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REVIEW

Overview of the Current Pathophysiology of Fatigue in Multiple Sclerosis, Its Diagnosis and Treatment Options – Review Article

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Abstract: Fatigue is a common, debilitating and often underestimated symptom in patients with multiple sclerosis (MS). The exact pathophysiological mechanism of fatigue in MS is still unknown. However, there are many theories involving different immunological, metabolic and inflammatory mechanisms of fatigue. Owing to the subjective nature of this symptom, its diagnosis is still very limited and is still based only on diagnostic questionnaires. Although several therapeutic agents have been used in the past to try to influence fatigue in MS patients, no single effective approach for the treatment of fatigue has yet been found. This review article aims to provide the reader with information on the current theories on the origin and mechanism of fatigue in MS, as well as diagnostic procedures and, finally, current therapeutic strategies for the management of fatigue in MS patients.

Keywords: fatigue, multiple sclerosis, orexin, sleep disturbances, physical activity, amantadine

Introduction

Multiple sclerosis (MS) is a chronic progressive demyelinating disease of the central nervous system (CNS), and is the most common cause of chronic neurological disability in young adults.[1] Typical symptoms are visual disturbances, sensory and motor deficits, vertigo, and cerebral and autonomic disturbances.[2]

Fatigue is one of the most commonly reported symptoms during MS outpatient follow-up.[3] Looking at the reported prevalence of this symptom in the available studies, we find that fatigue affects between 52% and 90% of people living with MS.[4]

The exact pathophysiology of MS-related fatigue is not fully understood, but it is thought to be multifactorial and may involve both physical and psychological factors. Studies suggest that MS-related fatigue may be caused by abnormalities in the structure and function of the CNS, including damage to the myelin sheath, altered neurotransmitter function and impaired cellular metabolism.[5] Factors such as sleep disturbances, depression and physical deconditioning may also contribute to the development of fatigue in MS.[6]

Fatigue is a complex phenomenon that can profoundly impact an individual's quality of life. It is characterized by a feeling of exhaustion, weakness and reduced energy.[7]

This article provides a comprehensive overview of the current pathophysiology of fatigue in MS, its diagnosis and treatment options. We systematically searched PubMed articles between January 2000 and January 2023 using the following search terms: (multiple sclerosis) AND (fatigue) AND (pathophysiology) AND (treatment) AND (diagnosis). In total, 393 results were obtained: 91 reviews and systematic reviews, 78 randomized controlled trials, no meta-analys es and 107 clinical trials. Only English-language manuscripts published in peer-reviewed journals were considered for inclusion, with the aim of including well-established, methodologically sound studies. The title, abstract and results of every article were searched to establish their links to MS-related fatigue. A total of 305 articles were excluded, mostly owing to their irrelevance to the article theme; therefore, a total of 88 articles were included.

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Fatigue Pathophysiology

The most common theories considered inflammation, endocrinopathies, and processes causing strategic white and gray matter lesions.

Immunological and Inflammatory Processes

White blood cells, especially lymphocytes, and their cytokine production play crucial roles in the development of MS and in relapse formation; therefore, both humoral and cellular mechanisms play their roles. However, immunological mechanisms can also play a significant role in MS-related fatigue, which is confirmed by numerous studies.[8] Key players in that process are cytokines and their proinflammatory and anti-inflammatory interplay or cytokine networks, the most commonly mentioned of which are interleukin-6 (IL-6), IL-1 and interferons. Cellular immunity is also considered in fatigue pathogenesis, which involves especially monocytes and microglia.[9] The most promising results are reported in case of IL-6 and tumor necrosis factor-α (TNF-α) elevation; however, studies exploring the association between inflammatory biomarkers and fatigue in MS have provided conflicting results. The fact that people with higher disease activity are more frequently and more severely affected by fatigue confirms the indisputable role of inflammation in fatigue pathogenesis. All study participants had experienced fatigue, depression and low desire for physical activity during infections and febrile states.[10] Furthermore, some disease-modifying therapies, such as interferon-β (INF-β) and vaccinations are connected to fatigue through this mechanism.[11–13]

There are a few proposed biochemical mechanisms by which cytokines alter neuronal signaling and metabolism. One of them is via a change in monoaminergic signaling (mainly synthesis of the neurotransmitters dopamine and serotonin, which are important elements in motivation, reward pathways and arousal). This process is based on GTP-CH1-cyclohydrolase (GTP-CH1), an enzyme that is necessary for neopterin formation. Production of neopterin then lowers production of tetrahydrobiopterin. Tetrahydrobiopterin is a necessary cofactor in dopamine and serotonin production. Furthermore, cytokines activate indoleamine 2,3-dioxygenase (IDO), an enzyme that is necessary for tryptophan degradation; the degradation of tryptophan then reduces the amount available for serotonin biosynthesis. Low serotonin levels are the most commonly presumed mechanism for the development of depression, and depression is also linked to fatigue. Therefore, fatigue in MS and depression may have similarities that need to be explored in additional studies.[12–14]

Cytokines are, moreover, able to change the neuroendocrine system, in particular the hypothalamic–pituitary–adrenal (HPA) axis. In that case, the release of corticotropin-releasing hormone from the hypothalamus stimulates the production of adrenocorticotropin and, finally, cortisol. The possible role of cortisol in fatigue will be discussed in next the section of the article (see Endocrinopathy).[15]

Cytokines are also able to use circumventricular organs as a path to cross the blood–brain barrier and exert direct effects by linking on to specific neuronal receptors; for example, IL-6 has a direct effect on brain endothelial cells to produce prostaglandin E_2. Lastly, immune mediators can trigger both central (microglia activation, projections to the thalamus and solitary tract) and peripheral (fever) immune processes. This neural immune-to-brain communication consists of mainly vagal afferents (that are activated by proinflammatory mediators); it is then transferred via the nucleus tractus solitarii to the ventromedial posterior thalamus and midinsular cortex. This interoceptive neural pathway is a crucial part of the immune-to-brain link during fever behavior, and is also a key element of metacognitive hypotheses of fatigue. By this pathway, peripheral immunological processes can regulate HPA axis activation (thus bringing together the immunological and endocrinopathic theories of fatigue).[16,17]

Another proposed key molecule in fatigue pathogenesis is orexin, which is a neuropeptide produced in the neuronal formation of the lateral hypothalamus. Orexin has a crucial role in vigilance and arousal (which is why it plays a major role in the pathogenesis of narcolepsy). It plays various roles, for example in the regulation of the sleep–wake cycle, reward pathways and food intake.[18] Animal studies suggest that inflammation-related lethargy is caused by low orexin neuronal activity induced by IL-1β and TNF-α activity, and that orexin levels correlate with levels of arousal and searching behavior. However, when researchers studied correlations between orexin levels in cerebrospinal fluid and fatigue, contradictory results were obtained.[19–21]

Endocrinopathy

Another proposed pathophysiological concept is endocrinopathy. Nowadays, we have enough evidence from other autoimmune disorders to show that endocrinological factors play a significant role in fatigue pathogenesis. The most commonly mentioned of these are low cortisol and dehydroepiandrostendione (DHEAS) levels in diseases such as chronic fatigue syndrome, lupus erythematodes and rheumatoid arthritis.[20–22] Whereas cortisol levels give conflicting results across studies, the finding of lowered DHEAS levels is a promising area for further research. Many MS patients taking corticosteroids report increased energy and less fatigue, which could also support a potential hormonal influence; however, because of their long-term adverse effects, corticosteroids are not a treatment of choice for chronic fatigue.[23]

The role of the HPA axis was mentioned in the previous section of this article (Immunological and Inflammatory Processes), in the context of cytokine activity. Hyperactivity of the HPA axis alone is not sufficient to prevent disease development; however, its hypoactivity could be linked to a severe clinical course of the disease, with a higher number of brain gadolinium-enhancing lesions.[24,25] Moreover, higher disease activity could be linked to more severe fatigue in the same matter, as in rheumatoid arthritis and chronic fatigue syndrome.[26]

Another important player is the thyroid gland and its hormones, thyroxine and triiodothyronine. Fatigue is the most commonly reported symptom of autoimmune disorders of the thyroid gland, especially with regard to its hypofunction. Thyroid hormones play significant roles in the vast majority of metabolic pathways and most importantly in energy metabolism, as they increase the number of mitochondria, Na^+/K^+-ATPase systems, glucose absorption, gluconeogenesis and lipolysis, as well as the basal metabolic rate.[27] MS and hypothyroidism share similar symptoms of muscle weakness, fatigue and depression; therefore, the possibility of coexisting hypothyroidism could be overlooked. Thyroid gland disorders are seen more frequently in MS patients than in the general population, which supports the concept of polyautoimmunity in people with certain variants of the human leukocyte antigen (HLA) system, for example, HLA-DRB1*15:01, which multiplies the risk by about three times.[28–30] Thyroid dysfunction could also be induced by treatment, most commonly by the induction of antithyroid antibodies; this may be caused by treatment with INF-β. This complication could affect up to 8.3% of patients treated with INF-β, as stated in a study conducted by Durreli et al.[30]

Strategic White and Gray Matter Lesions

White matter lesions disseminated in space and time are a necessary part of the revised McDonald criteria.[31] They are the result of demyelination and inflammation and, when left untreated, they lead to axonal damage and progressive neurodegeneration. However, in MS it is also possible to see gray matter lesions resulting from cortical demyelination due to subpial inflammation, retrograde neuronal degeneration and other degenerative mechanisms resulting from oxidative stress and glutamate excitotoxicity.[32] As we know from available volumetric studies, a higher lesion load leads to regional and whole brain atrophy, and some studies have found possible correlations between the level of brain atrophy and fatigue.[33,34]

White Matter Lesions

Many studies have investigated correlations between lesion localization and degree of fatigue, with conflicting results. Such conflicting results could be due to different study methodology, and especially the use of different magnetic resonance imaging (MRI) machines with different magnetic field strengths, but they could also be caused by global lesion load rather than precise lesion localization.[33,35,36]

The association of fatigue with specific white matter lesions may be caused by diminished synaptic connectivity (due to neural network impairment), which then leads to a slowing of the conduction speed and reduced reliability of axonal transmission.[37,38] The drug fampridine is thought to improve conduction velocity by blocking voltage-dependent potassium channels, and could be used as an agent for treating fatigue.[39]

Another proposed explanation is the disruption of communication within special nerve centers that have a connection to fatigue, especially with regard to motor planning and execution. Damage to these centers leads to the disruption of the smooth and direct performance of desired activities, and therefore may make them more energy demanding. Diffusion-weighted imaging studies show that white matter lesion and fatigue levels can be correlated with lesions in the internal capsule and anterior thalamic tract. Another possibility is damage to the arousal and motivation regions, especially to the

posterior hypothalamus and mesencephalon. Almost all of these regions share the same monoaminergicneurotransmitter systems, which could also be a link between all of these centers and their relationship with fatigue.[40,41]

Gray Matter Lesions

Gray matter lesions are dispersed diffusely in MS.[42] Neuropathological studies propose a higher occurrence of lesion in regions with deep invaginations, such as the insular and anterior cingulate cortex, areas that are responsible for interoception. Damage to the gray matter cortex occurs through oxidative stress (reactive oxygen and nitrogen species) and retrograde neurodegeneration due to damage to the nerve terminals. Regarding subcortical regions, the most commonly affected structures are the thalamus, basal ganglia, amygdala, substantia nigra and hypothalamus (regions associated mainly with movement disorders).[43,44]

As in the case of white matter lesions, there are a few possible explanations for the connection of fatigue with gray matter lesions. First, these lesions alter neuronal connectivity and neural functional networks, thereby impairing the performance of gentle and precise movements. With this impairment, there is a necessity for additional compensatory or corrective measures, which cost additional energy. This theory is part of the metacognitive theory of fatigue.[45,46]

Another suggested explanation is that damage to deeply localized structures is closely related to vigilance, arousal and motivation. The role of the hypothalamus in this process is stated in most available studies. The hypothalamus is a frequent target in MS and its role in homeostasis and orexin production is an important part of many fatigue theories. (The function of orexin in fatigue was mentioned earlier in this article, in the section "Immunological and Inflammatory Processes".)[47,48]

The third possibility is damage to the brainstem, especially lesions of dopaminergic, serotonergic or noradrenergic nuclei in the brainstem, and the subsequent reduction of these neurotransmitters in the cortex, which then leads to reductions in motivation and mood, which are typical in depression and fatigue.

Lastly, hypothalamic nuclei are closely related to the HPA axis. Damage to this system leads to disruption of endocrinological control. Lesions of the paraventricular nuclei of the hypothalamus may interrupt autonomic nervous system balance. This, in summary, could cause fatigue directly, for example, owing to a diminished energy supply or hypotension; or by the perception of prolonged dyshomeostasis.[49,50]

Maladaptive Network Recruitment During Task Performance

Functional imaging techniques have shown an increase in distributed brain activity during task performance in MS patients with fatigue and in healthy individuals, and the same can also be observed in the cervical spinal cord. In addition, impaired or failed physiological adaptation to activity can be seen in fatigued MS patients.[51]

A possible explanation for this may be linked to neural network impairment, which could be caused by structural lesions of the brain/cervical cord, or impairment due to inflammation or neurodegeneration. Therefore, for MS patients to achieve the same results as healthy controls, there is a necessity for compensatory recruitment of adjacent neural tissue, the use of alternative working pathways or higher activation of impaired networks. All of these measures are highly energy demanding and may lead to people becoming more easily fatigued.[52]

Another possible theory involves the impairment of neuromodulatory projections of the brainstem and therefore altered neurotransmitter production. This may lead to functional reorganization to maintain functioning cortical networks; these neuromodulatory neurotransmitters influence cortical activity and connectivity throughout the afterhyperpolarization current mediated by calcium-dependent potassium channels, and they can change synaptic plasticity through the activation of NMDA receptors. This functional reorganization has been observed in various human and animal studies, with most information coming from the study of stroke.[53,54]

Secondary Fatigue

So far, we have discussed primary mechanisms of fatigue; however, fatigue in MS is mostly secondary. The most commonly suggested factors are adverse effects of medication, sleep disorders and depression.

The most frequent causes of secondary fatigue are sleep disturbances, especially early awakening and problems with falling asleep. Patients may not perceive sleeping problems themselves; such problems are mainly reported by patients'

life partners. Partners tend to initially report problems such as somnambulism, restless legs syndrome (RLS) or snoring. All of these conditions alter sleep quality, although they are easily treatable.

RLS affects about 10% of the general population,[55] and may affect approximately three to five times more people with MS than in the general population.[56] The pathophysiology of this disorder in MS is poorly understood. Some authors propose a correlation between spinal pathology and RLS, most commonly impairment of the dopaminergic pathways in the spinal cord. Dysfunction of these dopaminergic pathways could decrease sensory thresholds and increase the susceptibility to RLS.[57] This hypothesis is supported by a study from Zhu et al, utilizing spinal cord diffusion tensor imaging in MS patients with and without RLS, which found that axonal integrity is lower in MS patients with RLS than in those without RLS.[58] Another causal factor could be iron deficiency, which is underestimated in general and especially in the female population. In addition, RLS could be the first symptom of iron deficiency anemia.[59]

Another possibility could be sleep-related breathing disorders, which are more common than previously thought, with an incidence varying between 0% and 87%. Lesions affecting brainstem respiratory centers in the reticular formation could lead to central apnea (Ondine's curse).[60–62] Another frequently seen disorder is obstructive sleep apnea. The most powerful risk factor for this disease is obesity, a problem that is often in encountered in the MS population: according to Russell et al, up to 67% of people with MS are overweight or obese.[62] The prevalence of sleep apnea in MS patients varies considerably between studies (from 0% to 58%).[63,64] There are a few main components that need to be taken into consideration to elucidate the pathophysiology; namely, an anatomically narrow or collapsible upper airway, insufficient upper airway dilator muscle responsiveness during sleep and a low respiratory arousal threshold.[65,66] Therefore, sleep studies (polysomnography) could also help in fatigue management, especially because of the relatively high levels of obesity in this population.

Next in line could be chronic insomnia and circadian rhythm abnormalities. These problems may arise as a consequence of chronic pain, spasticity, depression, nocturia and medication effects. In addition, some medications could change the sleep architecture. The sleep studies that have studied sleep architecture and circadian rhythm variability in MS using polysomnography had small population sizes (Braley and Chervin included 48 MS patients with fatigue[67] and Kaynak et al 37 MS patients[60]). Studies have shown that MS patients, regardless of their level of fatigue, had a significantly higher frequency of RLS, and higher scores on the Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index. The time in bed, waking time after sleep onset, total arousal index, limb movement arousal index and periodic limb movement arousal index was increased compared to healthy controls.[61,68]

Fatigue may also be mimicked by depression, and many psychiatric studies have found a correlation between fatigue and depression severity. Depression and anxiety disorders often accompany MS; for example, a meta-analysis by Boeschoten et al reported this phenomenon in over 50% of MS patients (30.5% depression and 22.1% anxiety).[68] Patrick et al found a significant correlation between the level of fatigue and the severity of depression in MS patients.[69,70]

Lastly, fatigue may be caused by the adverse effects of drugs. Many drugs used in MS-related symptom management include fatigue in their adverse effects sheet; these are mostly benzodiazepines (diazepam, oxazepam) and myorelaxans (baclofen, tizanidine), which are used for spasticity or tremor and for sleep disturbances.[71] Another drug group that can cause fatigue and sleepiness is painkillers, and especially opioids (most frequently tramadol, dihydrocodeine or oxycodone), which are used also for radiculopathies and neuropathies, which are more common in MS patients than in the general population.[72] Fatigue may also be induced by disease-modifying drugs such as interferon; on the other hand, natalizumab and glatiramer acetate (GA) are thought to reduce fatigue.[73,74]

Diagnosis of Fatigue

At this point, it is necessary to admit that despite more than 100 years of ongoing research, we still do not have a tool to objectively measure fatigue.

The diagnosis of fatigue is complicated and carries a burden of high subjectivity because it is based almost entirely on validated questionnaires, which were invented primarily for diseases such as myalgic encephalomyelitis/chronic fatigue syndrome or for rheumatological disorders such as lupus erythematodes. In 2004, Dittner et al proposed the most comprehensive review of available diagnostic questionnaires.[75] A few pivotal studies have used functional neuroimaging

as a tool for the study of fatigue; however, its use in clinical practice is still in its infancy.[74] The use of MRI techniques in fatigue is mostly limited to the study of fatigue pathophysiology, rather than in clinical practice.

Braley and Chervin, in their work from 2010, proposed a simplified algorithm for the diagnosis of fatigue in MS patients (Figure 1).[76]

Validated Questionnaires

Currently, questionnaires are the only validated tools available for objectifying fatigue in MS. There are many available questionnaires, such as the Modified Fatigue Impact Scale, Rochester Fatigue Diary, Fatigue Descriptive Scale, Fatigue Impact Scale, Fatigue Assessment Instrument, Single-Item Visual Analog Scale of Fatigue and Fatigue Severity Scale. Each questionnaire has its own advantages and limitations. In this article, we discuss the three most commonly used questionnaires in clinical studies of MS related fatigue.

Modified Fatigue Impact Scale (MFIS)

This scale is derived from the 40-item Fatigue Impact Scale (FIS) and contains only 21 items. It evaluates several fatigue domains: physical (nine items), psychosocial (two items) and cognitive (10 items), and the total score is calculated from the sum of the points scored in its subdomains. Administration of this test takes only approximately 5–10 minutes, so it is easy to administer, and it focuses on the ways in which MS-related fatigue affects everyday life. However, the MFIS as an outcome measure also has limitations owing to its simplicity, and studies have reported limitations in interpreting the scores, as stated by Mills et al.[77] The interpretations of studies using this measurement tool need to be re-evaluated because it does not consider the possible effects of confounding variables, specifically depression, on MFIS scores, which may lead to misinterpretation of the results of uncontrolled studies. The biggest limitation regarding MFIS score interpretation is the lack of objective pillars.[6,78]

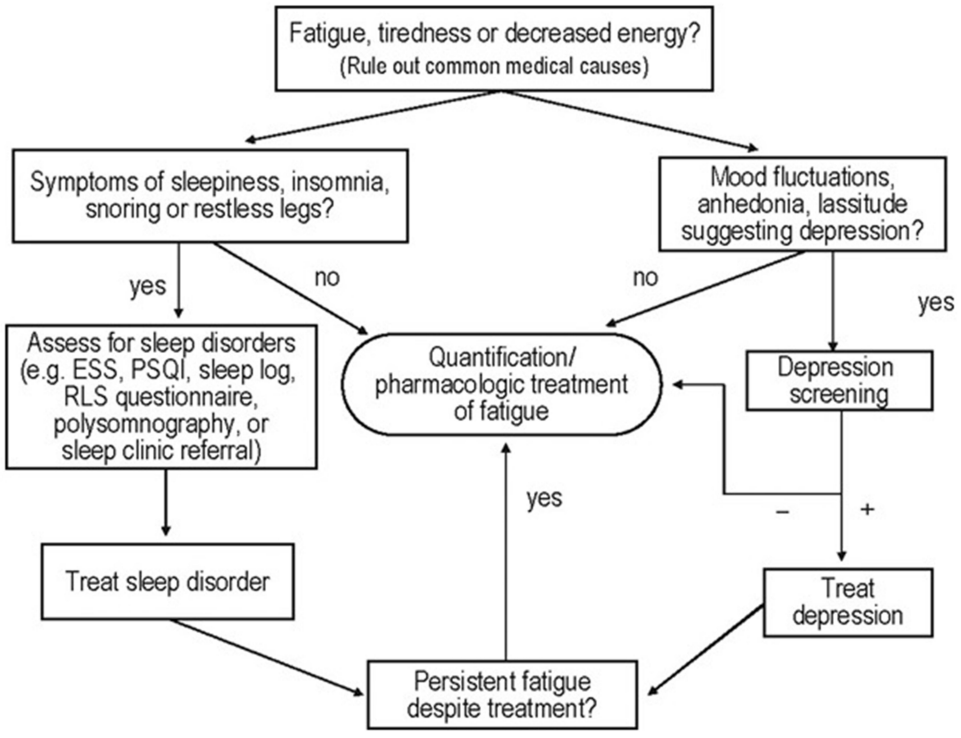

Figure 1 Simplified algorithm for diagnosis and treatment of fatigue in MS patients.
Note: Reprinted from Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep*. 2010;33(8):1061–1067, by permission of Oxford University Press.[76]
Abbreviations: MS, multiple sclerosis; RLS, restless legs syndrome; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.

Fatigue Severity Scale (FSS – Krupp)

This scale was initially designed for both MS and lupus patients, and in contrast to other scales, it focuses mainly on the physical domain. It has nine questions, which are scored from 1 to 7 (1 = strong disagreement and 7 = strong agreement); therefore, total scores are between 9 and 36 points, with more points indicating higher fatigue. As proposed by Rosti-Otajärvi et al and Valko et al, the main limitation of this scale is the possible misinterpretation of scores caused by unrecognized confounding factors, mainly depression.[79,80]

Chalder Fatigue Scale

This scale is one of the most frequently used fatigue scales in the world and was originally designed for patients with chronic fatigue syndrome; however, it was soon used in various other diagnoses. The scale consists of 11 items scored from 1 to 3 points, with a maximum of 33 points (more points indicate more severe fatigue). This scale has many limitations, the most discussed of which is its ceiling effect, because patients with myalgic encephalomyelitis/chronic fatigue syndrome often record the maximum score on most of the 11 questions. As a result, patients cannot indicate a worsening of their fatigue, which may influence the findings of randomized trials. In other words, if patients record the maximum score, and then half of them improve while the other half deteriorates during follow-up, then only the improvement will become visible on the questionnaire.[81–83]

Neuroimaging Techniques

As mentioned in "Strategic White and Gray Matter Lesions", strategically placed lesions can be linked more frequently to fatigue. Current developments in the field of radiodiagnostics have helped in the more frequent use of quantitative techniques, including relaxometry, magnetization transfer imaging (MTI), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS), all of which are used in the elucidation of MS-related fatigue pathophysiology; however, their use in the daily clinical diagnosis of MS-related fatigue is still limited.

Basic structural imaging using T2-weighted and contrast-enhanced T1 images is an essential tool for the clinical diagnosis of MS and further surveillance in patients with MS, and can also quantify lesion load, atrophy or cortical thinning. A paper by Arm et al, published in 2019, stated that the majority of performed studies failed to find a significant correlation between lesion load and the level of fatigue.[84]

Researchers have turned their attention to MRI volumetry, especially global brain volume and thalamus volume, which can be associated with the level of fatigue. Many studies have demonstrated a correlation between the level of brain atrophy and cognitive or motor fatigue. The strongest correlation was found in the occipital lobes (mainly the right superior/inferior occipital gyrus),[85] temporal lobes, including the right inferior temporal gyrus (ITG), frontal lobe (dorsolateral prefrontal cortex [DLPFC], left superior frontal gyrus [SFG], right inferior frontal gyrus [IFG] and forceps major),[86,87] parietal lobe, precuneus,[85] primary sensorimotor area, including the precentral gyrus,[88] supplementary motor area (SMA), such as the paracentral gyrus, bilateral precentral motor cortex and the brainstem. A combined positron emission tomography (PET)/MRI study performed by Gerache et al found a negative correlation between fatigue and GM atrophy in many areas of the frontal, temporal, parieto-occipital and bilateral thalami, and with the resting cerebral metabolic rate of glucose.[89]

DTI in assessments of MS-related fatigue found inverse correlations between fatigue scores and decreased fractional anisotropy (FA) and increased mean diffusivity values and radial diffusivity (MD/RD) in a range of brain regions, especially the right anterior thalamic radiation,[34] right uncinate fasciculus and forceps minor,[85] thalamus and basal ganglia,[40] anterior internal capsule,[32] inferior fronto-occipital fasciculus,[90] corpus callosum,[39] fibers between the posterior hypothalamus and mesencephalon,[91] and fronto-subcortical disconnections.[92]

Functional imaging performed by DeLuca et al and another study performed by Tartaglia et al suggested functional reorganization or unmasking of existing motor pathways in MS patients, which then leads to additional effort required to perform a task adequately, which subsequently uses more brain areas than in healthy subjects.[92,93]

In conclusion, as stated in the first part of this section, the use of these techniques is still limited to scientific and not clinical purposes.

Treatment Strategies in Fatigue

Fatigue management remains challenging. Owing to the subjective nature of fatigue manifestations, symptoms of fatigue are often clinically overlooked during MS treatment. In clinical practice, MS-related fatigue should be assessed and managed by a multidisciplinary team, involving neurologists, MS nurses, occupational therapists and physiotherapists. This team will also identify the best combination of therapeutic options for each individual, based on the severity of the fatigue and the presence of comorbidities.[94]

Influence of the Basic MS Treatment on Fatigue

Several studies have demonstrated an improvement in fatigue with both background therapy with INF-β and GA.[72] GA seems to reduce fatigue more than INF-β; however, since the studies were not designed as comparative, no reliable statement can be made on this. There is still a lack of randomized studies with fatigue as an endpoint in this context.[95]

The effect of natalizumab on fatigue cannot be clearly estimated based on the current studies.[96] So far, there is no evidence of any relief of fatigue under therapy with teriflunomide.[97]

Calkwood et al reported a significant alleviation of fatigue after switching therapy from INF-β_{1a} or INF-β_{1b} to fingolimod.[97] Since there are no placebo-controlled studies with fatigue as the primary endpoint, the available data should be interpreted with caution. In summary, the study situation suggests that fatigue can be alleviated under therapy with GA and interferons, although the effect appears to be more pronounced under GA.[98]

Pharmacotherapy

No specific drugs have fatigue as a specific indication, and many drugs have been repurposed in the past few decades to pharmacologically manage MS fatigue.

Currently, different pharmacological agents are used for the treatment for fatigue in patients with MS, including amantadine, modafinil and pemoline.[99,100] Of these, the most commonly used is amantadine. Its main mechanism of action is not yet fully understood, although its effects on fatigue seem to be related to its dopaminergic effects, supporting the dopamine imbalance theory for MS-related fatigue.[101] In general, all trials that compared amantadine with placebo showed a significant effect of amantadine on fatigue. However, the results of these trials need to be interpreted with caution because of the low number of participants included in the trials and the short duration of the interventions.[8] The daily dose of amantadine used in all published studies was 200 mg, which is the standard amount administered today. Amantadine is the only oral treatment that is currently recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of MS-related fatigue.[102]

Yang et al found that acetyl-L-carnitine may have the same therapeutic effect as amantadine. However, it should be kept in mind that the number of respondents in the studies included in their review is too small to definitively make this statement. The mechanism of acetyl-L-carnitine (ALC) potentially offers neuroprotective benefits and improves mitochondrial energetics and function.[103]

Modafinil, a drug currently approved for the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy, has also been frequently evaluated in clinical trials for patients with MS-related fatigue.[8] A randomized placebo-controlled trial in 2009 evaluated the effect of modafinil in 21 patients with MS. Modafinil administered for 8 weeks had a significant effect not only on fatigue scores but also on an upper limb motor task and cognitive tests. It also resulted in an increase in the amplitudes of motor-evoked potentials, suggesting that modafinil may have an effect at the level of motor cortex function.[104] On the other hand, a methodologically similar study with a larger number of respondents showed negative results.[105] Thus, the overall evidence supporting the effect of modafinil on MS-related fatigue is weak, and in the last edition of the NICE guidelines modafinil was not included as a recommended treatment for MS-related fatigue.[102]

Other pharmacological approaches have also been mentioned in the literature, such as intramuscular injections with vitamin B_{12}. However, the NICE guidelines recommend not offering drugs to treat MS-related fatigue if scientific evidence is lacking.[102]

Non-Pharmacological Treatment

Non-pharmacological interventions can be divided into physical, psychological/cognitive and mixed approaches.

Physical Approaches

One of the most frequently assessed physical approaches is aerobic exercise. For example, a trial by Garrett et al showed beneficial effects on MS fatigue for aerobic exercise compared to placebo. This trial compared physiotherapist-led exercise, fitness instructor-led exercise, yoga and placebo (patients without intervention), and showed that all three interventions were effective (compared with placebo) in alleviating fatigue.[106] Another study found an association between the decrease in fatigue levels after regular exercise in patients with MS and changes in the expression of genes related to modulation of the systemic response to interferon. Although the results of this study need to be replicated in larger cohorts, it provides a possible biological explanation for the beneficial effect of exercise in MS.[107] The study by Hebert et al provides strong evidence of the positive effect of vestibular rehabilitation in reducing fatigue in MS patients and in maintaining upright posture. The large treatment effects occurred after a relatively short intervention period, suggesting that vestibular rehabilitation is a viable treatment option for patients with MS who experience fatigue and impaired upright postural control.[108,109]

Psychological/Cognitive Approaches

Mindfulness interventions, cognitive behavioral therapy and fatigue management programs are effective in the treatment of fatigue. Cognitive–behavioral therapy aims to address the behavior of people with MS in order to improve their levels of fatigue. Its efficacy has been proved in several studies, either alone or in the context of more comprehensive programs with other non-pharmacological approaches.[102] Fatigue management approaches try to help patients to save energy through the implementation of different strategies, such as work simplification or the use of labor-saving and ergonomic equipment. Mindfulness-based interventions are derived from Buddhist practice and have been used for a number of psychological and somatic conditions, including MS-related fatigue. For that reason, their use is currently recommended by the NICE guidelines, among other psychological approaches.[102]

Conclusion

Fatigue is one of the most commonly reported symptoms during MS outpatient follow-up, affecting between 52% and 90% of patients. The exact pathophysiology of MS-related fatigue is not fully understood, but it is thought to be multifactorial and may involve both physical and psychological factors. The most commonly proposed theories deal with immunological and inflammatory mechanisms; these theories link fatigue to the production of cytokines that alter neuronal signaling and metabolism.

Endocrinopathies and hormonal imbalances should also be mentioned, and especially the role of low cortisol and DHEAS levels. Current pathophysiological studies concentrate, however, on orexin, which may play a crucial role in fatigue perception. Damage to certain brain regions in the gray and white matter may also be linked to fatigue. During the diagnostic process, secondary causes of fatigue, mainly adverse effects of medication, sleep disorders and depression, should also be excluded.

The diagnosis and verification of the degree of fatigue in MS are complicated and based on the subjective assessment of the patient, as they are still based only on diagnostic questionnaires. So far, there are no validated biomarkers that can demonstrate or quantify the level of fatigue in MS. The search for such biomarkers should be an avenue for further research in this field.

Treatment of fatigue in MS is limited because of the low number of case–control studies comparing drugs with placebo. The most promising results have been observed with fampridine and with non-pharmacological treatment, such as physiotherapy, cognitive–behavioral therapy or mindfulness.

Although fatigue is a frequent and debilitating symptom of MS, knowledge of its pathophysiology, diagnosis and treatment is very limited. Given these limitations, further research in this field will be needed in the future.

Disclosure

The authors report no conflicts of interest in this work.

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