, oxidative stress markers such as malondialdehyde (MDA) and protein carbonyls have been found to be elevated in CFS patients compared to healthy counterparts[71].

Fatigue management in MS and CFS

Management of fatigue in both MS and CFS involves a multidisciplinary approach that includes lifestyle modifications, medications, and psychological interventions.

In MS, management focuses on addressing physical disability, depression, and other psychosocial factors that can contribute to fatigue. Exercise, sleep hygiene, and energy conservation techniques are important lifestyle modifications that can help manage fatigue in MS. Medications such as amantadine, modafinil, and methylphenidate have been used to improve alertness and for fatigue reduction in MS. Cognitive behavioral therapy (CBT) and mindfulness were some of the psychological interventions that have also shown promise in managing fatigue in MS. A study found that CBT interventions had a small but significant effect on reducing fatigue severity in individuals with MS[72].

In CFS, symptom-based management approaches, such as CBT and graded exercise therapy (GET), are used commonly. CBT aims to address the negative thoughts and behaviors that can perpetuate fatigue and improve coping skills. GET involves gradually increasing physical activity levels in a supervised and structured program. However, these interventions have been the subject of controversy and debate, with some individuals reporting adverse effects from GET[73]. A recent review concluded that GET can be effective in improving fatigue and physical function in individuals with CFS, but emphasized the importance of careful monitoring and individualized treatment plans[74]. In addition to CBT and GET, medications such as stimulants and antidepressants may also be used to manage fatigue in CFS.

It is noteworthy to acknowledge that the management of fatigue in individuals with MS and CFS is a highly personalized process, and the best method will be tailored to each person's unique need and set of circumstances. Therefore, a comprehensive assessment by a healthcare provider with experience in managing fatigue in these conditions is essential to developing an effective management plan.

Sleep disorders in multiple sclerosis

Patients diagnosed with MS have a higher risk of suffering from SDs and this can significantly affect their well-being and their life quality. However, these issues are often neglected. The major sleep disturbances in MS are breathing disorders, insomnia, as well as RLS[75]. Other disturbances include circadian rhythm disorder (CRD), narcolepsy, along with rapid eye movement (REM) sleep behavior disorder (RBD) (Fig. 1)[76]. OSA and CSA are the most common types of breathing issues during sleeping[77].

SD frequency is greater in patients diagnosed with MS compared to the general population, according to studies[77]. Self-reported sleep problems are common among MS patients, with prevalence ranging around 50%, and objective sleep disturbance is also correlated with this finding[78,79]. However, it is important to keep in mind that older studies, particularly those carried out over a decade ago, may have exaggerated the prevalence of SD in MS patients. This is due to the possibility of including individuals with other demyelinating conditions, such as neuromyelitis optica spectrum disorders (NMOSDs)[80].

While there is no significant difference in sleep disturbance across different phenotypes of MS, a higher prevalence is seen in women with MS compared to men[81]. Several factors may contribute to differences in SD between males and females, including estrogen and testosterone hormones, genetic mechanisms, psychosocial factors, as well as physical factors like pain or bladder dysfunction. In women, SD is often linked to depression and anxiety, while in men, it is associated with pain[82]. In the case of MS, SD can either be a secondary symptom resulting from other psychological or physical symptoms, or it can be a primary issue. In both cases, there is a reciprocal relationship between MS and SD[82]. These SDs are associated with several debilitating MS symptoms, such as pain, fatigue, depression, as well as cognitive dysfunction (CD) resulting in low quality of life[83].

Even though these disorders can have serious long-term consequences and affect the quality of life, there are no established guidelines for identifying and investigating sleep problems in MS. MS patients may benefit from the same overarching criteria for evaluating sleep disturbances as those with neurodegenerative illnesses and stroke. However, due to the multifocal nature of MS, it is important to consider sleep-related symptoms in the clinical evaluation of MS. A unified multidimensional sleep metric could provide a comprehensive approach to evaluating sleep in MS[83,84]. One potential cause of SD in PwMS is the negative effects of their medication. However, there is limited knowledge about how disease-modifying therapies affect sleep. A

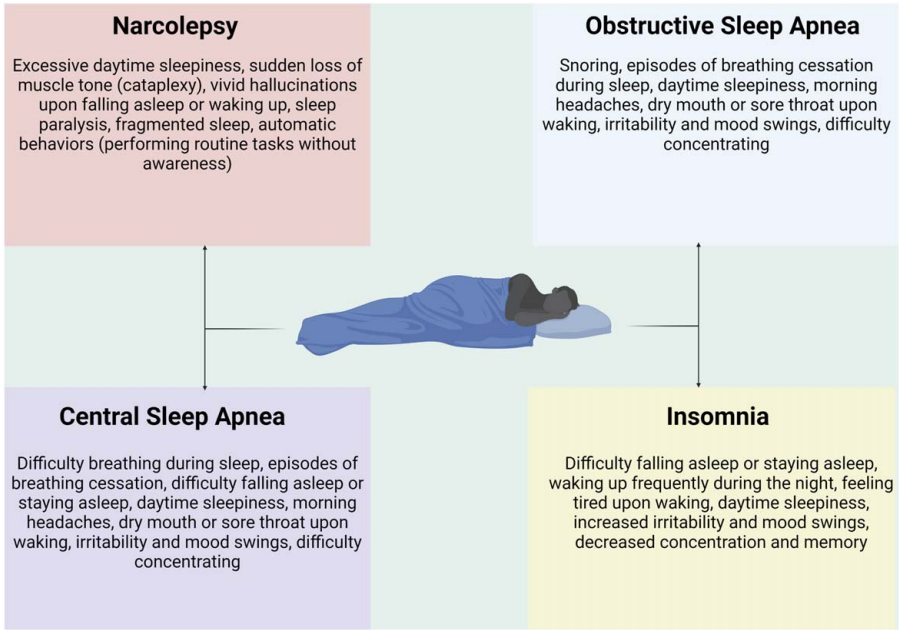

Figure 1. Commonly encountered sleep disorders in multiple sclerosis and their characteristic features (original figure). Created with BioRender.

study found that injections of IFN-β were associated with less restful sleep, possibly due to the flu-like side effects and alterations of cytokines caused by the drug[85].

Sleep disorders and cognitive dysfunction in multiple sclerosis

Clinical investigation has demonstrated that individuals diagnosed with MS who report symptoms of sleep disturbance are also likely to exhibit signs of CD[79,86,87]. The areas of cognition most affected are memory, attention, executive functions, and information processing speed[81,82]. In the memory domain, visual memory appears to be notably affected[81]. A significant association between decreased sleep efficiency and prolonged periods of wakefulness during the night with impaired performance in cognitive domains related to memory and attention was found, while reduced REM sleep was associated with poor attention performance. Sleep disturbance has been identified as a predictor of future cognitive decline in MS[82]. However, while self-reported insomnia was found to be predictive of self-reported general CD, it was found to be a poor indicator of objective CD[79].

Sleep disorders and exercise in multiple sclerosis

Among MS patients, those with significant improvements in their sleep quality are the ones who participated in aerobic exercise or endurance training. Studies found that aerobic exercises showed a significant increase in serotonin levels over 6 weeks[88]. Though pathophysiology is unclear, it was suggested that the increase in the levels of serotonin in turn increases the levels of melatonin, thus improving the quality of sleep indirectly. Irrespective of the underlying mechanism, moderate-intensity aerobic exercise might be a promising treatment to alleviate symptoms in MS patients with SD[87,88].

Sleep-related breathing disorders

The frequency of sleep-related breathing disorders (SRBD) in MS studies varies greatly because studies employ different scoring methodologies and cut-off values[89]. So, it is recommended to use polysomnography, which is considered the gold standard option for scientifically evaluating and identifying sleep-related breathing issues[90]. Patients with SRBD may exhibit symptoms such as fatigue, reduced concentration, mood swings, mood changes, nocturia as well as erectile dysfunction. Polysomnography can reveal five or more apneas or hypopneas per hour, and patients may experience sleep apneas, choking incidents, and snoring at night[76].

Collapsing of the pharyngeal muscles leads to obstructive apnea and hypopnea; on the other hand, failure of the medullary respiratory signal results in central apnea. Nighttime hypoxemia, awakenings, and drowsiness throughout the daytime are all possible outcomes of these occurrences. Demyelinating lesions in the medullary reticular formation are associated with SRBD and even sleep-related breathing cessation (Ondine's curse) in individuals who have MS[78].

Obstructive sleep apnea

As mentioned earlier, during sleeping, collapsing of the upper airway results in OSA, which disrupts sleep and causes periodic hypoxemia[91]. It is the most common type of SRBD, with varying reported prevalence rates in different studies. The observed variations in the patient populations may be attributed to differences in BMI, although the matter remains inconclusive as not all studies have provided the BMI data of their respective patients.

Given that fatigue is a common symptom among individuals with MS, it is important to consider the possibility of undiagnosed OSA as a contributing factor. Therefore, it is recommended that a considerable proportion of MS patients who report fatigue undergo polysomnography to assess for the presence of OSA[75]. It is important to note that the distribution of MRI lesions in individuals with OSA was not significantly different from that in patients without OSA[76]. In specific instances, MRI may uncover multiple lesions within the pontine tegmentum and dorsal medulla. It has been observed that individuals suffering from OSA, regardless of their MS status, may derive advantages from various lifestyle modifications. These modifications include, but are not limited to, weight reduction, smoking cessation, the employment of dental appliances, positional therapy, positive airway pressure, and surgical intervention, if deemed necessary[92].

Central sleep apnea

CSA is another SRBD that can occur in people with MS and is much less common than OSA[91]. Apneic events are observed to occur when there is a dysfunction in the respiratory control centers located in the brainstem. This dysfunction affects the inputs that drive breathing as well as the descending pathways that trigger respiratory muscles. As a consequence, breathing is observed to stop during these events[93]. PwMS who have been diagnosed with lesions in the brainstem are more likely to have an increased apnea–hypopnea index and central apnea index, according to a retrospective study[94]. Central alveolar hypoventilation syndrome, sometimes known as 'Ondine's curse', has also been linked to MS, and it is thought to manifest itself most frequently in the medullary and/or upper cervical regions. Usually, seen as a congenital condition, this syndrome is also seen in ischemic, inflammatory, or neoplastic etiologies[76].

Insomnia

The prevalence of insomnia has been observed to be high among individuals diagnosed with MS, with ~25–50% of them experiencing difficulty initiating or maintaining sleep. The literature on insomnia prevalence among MS patients in comparison to the general population is scarce. However, observational studies indicate that MS patients display higher rates of insomnia than their general population counterparts[75,78,89]. Early morning awakening is the most common symptom experienced by MS patients with insomnia[95].

According to a study, insomnia appears to be more widespread among elderly individuals diagnosed with MS. Nevertheless, no correlation between illness duration and insomnia was seen[96]. Nocturia, pain syndromes, muscular spasms, periodic limb movements, RLS, drug side effects, and mental diseases, including depression, all contribute to sleep discomfort in MS patients. Nocturia or urinary incontinence is the most common problem affecting up to 80% of them by causing repeat awakenings and sleep disruption[78,89]. Also, it is important to evaluate PwMS for both substance use and current medication use, especially the use of immunomodulatory drugs, as they have been linked to poor sleep quality[84].

It has been observed that patients diagnosed with MS could potentially witness noteworthy enhancements in their overall well-being owing to the identification and management of a frequently neglected factor of sleep disruption. Various interventions such as fluid limitation, intermittent catheterization, anticholinergic agents including propantheline or oxybutynin, and the administration of the hormone Desmopressin have been considered as plausible strategies for addressing nocturnal bladder spasticity in this patient population[78,97].

Similar to the general population, the treatment of insomnia in MS patients requires a multifaceted approach that includes both non-pharmacological and/or pharmaceutical therapy, with a primary focus on the root causes and related comorbidities[98]

CBT, biofeedback (primarily electromyographic), paradoxical intention, sleep hygiene instruction, sleep restriction, as well as stimulus control, are some of the non-pharmacological treatment options. Autogenic training, guided visualization, self-hypnosis, and meditation are less popular methods[95]. For individuals with chronic (longer than one month) insomnia, CBT alone or in combination with medication is helpful[84].

Pharmacological interventions include antidepressant medications that act on 5-HT2, melatonin, benzodiazepine, and antihistamines with sedative properties. These have been shown to decrease the time it takes to fall asleep and improve the continuity of sleep, although the effectiveness is unclear. It is not recommended to use these medications in the long term due to the risk of tolerance and addiction. Other drugs that may be used to treat insomnia include neuroleptics, melatonin, and herbal remedies like valerian[84,95,98,99].

Narcolepsy

Excessive daytime drowsiness, sleep paralysis, hypnagogic hallucinations, and cataplexy are all symptoms of narcolepsy, a sleep disease that disrupts normal sleep patterns[100]. Its prevalence is higher in the Japanese population but much lower in the Israeli population. Hypocretin (orexin) neurons in the hypothalamus have been implicated as a possible narcolepsy trigger, alongside genetic predisposition. Hypocretins are a class of neuropeptides that increase both alertness and metabolic rate. A lack of the ligand hypocretin in the brain and CSF has been associated with narcolepsy-cataplexy[76].

On the other hand, hypocretin system malfunction due to MS can cause low CSF levels of hypocretin-1, which can cause a reversible narcolepsy-like condition. Methylprednisolone treatment corrected CSF hypocretin-1 levels in individuals with excessive daytime drowsiness[89], lending support to this theory. Many years of research has supported the hypothesis that narcolepsy and MS have a genetic component. Human leukocyte antigens (HLAs) like HLA-DR2, HLA-DQB10602, HLA-DQA10102, and HLA-DQw1 have been linked in studies involving individuals of various racial and ethnic backgrounds to narcolepsy with cataplexy. HLA-DR2, HLA-DQB1, HLA-DQA1, HLA-A3, HLA-DQw1, and HLA-B7 are all more common in the MS population[78].

Patients' hypothalamic lesions were found to be bilateral on MRI, providing more evidence linking MS and narcolepsy. Lesions in the supratentorial white matter or the upper cervical medulla have been seen in some individuals without signs of hypothalamic involvement, and this variance should be further researched[89].

While there is currently no cure for narcolepsy, the symptoms can be managed in the same ways they are for those without MS and include lifestyle changes, counseling, and medications that target symptoms like sleepiness and cataplexy. Pharmaceutical interventions, namely modafinil and methylphenidate, have been implemented for the purpose of promoting wakefulness. Additionally, certain antidepressants have been utilized to mitigate REM sleep and alleviate associated symptoms. For individuals with acute hypothalamic lesions and concomitant narcoleptic symptoms, the administration of high dosages of methylprednisolone has been proposed as a potential treatment option. Emerging evidence suggests the presence of a potentially shared immunopathophysiological mechanism underlying somnolence and fatigue in both narcolepsy and MS. Specifically, preclinical investigations have demonstrated that modafinil can activate lateral hypothalamic neurons, which are responsible for generating the wake-promoting peptide hypocretin-1. This finding has important implications for understanding the underlying mechanisms driving somnolence and fatigue in both disorders and could inform the development of novel therapeutic strategies[84,95].

Rapid eye movement sleep behavior disorder

In the context of MS patients, the incidence of RBD is comparatively infrequent when compared to other SDs[78]. Diagnosis of RBD is based on the presence of dream enactment and complex motor actions during REM sleep, along with the observation of REM sleep without atonia (RSWA) on polysomnography[101]. It has been noted that RBD arises from lesions in the pedunculopontine nuclei, which have afferent connections with the locus coeruleus and reticular formation and subsequently contribute to the development of hypertonic muscles. RBD can be caused by pons inflammatory destructive lesions in MS individuals[76]. Supporting this, lesions in the dorsal pontine brainstem have been observed in MRI reports of MS individuals with RBD[102].

Clonazepam is the preferred first-line therapy for RBD, including in MS patients, but side effects such as sedation and the potential for respiratory depression should be considered. Treatment with pulsed adrenocorticotropic steroid therapy can resolve RBD symptoms in PwMS[76,89]. Several studies have provided evidence supporting the effectiveness of melatonin and zopiclone in managing RBD in affected individuals. However, it is important to note that certain pharmacological agents commonly prescribed for depression, including tricyclic antidepressant agents (TCAs) and selective serotonin reuptake inhibitors (SSRIs), have the potential to induce RBD in patients. This highlights the importance of cautious selection and monitoring of medications when treating patients with RBD, particularly those with underlying psychiatric conditions[84,101].

Circadian rhythm disorders

Loss of biological rhythm due to damage to the suprachiasmatic nucleus, which resides above the optic chiasm, regulating the recurring pattern of natural processes, such as sleeping and waking, regulating body temperature, and hormone secretion, results in CRD[103]. It is uncertain whether CRD is more common in the general population or PwMS. Theoretically, CRD might result from demyelination, like that in MS, which could affect these pathways and interfere with the biological pacemaker's operation[84,103].

Patients with delayed sleep phase syndrome have been treated with chronotherapy, phototherapy, as well as melatonin in an effort to normalize their circadian rhythm. Although they have not been specifically researched in this demographic, these treatments may also be explored in MS patients[95].

Restless legs syndrome in multiple sclerosis

Epidemiology

RLS, a neurological disorder, is characterized by an irresistible urge to move one's legs in response to unpleasant sensations. This phenomenon, known as 'akathisia', is a hallmark symptom of the condition. Individuals affected by RLS may experience considerable discomfort and disruptions to their sleep patterns, leading to negative impacts on their overall quality of life. It is most commonly experienced during periods of inactivity, especially at night, and is alleviated by movement. RLS is considered both a sleep and movement disorder, as it often disrupts sleep and causes involuntary leg movements[104,105]. The clinical symptoms of RLS were used by the International Restless Legs Syndrome Study Group (IRLSSG) to create diagnostic criteria in 1995. In 2003, these standards were found to be reliable; in 2012, they were updated[106,107]. Standardized questionnaires are used to diagnose RLS in MS patients in the same way they are used in the general population. There are four clinical criteria included in these questionnaires: the need to move, pain or unpleasant feelings in the limbs, worsening symptoms when at rest, improvement when moving, and worsening symptoms when sleeping[108].

Unfortunately, MS patients typically suffer identical symptoms that intensify with immobility, making it difficult to distinguish between RLS and other sensory and motor symptoms of MS. Therefore, confirming all four RLS diagnostic criteria is crucial to avoid false positives. Although leg spasms and paresthesia are prevalent in MS, RLS is characterized by a worsening at night and improvement with movement[84,95]. It is also important to take into account that most people who have RLS also suffer from Periodic Limb Movement Disorder (PLMD) while they are sleeping. RLS is primarily diagnosed based on clinical symptoms, particularly involving the lower limbs, and polysomnography is often needed to detect PLMD contrasted by repetitive limb movements, including both the arms and legs during sleep[78,84]. Due to the significant overlap of symptoms, the diagnosis of RLS in MS patients should be approached with caution and require a thorough evaluation to avoid misdiagnosis.

RLS can be categorized into two forms: idiopathic and secondary RLS. Idiopathic RLS typically presents before the age of 50 and has a strong genetic component with four associated genes: BTBD9, MEIS1, PTPRD, and MAP2KP/SCOR1[109]. RLS can arise as a secondary complication due to a variety of underlying causes, including iron deficiency, renal failure, antidopaminergic therapy, and pregnancy. Additionally, certain neurological disorders, including peripheral neuropathy, essential tremors, myelopathies, Parkinson's disease, and spinocerebellar ataxia, have been linked to secondary RLS. Despite these associations, MS has not been consistently identified as a secondary cause of RLS, as studies examining the frequency of RLS in MS patients have produced inconclusive findings[110].

Although numerous studies suggest a higher prevalence of RLS among MS patients compared to the general population, there exists significant heterogeneity in the reported prevalence rates. This variability may be attributed to differences in study design, patient populations, and diagnostic criteria utilized. Further research is necessary to establish a more precise estimation of RLS prevalence among MS patients and to identify factors that may contribute to the observed heterogeneity in reported rates[104,110,111]. People over the age of 60, women, and those with a positive family history are at increased risk of developing RLS[89,95,109]. Studies of RLS in MS patients, however, have not shown a similar trend. The prevalence of RLS in MS patients is similar to those without RLS, according to most research[111,112], whereas some studies suggest that the pooled incidence of RLS in MS is greater in women than in men. Despite this, RLS should always be investigated in PwMS due to the high frequency of RLS in this population[95]. The origin of this association is unclear.

Pathophysiology

Although the exact cause of RLS is unknown, hypothyroidism and dopaminergic system changes have been linked to the disorder[105]. Dopaminergic dysfunction can result from damage to specific dopaminergic pathways in the brain or a disturbance in dopamine metabolism due to reduced iron storage[89].

Iron deficiency is strongly linked to RLS, both in the peripheral as well as the central nervous systems. RLS prevalence is higher in patients with hemosiderosis, iron-deficiency anemia, or conditions that lead to low serum iron levels, such as end-stage renal disease and pregnancy. RLS patients also have lower levels of serum ferritin and decreased iron and ferritin in their CSF compared to normal controls. Also, it was observed that the symptoms of RLS worsen at night, which is when serum iron levels are lowest. Additionally, iron deficiency may reduce the number of receptor regions that bind dopamine D2, leading to the symptoms[107,109]. Research has indicated that individuals with RLS have lower levels of brain iron stores, and the RLS severity in their symptoms is correlated with their levels of iron. However, it has been found that the distribution of iron in PwMS who also have RLS is not distinct. The ferritin levels of those with RLS, including those with and without MS, were not significantly different, according to recent research. This shows that MS-related variables, such as lesions in the central nervous system, are more likely than iron deficiency to explain the RLS type seen in MS patients[105,109].

Dopaminergic dysfunction causes hyper-excitability in spinal circuitry, leading to symptoms of RLS. Additionally, there is evidence that the spinal pathology of myelin integrity in the cervical spinal cord is significantly associated with an increased risk of RLS development in MS patients. This is consistent with the finding that people with MS and RLS tend to have more cervical cord lesions, which might disrupt the ascending and descending pathways and may contribute to RLS symptoms[104,112]. One possible explanation for why MS patients experience RLS is damage to the descending dopaminergic fibers that regulate motor and sensory pathways. Experiments showing that dopaminergic therapy is helpful for RLS caused by spinal cord injuries provide support for this theory[89,113].

The presence of cervical cord lesions, a frequent occurrence in MS, has been associated with a higher susceptibility to RLS[110]. It is suggested that RLS-positive MS patients exhibit more severe degeneration compared to RLS-negative MS patients, as evidenced by lower fractional anisotropy and a greater fractional histogram peak height in the spinal cord. This finding supports

the aforementioned assertion. And RLS-positive MS patients have more frequent cervical lesions and a higher number of lesions in the cervical spinal cord[109]. It is also suggested that RLS may be caused by dysfunction in the basal ganglion, and dopaminergic agents have been shown to have a positive effect on RLS. MS patients are more likely to have RLS, possibly because MS affects the basal ganglion. However, no difference in the basal ganglia was noted when a cranial MRI is used in MS patients with and without RLS. Cervical cord lesions were strongly associated with RLS, but there was no difference in the brainstem or thoracic cord between MS patients with and without RLS[107,114]. A voxel-based lesion imaging method was recently employed to locate brain areas linked to RLS in MS patients. Without symptom localization, the study showed that RLS was linked to T2-weighted MS lesions in the left hemisphere's white matter adjacent to the cortex. The area of white matter around the left precentral gyrus was the site of the observed lesion cluster. Patients diagnosed with RLS but not MS do not have these symptoms[115].

Despite all the available information, the exact anatomical background of RLS in relation to MS remains unclear and unexplained. Some have suggested an autoimmunological or genetic floor for this association[116,117]. The genetic basis of RLS in MS patients was investigated through a genetic association study. The study revealed a low association between the occurrence of RLS and a specific variant of the MAP2KP/SCOR1 gene and concluded that genetic factors may not be a significant contributor to the high prevalence of RLS in MS patients[116]. Inflammatory and immunological disorders are commonly associated with the development of RLS, and MS is an autoimmunological inflammatory disease. The possible connection in this domain was exclusively discussed in a review[117].

Therapeutic approach

Studies have shown that RLS symptoms tend to be more severe and of longer duration in MS patients compared to controls, but the reasons for this remain unclear[107]. The severity of RLS symptoms is also associated with sedentary behavior and the amount of physical activity of the individual[104]. More severe RLS is associated with more cognitive impairment, worse sleep, excessive daytime drowsiness, impaired function, and a decreased quality of life in terms of emotional well-being among MS patients[118,119]. Perceived deterioration in cognitive function and other symptoms have been linked to persistent sleep deprivation owing to RLS in certain research[120,121]. Likewise, the frequency of anxiety and depression is also more in MS patients having RLS compared to controls[119,122]. However, one study published in the year 2020, conducted on 275 patients, found that impaired sleep quality did not account for this relationship, indicating that other variables may be influencing the association[113]. It is important for future studies to investigate these relationships in a multifactorial approach and consider confounding factors, such as sleep abnormalities. The major limitations we observed in these studies were small sample sizes and reliance on self-reported symptoms.

Additionally, a few interesting observations are made by some studies. The findings of a particular study indicate that individuals diagnosed with MS who also exhibit symptoms of RLS possess a comparatively reduced thickness of the retinal layer located in the inferior quadrant, as opposed to those MS patients who do not experience RLS[121]. Compared to MS patients without RLS, those with RLS had significantly higher levels of both total body fat and trunk fat. Various reasons could account for this, which are linked to SD such as eating at night, lack of sleep, and metabolic and hormonal changes by sleep deprivation[105]. Overall, determining whether or not these diseases exist, and, if so, to what extent, is crucial for improving MS management and therapy.

Iron supplementation, dopaminergic drugs, anticonvulsants, opioids, and benzodiazepines are all pharmacological alternatives for treating RLS in the general population[78,123]. Patients treated with levodopa and dopamine agonists frequently experience a therapy-related exacerbation of RLS symptoms; this may be owing to the co-activation of distinct dopamine receptor subtypes or interactions with other receptors. These plasticities in the dopaminergic system have to be considered by emerging therapeutics[124]. The pharmacological approach for RLS in MS patients is similar to that of the general population, but more focused on dopaminergic agents[78].

Little evidence is found for the non-pharmacological approaches to RLS in the general population[123]. However, RLS in MS patients showed significant improvement with a non-pharmacological approach to physical activity. This approach led to a reduction in RLS severity, subjective sleep satisfaction, and increased total sleep duration and quality of life[125,126].

Conclusion

Fatigue is a frequent symptom of both MS and CFS, but both disorders differ in their form, onset, intensity, and effect. Both disorders may coexist together. MS-related tiredness can range from mild to severe and is often accompanied by pain and stiffness. CFS-related tiredness, on the other hand, is a primary symptom that can disrupt everyday living and impede function. Additionally, MS patients often have RLS-like symptoms, making diagnosis difficult. Sleep difficulties are common in MS patients and can negatively affect their health and quality of life. Sleep difficulties include insomnia, RLS, and sleep-related respiratory issues. A unified multidimensional sleep metric might give a complete approach to sleep evaluation. To better understand the pathophysiology and causes of fatigue in these illnesses and create more effective therapies, further study is needed.

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The authors declare that there are no conflicts of interest, financial or otherwise.

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