

What's in a name? That which we call *Multiple Sclerosis Fatigue*

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Abstract: Very limited progress has been made to date in the treatment of debilitating Multiple Sclerosis (MS) daily onset symptoms. These daily symptoms include motor, sensory, and cognitive impairments as well as an overwhelming feeling of tiredness, often referred to as “MS fatigue.” Although widely cited as a main cause of inability to work and poor quality of life in patients with MS, daily onset MS-related tiredness continues to defy definition, and, consequently, measurement and treatment. Beginning with a historical overview of observations of daily onset MS-related tiredness, this Topical Review demonstrates how the misnomer “MS fatigue” has introduced ongoing misunderstanding for patients, investigators, clinicians, and therapists. Finally, combining current findings in clinical neuroscience with the striking set of long-standing commonalities present throughout the past 200 years of clinical observations, we underscore the immediate necessity for conceptual and applied change, to be initiated by the renaming of this distinct syndrome.

Keywords: Multiple sclerosis, fatigue, Uhthoff's phenomenon, daily onset MS symptomology, quality of life

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Introduction

Since Charcot's 1865 lectures presenting the first synthesized pathogenesis of “sclerose en plaques,”¹ the prognosis for multiple sclerosis patients has seen changes so significant that, today, even the course of progressive types of MS may be altered via disease-modifying pharmacological therapies. Juxtaposing this progress, however, is the 200-year stalemate in improving daily onset MS symptomology. Diagnosed in over 2.3 million people, MS is the most common debilitating disease in young adults worldwide. Over 80% of patients with MS report being affected by a daily onset overwhelming sense of tiredness (currently known as “MS fatigue”); further, in ambulatory MS patients, this sense of tiredness has been widely shown to be the most disabling MS symptom and to significantly reduce quality of life.² Consider the following two patient-written descriptions, the first written 193 years ago and the second posted in an online blog forum 4 years ago:

..my strength of legs had quite left me, and twice in one day I fell down upon the floor in attempting to go to the closed stool without assistance. . .I find that were I to

attempt to travel far of a day I should be rendered incapable of proceeding. . .I am able to ride for three hours at a time with pleasure, or to walk for two hours without being overfatigued: but I cannot run, or dance, and even going down stairs was unpleasant to me. (1827)³

..I'm referring to that period of time after I've tried to act normal, when I've.. went out and actually did some sort of activity like most people do. . . For me, the day after an activity is typically filled with fatigue, pain, and even confusion that necessitates me doing next to nothing. . . For me, it's primarily that because my legs will be weak, any attempt at standing and walking is tough. Just making it to the bathroom becomes an adventure! I would happily try to sleep the day away because I am overwhelmingly fatigued. (2016)⁴

Though centuries apart, these patients' descriptions of daily onset MS symptom severity are strikingly similar. Both writers use versions of the words “fatigue” and “sleep”; however, their lengthy descriptions attempting to convey their cognitive, physical, and functional states make it clear that there is no single word that fully represents their experience. This

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experience, for both patients, includes weakness in the legs, an inability to move, a seemingly unnameable tiredness, and the inability to override this state either by conscious choice (i.e. the desire to join others in a basic daily activity) or bodily necessity (i.e. the need to go to the toilet). In order to move forward in the process of officially (re)naming this MS-specific set of daily onset symptoms, we must first examine the history of how passive emergence of the terminology “MS fatigue” in the mid-1900s has come to direct and, incidentally, thwart advancement in this clinical area. Upon understanding that the nomenclature “fatigue” is a misnomer in this context, we present the most consistent phenomena of daily onset MS symptomatology; combining these with current neurological findings yields novel clinical terminology for consideration.

Historical overview of observation and designation

The first research observations of daily onset MS symptoms date from 1890, when Uthhoff,⁵ an ophthalmologist investigating optic nerve lesions, reported the onset of a plethora of visual impairments in a group of MS patients after the patients engaged in exercise. At this time, Uthhoff also noted post-exercise motor and sensory loss in a patient who stood near a hot stove. In 1929, Ombredane⁶ reported a striking “fatigability” upon extensive psychiatric evaluation of 60 patients with MS, writing “the main loss was represented by difficulty in initiating mental effort toward the solution of problems and in the fatigability of mental functions.”

When scientific discoveries of the early 20th century enabled the identification of myelin damage and inflammation of the central nervous system (CNS) in patients with MS, major clinical meetings and publications emerged, all demonstrating concerted effort to problematize the common set of debilitating symptoms seen in patients;^{7,8} at this time, the inexplicable transitory daily tiredness remained unnamed. Within the mid-20th century, however, “fatigue” emerged as the clinical term used to describe the tiredness/lassitude described by and observed in MS patients.

In the late-20th century, the work of Krupp et al.⁹ was instrumental in providing a new direction for researching “fatigue” in MS. Introduced in 1989, Krupp et al.’s¹⁰ nine-question self-report fatigue severity scale (FSS) asks patients to “Disagree” or “Agree” on a seven-point Likert-type scale to statements such as: “Fatigue interferes with my physical functioning.” Since the turn of the century, the FSS has been used as

the primary (or sole) measurement in studies examining a range of clinical interventions for MS-related tiredness, including pharmacological treatment, diet, education, and exercise.¹¹

There have been few attempts to create other measures of daily onset MS-related tiredness in the past thirty years, and all measures continue to be derived from the definition of “fatigue” and rely fully upon patients’ subjective responses. For example, the fatigue scale for motor and cognitive functions (FSMC)¹² and the modified fatigue impact scale (MFIS)¹³ are self-report questionnaires that assess the impact of fatigue on physical, cognitive, and psychosocial functioning in MS patients. In addition to the usual self-report aspects that challenge validity, specific problems arise when asking patients with MS to interpret and self-report on physiological phenomena. That is, MS-specific neurological damage occurs in both efferent and afferent fibers in the CNS, impacting not only motor output but also sensory input. Impairment to patients’ sensory input may limit both understanding and self-realization of physiological phenomena—especially those which do not pre-date their MS onset—therefore yielding additional problems of data validity in self-report questionnaires.

The problems of inaccurate terminology

The much-identified impasse in defining daily onset MS-related tiredness appears—in the absence of an accurate label—to derive from the appropriation of the inaccurate nomenclature “fatigue.” In both current medical and colloquial usage, the word *fatigue* maintains much of the original meaningfulness of its French (15c.) and Latin roots; that is, tiredness which occurs after engaging in some type of activity (Fr.: *fatigue*, “that which causes weariness” and *fatiguer*, “to tire”; Latin: *fatigare* “to weary, to tire out”). Clinical specifications often draw upon this fatigue nomenclature, suggesting a causal link between activity type and fatigue type (e.g. motor fatigue is caused by excessive physical activity and cognitive/mental fatigue is caused by undertaking an excessive amount of cognitively based tasks). Along these lines, recent review articles highlight the challenges of definition and assessment of “MS fatigue,” proposing new taxonomies and frameworks for diagnosing and treating “MS fatigue,”¹⁴ and addressing the difficulty in distinguishing motor fatigue, tiredness, cognitive fatigue, central fatigue, performance fatigability and perceived fatigability, and the interactions thereof.¹⁵ However, in the case of daily onset MS symptoms, there are ample data (indeed, dating back to the early 1800s) showing that the type of activity in which a

patient engages does not necessarily reflect the type of impairment a patient experiences (e.g. cognitive activity may be followed by difficulty walking and socioemotional engagement may be followed by feelings of excessive tiredness).^{3,4,16}

Confusion with regards to definition and measurement of “MS fatigue” is also represented in the most recent therapeutic research in this area—that is, investigating exercise as an intervention strategy—as the object of investigation, itself, delimits the potential of recruiting a random sample.¹⁵ Indeed, in 2013—over 20 years after, herself, creating the FSS—Kluger *et al.*¹⁷ summarize the stagnation in research on daily onset MS tiredness: “Progress continues to be hampered by issues related to terminology and assessment.”

In the clinical context, Paul and Veauthier¹⁸ summarize the gap between MS patient and doctor when, specifically, “MS fatigue” is reported: “To improve the situation for affected patients, the nihilistic attitude that they face when reporting their symptoms to their treating neurologist must be challenged.” Reflecting this communicative breakdown, MS patients often describe their daily onset tiredness as “it does not feel like ordinary fatigue.”¹⁹ Misunderstanding of their own symptomatology has been shown to have negative effects on MS patients’ psychological state; furthermore, the inability to express their experience to family, friends, caregivers, clinicians, and other medical personnel has been shown to result in social isolation.²⁰

By preventing creation of objective measurement strategies, misunderstanding over what constitutes daily onset MS tiredness stymies all attempts at clinical trials of potential therapies, despite ample reports from clinicians and MS patients that the medications amantadine hydrochloride and modafinil as well as the vitamin-D supplement 1-hydroxycholecalciferol and the disease-modifying agent natalizumab have positive effects on daily onset tiredness.^{21,22} One of the first to directly note the significant difference between “fatigue” in chronic fatigue syndrome (CFS) and “fatigue” in systemic inflammatory diseases, Giovannoni explicates: “Uncertainties over the definition, pathogenesis, and measurement of MS-related fatigue are clearly hampering the testing of specific therapeutic anti-fatigue strategies.”²³ For example, one of the few pharmaceutical intervention trials investigating “MS fatigue” as the dependent variable reports positive results for modafinil, but the researchers caution: “..treatments cannot be appropriately evaluated until the clinically relevant variable being studied has been clearly defined.”²⁴ In turn, this constrains the European Medicines Agency (EMA) and

U.S. Food and Drug Administration (FDA) from assigning an indication for treatment of daily onset MS tiredness.

Renaming MS daily onset symptomology

Changing the name of a clinical diagnostic term, though not a novel idea, is not a straightforward process.^{25,26} Greater understanding of the neurological processes underlying daily onset MS tiredness as well as an official clinical description of the symptom and potentially co-occurring symptoms would aide in the process of (re)naming “MS fatigue”; however, as demonstrated by both the history of this symptom as well as the unequivocal conclusions of researchers in the field,^{17,22–24} research efforts are ineffectual when the object of investigation remains undefined (even though research is required to further define the object). In an effort to break this cycle, we conclude this Topical Review by aggregating the phenomena occurring with indisputable consistency throughout clinical observation and patient self-description of daily onset MS symptomology and, viewing these phenomena in light of current disease-specific neurological evidence,^{3–6,20} offer potential names in accordance with the most recent World Health Organization (WHO) best naming practices.²⁷

There are at least five major phenomena appearing consistently throughout over 200 years of clinical observation, research, and unsolicited patient description:

1. A transitory state of limited predictability: Unlike an MS attack, where medical treatment is required to reduce inflammation and avoid further permanent myelin loss, daily onset MS tiredness is a *state* that appears and dissipates on a daily basis. Consistently reported is that this state is both predictable (e.g. after physical, cognitive, and/or emotional engagement) and unpredictable (i.e. without currently identifiable causal link).²⁸ Per self-report questionnaire, patients with MS—in contrast to healthy controls—report that *fatigue* “prevents sustained physical functioning, comes on easily, interferes with physical functioning, and causes frequent problems.”⁹
2. A group of co-occurring symptoms: The state of daily onset MS tiredness is not limited to feelings of lassitude; patient descriptions and clinical observations note co-occurring motor (e.g. muscle weakness, including movement, ptosis, dysarthria, and reduced grip), sensory (e.g. reduced visual acuity, amblyopia, and visual field defects), and cognitive (e.g. impairments in working memory, vigilance, alertness, visuospatial processing,

- language production, and language processing) signs and symptoms.³⁻⁶
3. Undetermined by type of preceding activity: The type of activity that precedes daily onset MS symptomatology does not determine the type of impairment;^{3-6,29} for example, after engaging in cognitive tasks, an MS patient may experience transitory (or temporarily increased) motor and sensory impairments. In addition, patient descriptions overwhelmingly indicate within-patient consistency in the type of daily onset symptoms as well as high between-patient variability in symptom severity.³⁰ Investigation of potential correlations of within-patient symptoms with patients' lesion locations therefore arises as one future line of inquiry.
 4. Triggered by heat: Another hallmark of daily onset MS symptoms is heat responsiveness. Although motor and sensory heating reactions in patients with MS received much investigative attention between the 1920s and 1950s, it was not until the 1970s that Uhthoff's Phenomenon (1890) was understood as heat-induced (rather than exercise-induced) visual changes in patients with MS.^{5,31} Under experimental conditions in the mid-1900s, observed reactions to heat in MS patients included motor weakness, reduced grip, dysarthria, ptosis, incontinence, visual acuity, amblyopia, and visual field defects; an increased deep core body temperature accompanied the onset of these symptoms in some, but not all, MS patients.³¹ In comparison to healthy controls and patients with systemic lupus erythematosus, patients with MS self-report on questionnaires: (a) significantly greater exacerbation of "fatigue" in response to heat and (b) improvement of "fatigue" in response to cool temperatures.⁹
 5. Reflected in gait: Many MS patients describe increased mobility impairment accompanying daily onset MS tiredness.^{3-5,31} Focusing on *motor fatigue*, Sehle and colleagues^{37,38} show a significant correlation between subject-reported fatigue (while walking on a treadmill) and changes in gait. The complexity of investigating self-report measures and walking task performance is further discussed in Dalgas et al.³⁹ while reporting significant correlations between walking ability and scores on the self-report MFIS.

More recently, increased body temperature and brain temperature have been shown to correlate with recurring–remitting multiple sclerosis (RRMS) patients' reports of "fatigue-like" symptoms on the FSS.^{32,33} This aligns with studies in neurotypical persons showing that fluctuations from homeostatic brain temperature can result in myriad temporary and permanent impairments in cellular signaling.³⁴ Intracerebral processes produce immense amounts of heat, and—unlike body temperature—thermal regulation of the brain is not well understood.³⁵ Confirming that myelin plays an essential role in successful signal conduction during thermal stress, Davis, et al.³⁶ recorded a significant reduction in signal velocity along a major optic tract (i.e. medial longitudinal fasciculus) during whole-body temperature increase for MS patients with lesions to this tract (versus MS patients without optic lesions and neurotypicals).

Beginning the renaming discussion—Proposed terminology

Guided by the WHO²⁷ and the International Classification of Diseases (ICD-11) Alpha Content Model Reference Guide,⁴⁰ we propose the following novel terms as potential options for daily onset MS symptomatology (including tiredness): central neurophysiological dys-/de-innervation (NPD), transitory multi-focal CNS denervation (TMD-CNS), or cyclic lesion inflammation (CLI) in MS.

Conclusion

Although the prognosis for MS disease trajectory has improved greatly over the past 200 years, the prognosis for living with daily onset MS symptoms has not. Maintenance of the inappropriate label "MS fatigue" not only actively stymies clinical research but also negatively impacts patient quality of life. Here, we have provided the foundation for change by examining evidence of this impasse and aggregating the long-observed phenomena of daily onset MS tiredness. The concerted efforts of an MS initiative (e.g. ECTRIMS, ACTRIMS, RIMS, and/or the MS societies of several nations) will be needed to commission the establishment of a renaming committee and to introduce the committee's report to the WHO.

Authors' Contributions

A.L.H. was involved in conceptualization, original terminology, formal literature analysis, writing—review and editing, writing—original draft, funding acquisition, and resources; H.G. and H.L. were involved in writing—review and editing and supervision; H.L. was involved in administration and resources.

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