Review Article

Multiple sclerosis-related fatigue lacks a unified definition: A narrative review

Iman Adibi[1,2], Mehdi Sanayei[2,3], Farinaz Tabibian[2], Neda Ramezani[2], Ahmad Pourmohammadi[2], Kiarash Azimzadeh[2]

[1]Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran

Fatigue is the most common symptom in multiple sclerosis (MS). Although MS-related fatigue (MS-F) strongly affects quality of life and social performance of patients, there is currently a lack of knowledge about its pathophysiology, which in turns leads to poor objective diagnosis and management. Recent studies have attempted to explain potential etiologies as well as treatments for MS-F. However, it seems that without a consensus on its nature, these data could not provide a route to a successful approach. In this Article, we review definitions, epidemiology, risk factors and correlated comorbidities, pathophysiology, assessment methods, neuroimaging findings, and pharmacological and nonpharmacological treatments of MS-F. Further studies are warranted to define fatigue in MS patients more accurately, which could result in precise diagnosis and management.

Key words: Diagnosis, epidemiology, etiology, fatigue, multiple sclerosis, neuroimaging, physiopathology, risk factors, therapy

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INTRODUCTION

Fatigue is the most debilitating and frequent symptom in multiple sclerosis (MS). MS-related fatigue (MS-F) markedly influences mood, sleep, quality of life (QoL), work capacity, employment chances and social activities.[1,2] MS patients describe their fatigue as an uncontrollable apathy, detached feeling from environment, increased exertion while doing pre-learned tasks, or even visual impairment worsening after a long activity.[3] In scientific literature, MS-F is considered as a multidimensional symptom with physical, cognitive, and psychosocial components, that encompasses lack of physical or mental energy and interferes with usual and desired activities.[4,5] There are several studies attempting to develop definition, diagnostic tools and treatment for fatigue in MS, which are reviewed in this article in following sections.

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METHODS

For this review, we used the terms "MS" and "fatigue" as the main keywords to search in online databases including PubMed, Medline, Google Scholar, Clinical Trials.gov. For each section, we added related terms such as "epidemiology," "prevalence," "risk factors," "comorbidities," "pathophysiology," "assessment," "questionnaires," "neuroimaging," and "treatment" to the search.

EPIDEMIOLOGY

Prevalence of MS-F ranges from 52% to 88%, due to variety of studies' population and fatigue definition.[6] Accordingly, the annual incidence of MS-F also varies between 25% and 29.9%.[7,8] It is not clear whether this symptom is related to the age at onset or duration of disease.[9,10]

Address for correspondence: Dr. Iman Adibi, Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: i_adibi@med.mui.ac.ir

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SEMIOLOGY

Unlike physiological form of fatigue, MS-F may persist for months or even years.[11] It can appear at any time of the day, but becomes usually worse in the afternoon and may not respond to rest.[3,12] This symptom has two essential characteristics: First, it occurs independent of depression or muscle weakness;[3,12] second, it interferes with physical or mental performance.[13] Mental or physical activity, hot or humid environment, acute infection or food ingestion can also provoke an episode of fatigue.[1,3,5,12,14]

Fatigue can be classified as acute or chronic according to its time course. Acute fatigue refers to a new onset overwhelming tiredness or lack of energy felt for <6 weeks.[4,13,15] In contrast, chronic fatigue is defined as a symptom persisting for more than 6 weeks in at least half of the days.[1,11]

In addition to time course, fatigue is classified as central and peripheral. Some patients experience difficulties in arousal and attention which is called central fatigue,[11] whereas peripheral fatigue manifests as muscle exhaustion during physical exertion.[16]

Another classification of fatigue is as primary or secondary. Primary fatigue is caused directly by MS as a consequence of inflammatory and degenerative processes,[1,12,13,17] whereas secondary fatigue results from comorbid conditions such as depression, sleep disorders, use of medications particularly anti-spasticity agents, infections, thyroid dysfunction or electrolyte imbalances.[17] It is often difficult to distinguish between primary and secondary fatigue, as MS patients usually have concurrent comorbidities that can cause or worsen fatigue, simultaneously.[12,13,17]

RISK FACTORS AND CORRELATED COMORBIDITIES

Several cross-sectional studies have discovered comorbidities and factors correlated with MS-F, though more longitudinal data are needed to confirm them as risk factors.

Compared to relapsing-remitting MS, patients with progressive MS are at a higher risk of experiencing fatigue and also a more severe form.[6] Unlike limited consensus regarding the relationship between disability and MS-F, pain has been shown to increase fatigue in this population.[18]

Older age, less education, more children, and being divorced are considered as possible risk factors for MS-F in both men and women, however it's not clear whether gender affects prevalence of this symptom.[2,9,10] Social support has also been linked to MS-F, as higher support improves physical and cognitive fatigue.[19]

Depressive symptoms, anxiety, stress, pessimism, and loneliness have been associated with MS-related fatigue, and modifying these conditions has shown to alleviate its severity.[6,18,20] Additionally, some studies revealed an association between fatigue and sleep disorders such as subjective poor sleep quality, excessive daytime sleepiness, obstructive sleep apnea syndrome, and restless leg syndrome.[21]

Multiple studies have evaluated the relationship between cognitive disorders and MS-F using neuropsychological tests. Fatigue severity has a moderately positive correlation with MS neuropsychological screening questionnaire score.[6] Processing speed was slower in fatigued MS patients than nonfatigued ones.[22] Moreover, deterioration in attention and executive function in MS patients were significantly correlated with fatigue severity.[22,23]

Daily diet affects MS-F as well. Pommerich *et al*. have suggested a starchy plant-based, low-fat diet, excluding fish and vegetables oils, or a modified Paleo diet for less fatigue.[24] Healthier lifestyle and higher hydration level have been negatively correlated with fatigue.[20] Normal body mass index also reduced MS-F compared to being obese or overweight.[25] Patients with moderate use of alcohol or no history of smoking had lower fatigue.[25,26]

Physical activity correlates with physical and cognitive fatigue in MS patients.[18,27] There is supporting evidence that different forms of exercise can be beneficial.[28] MS-F has a moderate negative correlation with aerobic capacity and a weak association with muscle strength.[29]

Migraine and irritable bowel syndrome have been shown to be independently associated with fatigue in MS.[8] How they are related to fatigue is not well understood.

PATHOPHYSIOLOGY

Different systemic, central, and peripheral mechanisms have been proposed for development of MS-F, but its underlying pathophysiology is not quite clear.[13] Here we discuss each mechanism separately [Figure 1], though current evidence favors central mechanisms as the main cause of MS-F.[3]

Systemic inflammatory mechanisms

Fatigue has been developed in autoimmune and infectious diseases, as an immune-mediated symptom or medication side-effects.[1,12] Immune system dysregulation could be a major systemic cause of MS-F. However, the association between MS-F and elevated levels of circulating cytokines is not clear.[15,22,30] Also, studies considering gadolinium-enhanced lesions as a marker for inflammation state in MS, do not support its association

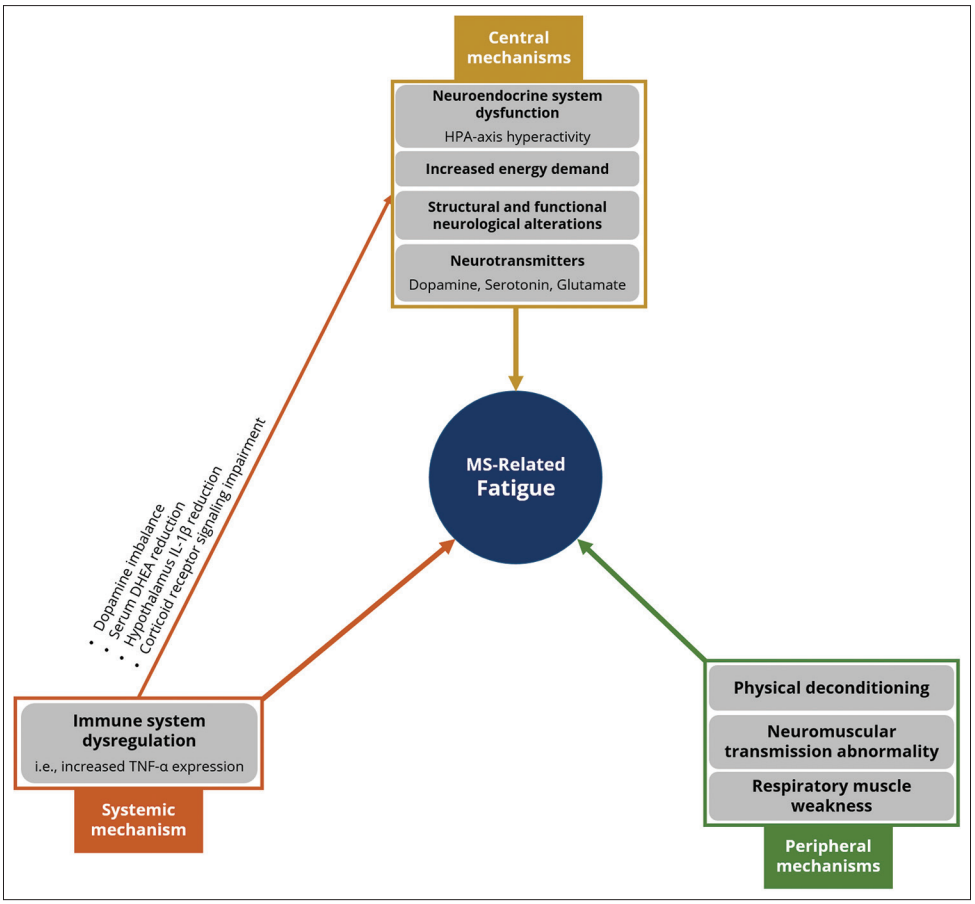

Figure 1: Central, systemic, and peripheral mechanisms in pathophysiology of MS-related fatigue. MS: multiple sclerosis, TNF-α: tumor necrosis factor alpha, HPA: Hypothalamic-Pituitary-Adrenal, DHEA: Dehydroepiandrosterone, IL-1β: Interleukin 1 beta

with fatigue.[12] Although we have a good understanding of pathways comprising inflammatory mediators, finding inflammatory pathway(s) causing fatigue needs further investigation.

Central mechanisms

Neuroendocrine system dysfunction

Neuroendocrine system dysfunction might be a contributing factor to MS-F. Hypo-activity of hypothalamic–pituitary–adrenal (HPA) axis was first seen in patients with chronic fatigue syndrome.[12] Considering that, as well as HPA activity imbalance in some MS patients raised the possibility that pro-inflammatory cytokines cause HPA imbalance and consequently fatigue.[1,12,14,22] One study found that elevated adrenocorticotropic hormone level was related to elevation of pro-inflammatory cytokines, through an impaired corticosteroid receptor signaling.[31] It was suggested that modulating these receptors by appropriate medication may improve MS-F.[15] A negative correlation was found between dehydroepiandrosterone hormone level and secretion of pro inflammatory cytokines as well as with HPA axis activity. This mechanism could be responsible for immune mediated MS fatigue.[14] Apart from the HPA axis, reduced Interleukin-1-beta in hypothalamus may cause neuroendocrine and autonomic dysfunctions in MS patients which can result in MS-F.[32]

Increased energy demand

Voluntary muscle contractions show a delay associated with impaired motor pathways in MS.[33] As a consequence of pyramidal tract lesions, there is a neuronal hypo-activity in α-motor neurons, resulting in muscle spasticity in MS patients. As a compensatory mechanism, there is a cortical excitation, which demands increased energy that is associated with MS-F.[1]

Structural and functional neurological alterations

Different structural and functional neuroimaging techniques have been used to obtain information about cerebral structural and functional changes related to MS-F.

Structural neuroimaging studies revealed a role for changes in cortico-striato-thalamo-cortical loops in the pathogenesis of MS-F.[34] There is a significant correlation between cortical atrophy, especially in frontal, temporal, and parietal lobes and MS-F.[23] Changes in deep gray matter (i.e., thalamus and striatum) as well as white matter lesions in cortico-striatal and cortico-thalamic tracts were also correlated with MS-F.[35]

Corpus callosum lesions, affecting the interhemispheric connectivity (via cortico-striatal-thalamo-cortical loops) have been found in brain magnetic resonance imaging (MRI) of MS patients with fatigue.[35] Chalah *et al*. reported that MS fatigue may be more severe in patients with larger caudate nuclei, and smaller left parietal cortex and hypothesized that dysfunctional or compensatory mechanisms could play a role.[36]

A decreased fractional anisotropy (FA) in the cingulum bundle, anterior internal capsule, amygdala, and cingulo-postcommissural-striato-thalamic, ventromedial prefronto-precommissuro-striatal, and temporo-insular pathways were correlated with fatigue severity. Mean diffusivity (MD), another index for characterizing microstructural changes, was reduced in different white matter tracts in fatigued MS patients.[37-40] Nevertheless, the correlation between MS-F and FA and MD findings could not be confirmed in all studies and remains challenging.[41]

Many recent functional studies showed abnormal findings in different brain regions in fatigued MS patients. These findings include: Increased activation of posterior cingulate cortex, decreased activation of anterior cingulate cortex in default mode network and altered functional connectivity of thalamic subregions, posterior cerebellum and sensorimotor pathways.[42-45] Functional MRI studies have previously shown that increased activation in motor areas, as well as reduced activation in parietal areas are correlated with MS-F. Additionally, interhemispheric and functional connectivity of cortical (e.g., parietal and frontal) and subcortical (e.g., thalamus) regions was altered in fatigued MS patients.[11,34] Neural activity in the precuneus region of the parietal lobe, lingual gyrus, and middle occipital gyrus was increased in MS-F.[46] Dobryakova *et al*. found a negative correlation between the activity in the fronto-striatal network and fatigue.[47] Increased functional connectivity between the insula and anterior cingulate cortex, which are involved in interoceptive perception, is also correlated with the self-reported severity of MS-F.[48] Some positron emission tomography (PET) studies showed reduced glucose metabolism in frontal, temporal, and parietal regions of patients who suffer from fatigue, which is consistent with results from other functional studies.[49]

Magnetic resonance spectroscopy studies of MS-F showed consistently a decrease in N-Acetylaspartate to creatine ratio (NAA/Cr), in corticospinal tracts, hypothalamus and white matter adjacent to frontal, parietal, and occipital lobes,[11] which may indicate a reversible neural dysfunction. Yarraguntla *et al*. found also a decrease in NAA + N-Acetylaspartglutamate to Cr + Phosphocreatine ratio (NAAG/PCr) in some brain regions associated with MS-F.[50]

Neurotransmitters

Neurotransmitters play a significant role in pathophysiology of MS-F mainly through altered brain areas involving neurotransmitters and medications' effects on them.[4,16,51-53] Here, we discuss the role of dopamine, serotonin, and glutamate, however, gamma aminobutyric acid (GABA) may also trigger central fatigue, given altered GABAergic cortical and spinal cord inhibitory mechanisms in MS.[54]

Dopamine

Dopamine is a modulatory neurotransmitter, produced in substantia nigra pars compacta (SNc), ventral tegmental area, and hypothalamus.[51,55] As the most common catecholamine in the central nervous system (CNS), it affects a variety of cognitive functions including working memory and effortful behavior.[56-58] Alteration in dopaminergic neurotransmission is considered to cause some of MS symptoms such as fatigue.[51,59,60] Hence, studies suggested that therapeutically targeting dopamine imbalance can modify the course of disease.[61]

MS lesions that disrupt the connection between striatum and prefrontal cortex (PFC), areas related to dopamine function, can cause fatigue.[51,62] PET studies revealed that patients with higher fatigue scores had lower glucose metabolism in PFC and striatum, compared to those without fatigue.[63,64] Functional MRI studies have proposed an involvement of dopaminergic projections, e.g., the meso-cortico-limbic pathway in people with neurological disorders who suffer from fatigue.[65,66] Besides, dopamine imbalance exists in the immune system of progressive as well as relapse-remitting MS patients and it may provoke MS-F through decreased dopamine level in CNS, in response to destruction of SNc neurons and production of interferon-gamma.[53,67,68]

Disease-modifying therapies, such as interferon beta, can increase dopamine production and reduce MS-F,[69] whereas dopamine agonists can increase the connectivity within dopaminergic pathways and improve fatigue.[70,71] Additionally, studies showed that medications with positive effects on fatigue (e.g., methylphenidate) increase dopamine levels in CNS.[72-74]

Serotonin

Serotonin (5-HT) is a neurotransmitter with receptors in almost all organs including brain.[75] Serotonergic neurons are located in dorsal raphe nuclei in midbrain and pons.[76] Serotonergic terminals project to some areas such as frontal cortices, limbic system, and basal ganglia.[77] It has been shown that in Parkinson's disease, fatigue is associated with reduced serotonergic function in the limbic system and basal ganglia.[78] Other studies have proposed an association between fatigue and availability of serotonin transporters (SERT) in cortical and subcortical regions.[79]

Insular SERT availability also correlates with depression and fatigue severity. Similarly, PET studies showed that the availability of SERT in anterior cingulate cortex as well as 5-HT_{1A} receptor activity are reduced in patients with chronic fatigue syndrome.[80,81] Serotonin imbalance, like dopamine imbalance, is considered as a cause of occurrence and exacerbation of MS-F.[79] 5-HT's role in pathophysiology of MS-F has been supported by studies that show fatigue improvement in MS patients after treatment with selective serotonin reuptake inhibitor (SSRI) medications.[51]

Glutamate

Glutamate is the most abundant neurotransmitter in CNS which exists in almost all excitatory synapses and has a prominent role in human cognitive functions.[82] Alteration in glutamatergic signaling is a consistent finding in neurological and psychiatric disorders, including MS.[83] Excitotoxicity, the pathologic process which damages neurons through excessive stimulation, could occur through excessive amounts of glutamate within synaptic cleft and is hypothesized to cause chronic mental fatigue.[84] Thus, clearing glutamate from synaptic cleft, via uptake by astrocytes or reuptake by presynaptic neurons, is critical in synapse function. Glutamate uptake by astrocytes occurs through astrocyte-neuron lactate shuttle and glutamate-glutamine cycle, which both are affected in MS patients especially in fatigued ones.[83] Although there is an increasing evidence for involvement of glutamate excitotoxic actions in pathophysiology of MS-F,[85] treatment with glutamate receptor antagonists failed to show improvement in cognitive function and fatigue in MS.[86] Hence, we can hypothesize that, regarding fatigue, excessive extracellular accumulation of glutamate as a product of hyperactive microglia and macrophages in MS patients may be the pathophysiological pathway, whereas generation of glutamatergic excitatory postsynaptic potentials is not involved.[83]

Peripheral mechanisms

Inability to recruit motor pathways and sustain muscle contraction during activities causes MS-F.[15] Peripheral mechanisms such as abnormalities in neuromuscular transmission can increase the work needed to attain a given level of muscle contraction.[13] Respiratory muscles weakness is an example of this mechanism, that has a positive causal relationship with fatigue.[87,88] Physical deconditioning due to MS or comorbidities also plays an important role in MS-F.[89]

ASSESSMENT

Objective assessment of fatigue focuses on two different qualities: Fatigue trait reflects the global status of fatigue that doesn't significantly vary over time. Fatigue state refers to a decrease in performance of a patient over time, following an acute and prolonged effort. Fatigue state is affected by several factors and can be tested using cognitive or motor tasks. Most previous studies have evaluated fatigue trait, while fewer have investigated state.[4]

Methods for evaluating MS-F are limited to subjective assessments. Common fatigue questionnaires are self-report tools assessing fatigue aspects, frequency, severity, or impact on QoL.[3,90,91] Moreover, a patient's diary is thought to be helpful for tracking daily changes of fatigue severity.[92]

In 1989, Krupp *et al*. developed fatigue severity scale (FSS).[64] This questionnaire measures the impact of fatigue on functional disability of MS patients and showed to be internally consistent, stable over time, and sensitive to clinical changes. In comparison to FSS, fatigue impact scale (FIS) provides more information about alterations in functional status of patients, in three different subscales: Cognitive, physical, and psychosocial functioning.[93] Modified fatigue impact scale (MFIS) was developed by the United States national MS society by eliminating FIS items with content redundancy or high inter item correlations.[94] Although it measures psychosocial and cognitive impacts of fatigue more precisely than FSS,[95,96] its global score was not valid enough as a universal measurement of fatigue.[97]

Fatigue scale for motor and cognitive functions (FSMC) was invented in 2009.[98] It's a 20-item questionnaire with cognitive and motor subscales. FSMC has high sensitivity and specificity as well as established internal consistency and structural validity.[99] Visual analogue scale has also been used as a measure of fatigue in scientific settings.[100,101] Despite low reproducibility, it indicates fatigue state, while other questionnaires indicate fatigue trait.

TREATMENT

Pharmacological treatments

Despite lack of strong evidence on current pharmacological treatments for MS-F, all were safe except Pemoline.[102,103] Although using Amantadine in fatigue is based on weak evidence,[104-108] it seems more effective than Modafinil, Acetyl-L-Carnitine, and Ondansetron.[106,109] A randomized double-blind crossover study showed that Aspirin and Amantadine were comparably effective in reducing MS-F.[110] Some studies reported that Acetyl-L-Carnitine and Aspirin have similar effects.[106,111,112] Studies on Modafinil had conflicting results. In a single-blind randomized clinical trial on 72 patients Modafinil improved FSS and MFIS scores, though larger studies failed to show its significant positive effect.[113] Based on systematic reviews and meta-analyses, only weak evidence supports efficacy of Modafinil for MS-F.[114-116]

Fampridine, previously prescribed for symptomatic treatment of muscle weakness in MS patients, has been recently used for MS-F. Two nonrandomized open-label studies showed significant improvement of fatigue in patients taking Fampridine.[117-119] A randomized double-blind placebo-controlled trial showed that Dalfampridine, a derivative of Fampridine, is an effective treatment for fatigue as well as specific domains of cognition.[120] Although the effect of Fampridine on cognition and fatigue was seen to be persistent over 2 years, evidence is still limited and conflicting.[121]

There is limited evidence for the impact of SSRIs on MS-F. In patients with relapsing-remitting MS and moderate to severe depression, SSRIs can reduce the severity of fatigue.[122] However, in a double-blind multicenter study Fluoxetine was not superior to placebo in improving MS-F.[123]

As far as we know, there is no blind controlled clinical trial evaluating the effect of disease-modifying treatments on MS-F. Some studies on Glatiramer acetate showed a prominent decrease in fatigue after 12 months, which was more effective than β-interferon.[124,125] Trials for Natalizumab could not demonstrate any significant effect on fatigue after 3 months, but some improvement in physical and cognitive fatigue after 6 months.[126-130]

Nonpharmacological treatments

Based on systematic reviews and meta-analyses the positive effects of nonpharmacological treatments can be plausible with moderate confidence.[102] Exercise therapy can significantly improve MS-F, but this effect differs from one type of exercise to another. Endurance training, mixed training and yoga seem to be the most effective types.[90] Learning of energy conservation, fatigue management, relaxation techniques and cooling therapy can be advised as add-on interventions. Systematic reviews and meta-analyses concluded a positive short-term effect for cognitive behavioral therapy on MS-F.[102]

CONCLUSION

As discussed, current evidence on pharmacological and nonpharmacological treatments of MS-F precludes any strong recommendation. Objective diagnosis and assessment of fatigue in MS have also no appropriate methods. These are due to unclear pathophysiology of MS-F that in turn leads to dissimilar definitions based on patients' subjective description and clinical characteristics of fatigue. Personalized diagnosis and management require further studies on pathophysiological aspects to establish a unified definition for MS-F as the first and most important step in finding better treatments.

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Conflicts of interest

There are no conflicts of interest.

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