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REVIEW

Is there a link between inflammation and fatigue in multiple sclerosis?

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Purpose: Among autoimmune diseases of the central nervous system stands multiple sclerosis (MS), which is characterized by demyelination, synaptopathy, and neurodegeneration. MS fatigue can affect up to 90% of patients and be very disabling, with a drastic impact on their quality of life. To date, the evaluation of MS fatigue has relied mainly on subjective scales, and actual therapeutic interventions are challenged by modest efficacy and numerous undesirable effects. Therefore, finding biomarkers of MS fatigue might help in optimizing evaluation and treatment strategies. The main objective here was to assess the relationship between MS fatigue and inflammatory or other immunomediated markers.

Methods: Research was conducted according to PRISMA guidelines. Computerized databases (ie, PubMed/Medline and Scopus) were consulted till February 2018 aiming to identify articles that addressed inflammation and MS fatigue. Studies in English and French published at any time were considered.

Results: A total of 27 studies matched the research criteria. Inconsistency existed regarding the relationship between fatigue and the orexin A system, hypothalamus–pituitary–adrenal axis, and cerebrospinal fluid inflammatory markers. As for peripheral markers, although there was scarcity in the available data, serum proinflammatory cytokines (ie, IL6, TNFα, and IFNγ) seem to be associated with MS fatigue. Finally, no link was found between MS fatigue and T-cell populations (ie, $CD3^+CD4^+$ T lymphocytes, regulatory T cells) or other peripheral markers of inflammation (ie, CRP, erythrocyte-sedimentation rate, soluble ICAM1).

Conclusion: Future large-scale studies would benefit from comparing the relationship between fatigue and immune measures in patients with different disease phenotypes with and without disease-modifying drugs. With the subjective nature of fatigue scales, finding objective biomarkers for fatigue would be of great help.

Keywords: pathophysiology, cytokines, interleukins, cerebrospinal fluids, inflammatory markers

Introduction

Among autoimmune diseases of the central nervous system (CNS) stands multiple sclerosis (MS), which is the second-most common cause of physical handicap in young individuals.[1–3] Its pathophysiological hallmarks are demyelination, synaptopathy, and neurodegeneration.[4,5] Throughout the disease course, MS patients can experience periods of acute symptom emergence separated by symptom-free intervals. This characterizes the relapsing–remitting (RR) MS phenotype, which usually converts to a secondary progressive phase where patients can experience steady clinical deterioration.[3] Primary progressive MS represents a third disease phenotype, where patients

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witness an evolutionary pattern of their disease from onset. Demyelination appears to be the fingerprint of the first type (ie, RRMS), whereas neurodegeneration/axonal loss seems to be the backbone of progressive types.[5] While an immunomediated attack by blood-borne autoreactive T lymphocytes would dictate the occurrence of demyelination, immunomediated processes involving immune cells and soluble cytokines could also lead to excitotoxic changes and neurodegeneration, based on experiments involving the animal model of MS.[5]

Regardless of the disease phenotype, patients may experience a panel of symptoms involving the sensory, motor, cerebellar, emotional, cognitive, and behavioral domains. Among the frequently encountered symptoms, MS fatigue can affect up to 90% of patients and be very disabling, with a drastic impact on their quality of life.[6] It is a challenging symptom that is described by patients as "malaise", "excessive tiredness", or "weakness" that seems to worsen throughout the day, as well as with hot and humid environments.[4] From a scientific perspective, MS fatigue is considered a multidimensional symptom with physical, cognitive, and psychosocial components. Among the available definitions, some authors consider fatigue a lack of physical and/or mental energy.[4,6] For another group of authors, fatigue designates a failure to initiate and/or maintain physical or mental activities requiring self-motivation in the absence of or not related to physical or cognitive dysfunction.[4,6]

Ever since the original work of Freal et al in 1984,[7] there has been growing interest in understanding the pathophysiology of MS fatigue, especially the fact that this symptom remains difficult to be reported by patients and managed by physicians. To date, the evaluation of MS fatigue has relied mainly on subjective scales, such as the Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS), and Fatigue Scale for Motor and Cognitive Functions (FSMC), among others, and actual therapeutic interventions are challenged by their modest efficacy in face of their numerous undesirable effects.[6] From this perspective, understanding the underlying mechanisms of this symptom might be of help in easing its evaluation and optimizing patient care. In a previous work, we addressed the cerebral anatomical correlates of MS fatigue.[4] Based on neuroimaging studies, pathological findings were observed in a corticostriatothalamocortical loop that was linked to MS fatigue. These findings included regional gray- and white-matter pathologies, as well as abnormal patterns of brain activation. The inflammatory and immune medium might be implicated as well in the context of MS fatigue. Therefore, the main aim of the current work was to assess the role of MS-related central and peripheral inflammation and immunomediated endocrine dysregulation in the development of this symptom.

Study selection

Research was conducted according to the PRISMA guidelines.[8] First, computerized databases that index peer-reviewed journals (PubMed/Medline and Scopus) were consulted till the end of February 2018. The research aimed to identify articles that addressed the relationship between MS fatigue and inflammatory, immune, and endocrine factors. Studies that were published at any time in English and French were considered. The following research terms were combined: ("fatigue" OR "fatigue severity scale" OR "FSS" OR "Modified Fatigue Impact Scale" OR "MFIS" or "Fatigue Scale for Motor and Cognitive Functions" or "FSMC") AND ("multiple sclerosis" OR "MS") AND ("inflammation" OR "inflammatory" OR "immune" OR "cytokine" OR "interleukin" OR "cerebrospinal fluid" OR "CSF" OR "lymphocytes" OR "blood cells" OR "endocrine"). In addition, both coauthors independently checked the references of the articles obtained, aiming to obtain additional sources. The initial search identified 503 articles in PubMed/Medline and 258 articles in Scopus. After removal of duplicates and excluding reviews, opinions, editorials, commentaries, viewpoints, and research articles involving healthy volunteers or patients with autoimmune diseases other than MS, 25 articles were retained. An additional two references were retrieved from the articles' reference lists, yielding a total of 27 articles that were considered in the qualitative synthesis. These comprised information on MS fatigue and inflammatory or neuroendocrine markers and addressed the relationship between fatigue and hypothalamic function (two about the orexin A system, eight about the hypothalamic–pituitary–adrenal [HPA] axis), cerebrospinal fluid (CSF) markers (one about humoral and cellular CSF markers, one about CSF cytokines), serum-cytokine or blood-cell expression (15), or other peripheral inflammatory markers (three). In addition, six studies assessed changes in fatigue and cytokine profiles following exercise (four) or pharmacological (two) interventions. For the sake of this work, data of the selected studies are classified as central inflammation and neuroendocrine dysregulation and peripheral inflammation.

Central inflammation, neuroendocrine dysregulation, and MS fatigue

The exploration of inflammatory patterns within the CNS is possible by means of CSF analysis. However, the procedure

consists of performing lumbar puncture, a procedure that is not only difficult to perform but also traumatizing for patients. This explains the scarcity of existing literature in this field. Available works on CSF analysis and MS fatigue focused on studying inflammation-related neuroendocrine dysregulation, humoral and cellular components, and cytokine levels. The remaining literature employed serum and salivary hormonal tests to assess specific hypothalamic functions and their relationship with fatigue.

To start, the hypothalamus plays a role in controlling several homeostatic functions. Some researchers were interested in assessing the relationship between MS fatigue and CSF levels of orexin A (also known as hypocretin 1), a hypothalamic peptide involved in arousal, motivation, energy, and circadian rythm.[9] In fact, consolidating night sleep and keeping adequate daytime activity seem to be respectively promoted by low and high orexin A levels.[10] Therefore, the rationale behind these works lay in the fact that neuroinflammation, such as that seen in MS, may impact the orexin A system.[11] As such, one can speculate that downregulation of the latter system might happen in the course of MS and result in sleep disorders and/or fatigue. The first insight on orexin A-system status in MS derived from case reports on patients suffering from hypersomnia displaying low CSF levels of orexin A.[12,13] Afterward, Papuć et al studied orexin A levels in MS patients and healthy controls.[14] In the absence of group difference (MS vs healthy controls) with regard to this peptide, significant positive correlation was found between fatigue severity and orexin A levels in the whole patient group. Although this positive relationship was unexpected, the authors of this work hypothesized that this might have occurred due to the activation of endogenous compensatory mechanisms. One year later, Constantinescu et al were not able to replicate this correlation.[15] Here, the authors found neither a group difference in orexin A levels between MS patients and other patients with inflammatory and noninflammatory neurological disease nor a correlation between orexin A levels and fatigue scores. Given the impact of daytime and season on orexin A levels,[16] there is a good chance that these two studies were performed in different seasons and/or at different times of the day, a finding that could provide an explanation for the difference in the reported results.

Besides regulating the orexin A system, the hypothalamus is involved in many axes, of which the most studied is the HPA axis. Facing physiological and stressful situations, the hypothalamus secretes the corticotropin-releasing hormone (CRH) to stimulate the activity of the anterior pituitary gland. The latter responds by producing the adrenocorticotropic hormone (ACTH) which in turn activates the adrenal glands (ie, zona fasciculata) yielding cortisol production. Proinflammatory cytokines can influence the activity of the HPA axis.[17] This might provide an explanation for the HPA-axis dysregulation that appears to occur in patients with MS.[18–23] In fact, the majority of studies on this topic have shown a hyperactive HPA axis, with fewer reports suggesting a hypoactivity pattern. Few studies have assessed the relationship between MS fatigue and HPA-axis activity.

Heesen et al employed combined dexamethasone–CRH challenge[24–26] and low-dose dexamethasone-suppression tests.[27] Both of these are used widely to measure activity of the HPA axis. The dexamethasone-suppression test consists of orally administering dexamethasone, a synthetic glucocorticoid, the night before blood sampling, in order to check the suppression of cortisol production (which is the normal physiological reaction). The combined dexamethasone–CRH-challenge test resembles the first, but CRH is also given intravenously the day of blood sampling and blood withdrawn at regular intervals to determine plasma levels of ACTH and cortisol levels at different times. In their four studies, the authors did not detect any significant association between MS fatigue and HPA-axis activity.[24,25] In line with these results, Akcali et al employed a more comprehensive neuroendocrine evaluation that included plasma levels of ACTH, cortisol, and other pituitary products, namely corticotropin-like intermediate-lobe peptide (CLIP), which is an ACTH variant, and melanocyte-stimulating hormone (α-MSH, β-MSH, γ-MSH), produced in the anterior pituitary gland[28] and previously found to be implicated in chronic fatigue syndrome (ie, α-MSH).[29] Although abnormal HPA measures were observed in MS patients compared to healthy controls (ie, higher ACTH, cortisol and α-MSH and lower CLIP levels among patients), these measures did not differ between fatigued and unfatigued MS patients, suggesting the absence of any relationship between HPA-axis activity and MS fatigue. Conversely, a third study by Gottschalk et al employed combined dexamethasone–CRH-suppression tests and found significantly higher ACTH plasma levels among fatigued compared to unfatigued counterparts.[30] The discrepancy in the results of the aforementioned works might have resulted from differences in clinical characteristics and treatments of the MS cohorts studied. Contrarily to Heesen et al[24–27] and Akcali et al,[28] who mostly enrolled patients receiving disease-modifying drugs, Gottschalk et al[30] recruited drug-naïve patients. Here, it is worth noting that immunotherapy may impact cytokine-expression levels and thus might influence HPA-axis activity.[31,32]

In addition to the previously mentioned studies, Powell et al and Gold et al focused on the assessment of the cortisol awakening response (CAR) in MS patients, using a salivary test.[27,33] CAR is a spike in serum cortisol around 30–45 minutes after awakening, and is crucial for sustaining normal circadian rhythm and wakefulness.[34] In the former trial, baseline fatigue scores, but not those obtained at the same day of CAR testing, were correlated with CAR.[33] In the latter, CAR did not predict MS fatigue, as per regression-analysis results.[27]

Among the other adrenal products stands dehydroepiandrosterone (DHEA) and its sulfated ester (DHEAS). Low DHEA and DHEAS levels have been linked to fatigue in some autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.[35,36] In the only available study addressing serum levels of DHEA and DHEAS in MS patients, lower levels of both components were detected in fatigued compared to unfatigued patients.[37] Interestingly, these results support those of an earlier pharmacological study, in which fatigue improvement was obtained following DHEA hormone replacement.[38] However, the results of the latter work should be interpreted with caution, mainly because of its nonrandomized design. These preliminary findings warrant further research on this matter.

In addition to studies on HPA axis and MS fatigue, some researchers were interested in evaluating humoral, cellular, and other immune CSF markers. For instance, Biberacher et al included an exploratory and a validation phase that contained several evaluations. Of interest, they assessed the relationship between fatigue and several cellular and humoral CSF markers.[39] No correlation was found between fatigue scores and any of the CSF markers. More interestingly, fatigue scores tended to correlate negatively with CSF CD4:CD8 ratio in the discovery group and correlate positively with the former ratio in the validation group. However, the multivariate model failed to detect associations between fatigue and CSF parameters in either group (exploratory vs validation). A recent work aimed to understand the relationship between MS-fatigue and CSF-interleukin levels, particularly IL6 and IL8. While IL6 took part in innate and adaptive immune responses, including differentiation of T helper 17 cells, IL8 was mainly implicated in innate immunoresponses and had cytokine- and chemokine-like functions. In this work, Brenner et al documented a significant correlation between fatigue scores and IL6 levels.[40] This relationship was only seen among patients not receiving MS treatment. This might explain the absence of association in Biberacher et al,[39] where >75% of patients were under MS therapies. Another difference between the studies lies in their methodological approach which consisted of cellular and humoral markers in the first versus interleukins in the second. The different clinical and demographic characteristics between the cohorts might present a third plausible explanation for the inconsistency in their results. Table 1 provides a summary of these studies.

Table 1 Studies assessing the relationship between multiple sclerosis fatigue and central inflammatory or neuroendocrine markers

Study	Population	Fatigue assessment	Measures	Results
Studies assessing the HPA axis				
Heesen et al[24]	40 patients (8 RR, 19 SP, 13 PP, sex details NA, treated, but details NA); 11 HCs (sex-matched, details NA)	MFIS, FSS	Dex–CRH test	HPA-axis hyperactivity among progressive patients (but not RR patients) No correlation between fatigue and HPA-axis activity
Gottschalk et al[30]	15 fatigued MS patients (all RR, 12F/3M); 16 unfatigued MS patients (all RR, 10F/6M); 19.4% of whole cohort treated	FSS, MFIS, VAS	Dex–CRH test	Higher adrenocorticotropin (but not cortisol) levels in the Dex–CRH test among fatigued patients Correlation analysis NA No influence of sex on fatigue
Heesen et al[25]	15 fatigued MS patients (6 RR, 8 SP, 1 PP, 9F/6M, 66.7% treated); 15 unfatigued MS patients (11 RR, 2 SP, 2 PP, sex-matched, 9F/6M, 60% treated)	MFIS, FSS	Dex-CRH test	No group difference in Dex-CRH test Correlation between fatigue and HPA-axis activity
Heesen et al[26]	50 MS patients (27 RR, 23 SP, 29F/21M, 48% treated)	MFIS	Dex–CRH test	Group comparison NA No correlation between fatigue and HPA-axis activity
Gold et al[27]	44 MS patients (all RR, all female, 59% treated)	MFIS, FSS	Dexamethasone-suppression test, salivary CAR test	Group comparison NA Dexamethasone-suppression test and CAR data did not predict fatigue

(*Continued*)

Table 1 (*Continued*)

Study	Population	Fatigue assessment	Measures	Results
Powell et al[33]	38 MS patients (38 RR, 31F/7M, 39.5% untreated); 38 HCs (sex-matched, 31F/7M)	Eleven-item Fatigue Scale	Salivary CAR test	Higher CAR in the patient group Association between recalled baseline fatigue (but not same-day fatigue) and CAR
Akcali et al[28]	26 fatigued MS patients (all RR, 14F/12M); 28 unfatigued MS patients (all RR, 15F/13M); 87.1% of cohort treated; 26 HCs (13F/13M); sex-matched groups	FSS, NFI-MS	ACTH, cortisol, α-MSH, β-MSH, γ-MSH, and CLIP	Higher ACTH, cortisol, and MSH and lower CLIP among MS patients compared to HC; no significant differences between fatigued and unfatigued MS patients No correlation between fatigue and hormones studied
Téllez et al[37]	29 fatigued MS patients (20 PP, 9 SP, 20F/9M, 51.7% treated); 9 unfatigued MS patients (5 PP, 4 SP, sex-matched, 5F/4M, 66.7% treated)	FSS	Serum levels of DHEA, DHEA–sulfate conjugate, and cortisol	Lower levels of DHEA and its sulfated conjugate among fatigued MS patients Inverse correlation between fatigue and DHEA levels
Studies assessing the hypothalamic orexin A system				
Papuć et al[14]	28 fatigued MS patients (15F/13M); 10 unfatigued MS patients (6F/4M); cohort characteristics 25 RR, 13 SP, all untreated; 15 HCs (8F/7M); sex-matched groups	FSS	CSF levels of orexin A	No group differences regarding orexin A levels Correlation between fatigue and orexin A levels
Constantinescu et al[15]	34 MS patients (26 RR, 2 SP, 6PP, 22F/12M, treatment NA); 24 patients with other inflammatory neurological diseases (7F/17M); 42 patients with noninflammatory neurological diseases; significantly more females in MS-patient group	FSS	CSF levels of orexin A	No significant group differences regarding orexin1 levels No correlations between CSF levels of orexin A and fatigue
Studies assessing other CSF markers				
Biberacher et al[39]	Two phases: 68 MS patients (discovery cohort, 7 CIS, 60 RR, 1 SP, 49F/19M, 77.9% treated); 81 MS patients (validation cohort, 9 CIS, 71 RR, 1 SP, 51F/30M, 75.3% treated)	FSMC	CSF cell count, glucose, lactate, albumin CSF:serum ratios, intrathecal immunoglobulin synthesis, $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+$/CD8 ratio, $CD19^+$ B cells, $CD19^+CD138^+$ plasmablasts, $CD56^+$ natural killer cells, $CD14^+$ monocytes	Group comparison NA No correlations between fatigue and any CSF parameter
Brenner et al[40]	47 MS patients (all RR, 31F/16M, untreated)	MFIS	CSF levels of IL6 and IL8	Group comparison NA Correlation between fatigue and IL6 levels

Abbreviations: ACTH, adrenocorticotropic hormone; CAR, cortisol awakening response; CIS, clinical isolated syndrome; CLIP, corticotropin-like intermediate-lobe peptide; CSF, cerebrospinal fluid; Dex–CRH, dexamethasone–corticotropin-releasing hormone-suppression; DHEA, dehydroepiandrosterone; F, female; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; HCs, healthy controls; HPA, hypothalamic–pituitary–adrenal; M, male; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; MSH, melanocyte-stimulating hormone; NA, not available, NFI, Neurological Fatigue Index; PP, primary progressive; RR, relapsing–remitting; SP, secondary progressive; VAS, visual analog scale.

Peripheral inflammation and MS fatigue

Immunodysregulation constitutes the core of the disease process in MS.[41–43] The role of peripheral inflammation in the development of MS fatigue has been considered in few immunological studies that assessed serum levels of cytokines, cytokine-producing cells, or other inflammatory markers. The first evidence on this matter dates back to 1990.[44] In a series of eight fatigued MS patients, the authors assessed serum levels of IL2 and its soluble receptor, an interleukin that was suggested to intervene in CNS demyelination in MS and was previously found to be associated with the disease state in an animal MS model. The authors reported that in all patients, the variables studied were below the level of sensitivity of the test used (enzyme-linked immunosorbent assay [ELISA]), and thus denied the association between MS fatigue and

IL2 levels. Afterward, Flachenecker and colleagues applied real-time polymerase chain reaction (RT-PCR) to compare the expression (mRNA) of circulating proinflammatory (ie, TNFα, IFNγ) and anti-inflammatory cytokines (IL10) in fatigued and unfatigued MS patients.[45] TNFα expression was heightened among fatigued patients, with no group differences regarding IFNγ and IL10 expression. The role of TNFα has also been suggested in some studies that documented a decrease in TNFα levels following exercise therapy, a finding that was paralleled by an improvement in MS fatigue.[46–48]

In a similar way to these studies, the same cytokines were assessed in two trials by Heesen et al.[25,49] ELISA was employed in both works. In the first, only fatigued MS patients were recruited and compared to healthy controls at baseline following a cognitive task that assessed psychological stress.[49] No group difference was observed at baseline with regard to cytokine levels but following the cognitive task the MS group had relatively diminished IFNγ response compared to the healthy group. No significant correlations were observed between fatigue scores and cytokine levels. In the second study, the authors recruited two groups of MS patients with and without fatigue and obtained positive findings.[25] That is to say that, compared to unfatigued patients, the fatigued ones had higher proinflammatory cytokines (TNFα and IFNγ), with no group differences observed with regard to the anti-inflammatory cytokine (IL10). A correlation was also found between fatigue scores (MFIS and FSS) and TNFα and IFNγ levels. The difference between the studies might lie in differences in the study populations, where the first considered only fatigued patients, whereas the second also considered an unfatigued patient group.

The same group of authors performed a third study that highlighted the role of IFNγ-producing $CD8^+$ T cells as the only significant predictor of fatigue scores.[27] The contribution of IFNγ to the pathophysiology of MS fatigue was also assessed by Pokryszko-Dragan et al.[50] Using flow cytometry, they studied the production of this cytokine by $CD3^+CD4^+$ T lymphocytes. Heightened IFNγ production was observed among fatigued patients compared to unfatigued patients and healthy controls, a finding that also tended to correlate with fatigue scores (FSS and MFIS). However, when multiple regression analysis was run, fatigue scores were not linked to IFNγ. The role of interferon signaling was also highlighted in a pilot study by Mulero et al.[51] Here, compared to healthy controls, fatigued MS patients had significant activation in genes participating in the systemic interferon response.

Another important factor in the context of MS is IL17 which appears to be implicated in glutamate-mediated excitotoxicity and thus may explain the potential link between inflammation and neurodegeneration in MS.[52] The relationship between fatigue and IL17 levels has been addressed by three works that yielded inconsistent outcomes, with two studies confirming such a correlation[47,53] and one denying it.[56]

Other circulating cytokines were the subject of a study by Malekzadeh et al, who compared serum levels of a panel of proinflammatory (IL1β, IL2, IL6, IL8, IL12p70, IL17, TNFα, and IFNγ) and anti-inflammatory cytokines (IL4, IL5, IL10, and IL13) in fatigued and unfatigued MS patients using an electrochemiluminescence-based multiplex immunoassay.[53] In the absence of group differences with regard to these variables, a significant correlation was found between IL6 levels and fatigue scores. Of interest, the IL6 levels were found to diminish in another work following the administration of antifatigue pharmacological therapies such as amantadine and pemoline, a finding that was paralleled by fatigue improvement.[54]

An additional study by Akcali et al evaluated serum levels of TNFα, IL10, and other interleukins (IL1β, IL2, and IL35) in MS patients and healthy controls.[28] Compared to healthy controls, the only group difference was observed with regard to IL35 and IL2, which were higher in the patient group. However, neither was there a difference between fatigued and unfatigued patients nor was there any correlation between fatigue scores and the markers considered.

Again, inconsistency in results across studies might have been related to cohort characteristics and sample-size difference, but also to other plausible factors. For instance, levels of pro/anti-inflammatory markers can fluctuate during the disease course and disease-modifying therapies can impact cytokine expression.[28,55] To overcome this limitation, recent studies by Alvarenga-Filho et al enrolled drug-naïve MS patients.[47,56] Here, higher IL6 and TNFα levels were observed among fatigued patients,[47] and fatigue scores were correlated with IL6 and TNFα levels[47,56] and tended to correlate with IFNγ levels.[47] Another factor to consider is differences in methods adopted in measuring cytokine levels. This is obviously illustrated with regard to IFNγ. In reality, IFNγ was found to be unrelated to fatigue when using RT-PCR[45] and a multiplex kit[53] and associated or tended to associate with fatigue when using ELISA[25,56] and flow cytometry.[50] As such, these tests seem to have different sensitivity/specificity profiles, and this would hamper the possibility of drawing formal conclusions from the existing literature. Moreover, even when using ELISA, results might vary between in vivo and in vitro approaches. The best documentation of this variability can be found in the

studies on IL17 (ie, serum-cytokine levels in vivo[47,53,56] versus stimulated cytokines production in vitro[47,56]). In fact, one of these works simultaneously adopted both approaches, but only documented a significant correlation between fatigue and in vitro IL17 production.[56] In addition, differences in statistical approaches might explain differences in results reported. While positive studies IFN-γ employed group-comparison and correlation analysis,[25,47,50,56] studies that failed to demonstrate this relationship adopted group comparison without correlation analysis[45] or multiple regression analysis.[53]

Given the role of T cells in the pathophysiology of MS, few works have addressed the relationship between circulating T-cell populations and MS fatigue and failed to document any association. Fatigued and unfatigued MS patients did not differ with regards to the amount of IFNγ-producing $CD3^+CD4^+$ T lymphocytes in one study[50] or the number of leukocyte and lymphocyte subsets including regulatory T cells and its suppressive function in another study.[57]

Finally, three studies included markers of peripheral inflammation in the assessment of MS fatigue. In the first, Giovannoni et al failed to demonstrate any relationship between fatigue and serum (ie, CRP, soluble ICAM1) or urinary (daily urinary neopterin excretion measured over 2 weeks) markers.[58] Similarly, in a second study by Flachenecker et al, the erythrocyte-sedimentation rate, a marker of systemic inflammation, did not differ between fatigued and unfatigued MS patients.[45] Finally, in a third study by Adamczyk-Sowa et al, no correlation was found between MS fatigue and plasma lipid hydroxyperoxides or homocysteine concentration, which are markers of oxidation.[59] Table 2 summarizes these studies.

Table 2 Studies assessing the relationship between multiple sclerosis fatigue and peripheral inflammation

Study	Population	Fatigue assessment	Method	Results
Studies assessing peripheral cytokines				
Rudick and Barna[44]	Eight fatigued MS patients (disease details NA, 6F/2M); 50 HCs	NA	Serum levels of IL2 and its receptor (using ELISA)	No group difference with regard to IL2 or its receptor level Correlation NA
Flachenecker et al[45]	26 fatigued MS patients; 11 unfatigued MS patients; cohort characteristics, 29 RR, 8 SP, 27F/10M, 54% treated	FSS	Serum mRNA expression of IFNγ, TNFα, and IL10 (using RT-PCR)	Higher TNFα (but not IFNγ or IL10) mRNA expression among fatigued patients Correlation analysis between fatigue and cytokine mRNA expression NA
Heesen et al[49]	23 fatigued MS patients (19 RR, 3 SP, 1 PP, 18F/5M, 60.9% treated); 25 HCs (sex-matched, 20F/5M)	MFIS	Whole-blood stimulatory capacity for TNFα, IFNγ, and IL10 (using ELISA); cognitive task to examine the immunoresponse (cytokines) to psychological stress	No significant group difference in baseline cytokines Blunted response of IFNγ among MS patients following psychological stress (no group difference in TNFα or IL10 responses) No correlation between fatigue and cytokine levels
Heesen et al[25]	15 fatigued MS patients (6 RR, 8 SP, 1 PP, 9F/6M, 66.7% treated); 15 unfatigued MS patients (11 RR, 2 SP, 2 PP, sex-matched, 9F/6M, 60% treated)	MFIS, FSS	Whole-blood stimulatory capacity for TNFα, IFNγ, and IL10 (using ELISA)	Higher levels of TNFα and IFNγ (but not IL10 levels) in fatigued MS patients Correlation between fatigue scores of TNFα and IFNγ
Gold et al[27]	44 MS patients (all RR, all female, 59% treated)	MFIS, FSS	Serum intracellular levels of cytokines IFNγ and TNFα (using flow cytometry)	Frequency of IFNγ-producing $CD8^+$ T cells predicted of fatigue scores (regression analysis)
Pokryszko-Dragan et al[50]	20 fatigued MS patients; 20 unfatigued MS patients; cohort characteristics, 30 RR, 10 SP, 30F/10M, untreated; 25 HCs (sex NA)	MFIS, FSS	Levels of IFNγ (using flow cytometry)	Higher IFNγ production among fatigued MS A trend toward correlation between fatigue and IFNγ
Malekzadeh et al[53]	21 fatigued MS patients (15 RR, 5 PP/SP, 1 missing, 10F/7M, 47.6% treated); 14 unfatigued MS patients (11 RR, 3 PP/SP, sex-matched, 10F/4M, 50% treated)	Self-reported checklist: individual strength, fatigue subscale	Serum levels of IL1β, IL2, IL6, IL8, IL12p70, IL17, TNFα, and IFNγ, IL4, IL5, IL10, and IL13 (using electrochemiluminescence-based multiplex immunoassay)	No group differences with regard to variables measured Association between fatigue and IL6 levels (regression analysis)

(*Continued*)

Table 2 (*Continued*)

Study	Population	Fatigue assessment	Method	Results
Mulero et al[51]	Seven fatigued MS patients (all RR, 5F/2M, 85.7% treated); 7 HCs (details NA)	MFIS	Whole-blood gene expression (using microarrays and RT-PCR)	Activation of IFN-response genes among fatigued MS patients Correlation NA
Alvarenga-Filho et al[47]	18 MS patients (all RR, 15F/3M, untreated); 10 HCs (age-matched 8F/2M)	FSS	In vivo and in vitro assessment of peripheral levels of IL6, IL10, IL21, IL22, IL17, TNFα, and IFNγ (using ELISA)	Higher IFNγ, IL6, TNFα, IL17, and IL22 among MS patients In vivo: correlation between fatigue and each of IL6 and TNFα and a trend toward a correlation with IFNγ In vitro: correlation between fatigue and of IL6, TNFα, IFNγ, and IL22 levels
Alvarenga-Filho et al[56]	15 fatigued MS patients (all RR, 11F/4M, untreated); 15 unfatigued MS (all RR, sex-matched, 10F/5M, untreated)	FSS	In vivo and in vitro assessment of peripheral levels of IL6, IL10, IL12, IL17, IL21, IL22, IL23, TNFα, and IFNγ (using ELISA)	Higher IL6 and TNFα levels in fatigued MS patients In vivo: correlation between fatigue and IL6 and TNFα levels and a trend toward a correlation between fatigue and IFNγ In vitro: correlation between fatigue and IL1β, IL6, IL17, IL22, and IL23 levels
Akcali et al[28]	26 fatigued MS patients (14F/12M); 28 unfatigued MS patients (15F/13M); cohort characteristics, all RR, 87.1% treated; 26 HCs (13F/13M); sex-matched groups	FSS, NFI-MS	Serum IL1β, TNFα, IL35, IL2, and IL10 (using ELISA)	Higher IL35 and IL2 (but not IL1β, IL10, or TNFα) in the patient group compared to HCs No group differences between fatigued and unfatigued patients for any measure No correlation between fatigue and any cytokines studied
Studies assessing peripheral blood-cell populations				
Yaldizli et al[57]	20 fatigued MS patients (13 RR, 6 SP, 1 PP, 13F/7M, untreated); 20 unfatigued MS patients (12 RR, 7 SP, 1PP, 12F/8M, untreated); 19 HCs; sex-matched groups	FSS	Lymphocyte subsets in peripheral blood mononuclear cell cultures (using flow cytometry); suppressive function of regulatory T cells (using antigen stimulation)	No difference in leukocyte and lymphocyte subsets, including regulatory T cells between fatigued and unfatigued MS patients The entire patient group tended to have lower suppressive regulatory T-cell activity compared to HCs, with no differences between fatigued and unfatigued patients Correlation NA
Pokryszko-Dragan et al[50]	20 fatigued MS patients; 20 unfatigued MS patients; cohort characteristics, 30 RR, 10 SP, 30F/10M, untreated; 25 HCs (sex NA)	MFIS, FSS	Percentage of IFNγ-positive $CD3^+CD4^+$ T lymphocytes (using flow cytometry)	No group difference with regard to percentage of IFNγ-positive $CD3^+CD4^+$ T lymphocytes No correlation between fatigue and percentage of IFNγ-positive $CD3^+CD4^+$ T lymphocytes
Studies assessing other peripheral markers				
Giovannoni et al[58]	38 MS patients (16 RR, 9 SP, 13 PP, 17F/21M, all untreated)	FQS, FSS	Serum CRP and sICAM-1 levels; urinary neopterin excretion (measured daily for 2 weeks)	Patients with raised serum CRP had higher FSS (but not FQS) scores than patients with normal CRP levels No correlation between fatigue (FSS, FQS) and any variable measured
Flachenecker et al[45]	26 fatigued MS patients; 11 unfatigued MS patients; cohort characteristics, 29 RR, 8 SP, 27F/10M, 54% treated	FSS	Serum ESR	No group differences in ESR values Correlation analysis NA
Adamczyk-Sowa et al[59]	102 MS patients (85 RR, 17 PP/SP, 67F/35M, 79.4% treated); 20 HCs (sex-matched)	MFIS	Plasma lipid hydroxyperoxides and homocysteine concentrations	Higher lipid-hydroxyperoxide levels among MS patients compared to HCs No correlation between fatigue and biochemical measures

Abbreviations: ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte-sedimentation rate; F, female; FSS, Fatigue Severity Scale; FQS, Fatigue Questionnaire Scale; HCs, healthy controls; M, male; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; NA, not available, NFI, Neurological Fatigue Index; PP, primary progressive; RR, relapsing–remitting; RT-PCR, real-time polymerase chain reaction; SP, secondary progressive.

Conclusion

This work has evaluated the contribution of central and peripheral inflammatory processes to MS fatigue. Among the selected studies dealing with central inflammatory and neuroendocrine processes, an inconsistency existed regarding the relationship between fatigue and orexin A system (present in one study,[14] absent in one[15]), the HPA axis (present in two studies,[30,34] absent in five studies[24–28]), and some CSF markers (present in one study assessing cytokines,[40] absent in one study assessing cellular, humoral, and other CSF parameters[39]). As for peripheral markers, although there was scarcity in the available data, serum proinflammatory cytokines (ie, IL6, TNFα, and IFNγ) seemed to be associated with MS fatigue. However, given the existence of some conflicting data in this domain, such an association merits further investigation. Finally, concerning T-cell population (ie, $CD3^+CD4^+$ T lymphocytes[50] or regulatory T cells[57]) or peripheral markers of inflammation (ie, CRP, erythrocyte-sedimentation rate, and soluble ICAM1),[45,58,59] few data were available, and these studies failed to find a link between MS fatigue and these measures. It is also worth noting that studies differed greatly in the clinical characteristics of their cohorts, especially concerning treatment profiles. The fact that MS treatment can modulate the inflammatory milieu[30,31] would stand behind the differences observed in study outcomes, with studies including untreated patients yielding positive results on the relationship between fatigue and inflammation.[14,40,47,50,56] Of note, several trials have documented differences in immune/inflammatory profiles between treated and naïve MS patients. That is to say, downregulation of proinflammatory cytokines was observed among MS patients treated with disease-modifying therapies such as IFNβ,[60–63] glatiramer acetate,[64] dimethyl fumarate,[65] fingolimod,[66] natalizumab,[67] and teriflunomide.[68]

Another issue to consider is the possible impact of MS treatments on fatigue per se. Few reports are available on this matter. In a cross-sectional study, higher fatigue rates were observed among MS patients treated with IFNβ or glatiramer acetate compared to age- and sex-matched patients receiving natalizumab.[69] In other works, rituximab seemed to induce fatigue in MS patients,[70] natalizumab appeared to improve fatigue,[71–74] and fingolimod did not seem to modify symptom severity.[75] Therefore, more research is needed to understand the potential effects of MS therapies on fatigue perception and cytokine profiles.

Another difference among studies concerned fatigue scales, which consisted of the FSS, MFIS, FSMC, visual analogue scale for fatigue, eleven-item Fatigue Scale, Neurological Fatigue Index – MS, self-reported checklist – individual strength (fatigue subscale), and Fatigue Questionnaire Scale. This adds more difficulty in comparing study outcomes. While some of these scales (eg, FSS) mainly address the physical component of fatigue, other scales (eg MFIS) reflect the physical, and, the cognitive and psychosocial dimensions of this symptom. This difference might not have had a large impact on group differences (fatigued versus unfatigued) but may have affected the correlation between fatigue severity and cytokine levels and could partly explain the discrepancies observed among studies.

Using different immunological techniques (ie, ELISA, RT-PCR, genetic analysis, flow cytometry, and electrochemiluminescence-based multiplex immunoassay) might have been behind interstudy differences, particularly those evaluating peripheral cytokines. Another point to consider is the relationship between sex, hormones, and immunodysregulation. Like many autoimmune diseases, MS is more prevalent in women than men, and hormones seem to exert an immunomodulatory effect and might influence damage repair in the CNS.[76] Interestingly, sex dysmorphism was observed with regard to cytokine production in MS patients.[77] In this context, it is of importance to note that although some studies controlled for sex effects by including sex-matched controls,[14,24,25,28,30,33,37,47,49,53,56,57,59] other studies enrolled cohorts predominantly[15,39,40,45] or exclusively[26] composed of female patients or did not provide sufficient details on the matter.[24,44,45,50,51] Therefore, future work could benefit from comparing fatigue and cytokine production between male and female patients.

Moreover, studying the impact of environmental, genetic, and epigenetic MS risk factors on MS fatigue would be of great interest. These factors include ultraviolet-radiation exposure, vitamin D intake, smoking, dietary, and exercise habits, and body-mass index.[78] It is also of importance to control for some confounders that occur frequently in MS and can impact MS fatigue. These include physical disability,[6] emotional symptoms,[79,80] and sleep disorders.[81] There is still a long way to go to define the utility and place of the aforementioned measures in clinical wards. Future large-scale studies are critically needed to conclude on this matter and would benefit from comparing the relationship between fatigue and inflammation in patients with different disease phenotypes (RR vs primary progressive vs secondary progressive) with and without disease-modifying drugs. From this perspective, applying different measures might help to decide on the optimal target to serve as an immunological surrogate of MS fatigue. Facing the subjective nature of fatigue scales, developing objective biological markers for fatigue, as those visited here, would be of great help.

Disclosure

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