Toward biologically meaningful categories of MS-related fatigue

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How do you put out a fire? This first depends on the type of fire one seeks to extinguish. Water is an effective strategy when paper or wood is burning, but splashing water on a grease or electrical fire only exacerbates the situation. We use the word “fire” to describe each instance, and the term conveys something intuitive and essential, but one must identify the specific type of fire in order to choose the right method of extinguishing it.1

Clinicians and researchers in the field of multiple sclerosis (MS) have long recognized fatigue as a prevalent, debilitating, and often refractory symptom of this disease.2 Like fire, the concept of “fatigue” is intuitively appealing and broadly inclusive, but requires further differentiation into distinct types warranting specific treatment approaches. Despite its pervasiveness, fatigue confounds our fundamental approaches to categorization in MS. MS fatigue is neither the specific consequence of an MS relapse nor is it sufficient to be evidence of MS progression. It does not oblige our inclination to localize and is not clearly referable to a specific lesion or lesions. We do not know with certainty the extent to which MS fatigue is due to inflammation or neurodegeneration, or perhaps to something else entirely. The word “fatigue” itself may serve as a barrier to understanding and treating this symptom complex, as the term gives the false impression that MS fatigue is a specific and singular pathophysiologic entity.

In this issue of *Multiple Sclerosis Journal*, Palotai and colleagues take a step toward parsing fatigue into distinct phenomenological categories.3 They report the results of a study identifying temporal patterns of fatigue impact in an effort to address the way the dynamic nature of this symptom precludes the identification of reproducible neuroimaging correlates. Drawing from the CLIMB cohort, they stratify patients based on Modified Fatigue Impact Scale (MFIS) cutoffs into groups they define as sustained fatigue (SF), 1-time fatigue, reversible fatigue (RF), and never fatigued (NF). They then evaluated neuroimaging associations using brain parenchymal fraction and total T2 lesion volume and found that patients grouped as both “SF” and “RF” had a higher T2 lesion volume, though this association was stronger for the SF group. The central observation is that repeated measures of fatigue’s impact may offer more robust associations with neuroimaging findings than have been previously observed.

While this result—that repeated measures of fatigue’s impact may be an indicator of the severity or persistence of fatigue-related symptoms—may support the use of longitudinal assessments in future fatigue research, this study only scratches the surface of the need to truly phenotype fatigue to inform the development of targeted treatments. That the authors selected patients with at least five separate fatigue assessments in order to categorize fatigue in this existing dataset may have introduced selection bias, and this approach would also limit the applicability of this categorization scheme in clinical practice where such numerous longitudinal fatigue assessments may not be available. Furthermore, it is important to note that the MFIS is designed to assess fatigue’s impact over the past 4 weeks. Dividing MS patients into groups of “RF” or “SF” on the basis of changes in these scores over several years may not provide sufficiently granular information about fatigue phenomenology or severity. There is great heterogeneity to the fatigue patterns shown for individual patients, and yet perhaps the most important features—fluctuations on a day-to-day basis, or time of day, or relationships with sleep disturbance or other factors—cannot be elucidated.

The MFIS utilized in this study (and many other studies) may be an apt tool for examining possible consequences of fatigue; however, like all self-report measures, it is flawed in its inability to provide information regarding short-term temporal fluctuations, as...
well as in its susceptibility to recall bias. Also, referring back to our analogy, examining possible consequences of a fire does not reveal its root cause or categories. The MFIS is also inadequate by design to be a tool to generate specific fatigue phenotypes. Although the impact of fatigue may be somewhat related to fatigue severity, it is also influenced by a host of factors not related to the underlying mechanisms of fatigue: how well someone copes with and adapts to their fatigue, their lifestyle, their vocational and personal obligations, their resilience, and so on. This poses a problem when looking for correlations with structural brain changes, since the impact of fatigue comprises both fatigue severity and the person’s compensatory ability, and magnetic resonance imaging (MRI) metrics which may contribute to these divergent aspects cannot be individuated.

The MFIS examines multidimensional components of the consequences of fatigue on a 0–4 scale and groups these into physical, cognitive, and psychosocial sub-scales. The physical subscale includes items such as “I have been clumsy and uncoordinated” and “my muscles have felt weak.” Although motor fatigue has been demonstrated in MS, the physical component of MFIS may conflate the level of MS-related disability with that of the impact of fatigue specifically. Similarly, the cognitive subscale of the MFIS includes “I have had difficulty paying attention for long periods of time” as well as “I have been forgetful” and “My thinking has been slowed down.” It may be the case that attention, memory, and processing speed are affected differently by fatigue. The MFIS attempts to quantify the impact of fatigue without specifically asking about the presence or severity of fatigue itself. The MFIS does however begin with the prompt “because of my fatigue . . .,” but this puts the onus on the respondent to differentiate the degree to which any physical or cognitive symptom is the direct consequence of fatigue versus another etiology.

MRI is an invaluable tool in MS research and clinical practice, but the use of global metrics of cerebral atrophy and T2 lesion volume may be too non-specific to identify precise mechanisms of fatigue, and this approach is based on an underlying assumption that fatigue can be explained by structural brain changes detectable by MRI. Further research is needed to tease out the extent to which MS fatigue is a consequence of reduced conduction through demyelinated tracts and resultant changes in network function (as shown by functional magnetic resonance imaging (fMRI) studies); a failure of intracellular energy metabolism; a consequence of systemic inflammation; or other as yet unrecognized mechanisms that manifest as this most common, and most protean of MS symptoms. The underlying etiology of fatigue likely differs across patients. As such, no single mechanism of action of an investigational therapy for fatigue can be expected to address such diverse potential underlying causes. Moreover, like throwing water on a grease fire, certain treatment approaches (e.g. stimulants) may actually exacerbate some fatigue phenotypes (e.g. fatigue secondary to sleep disturbance). Clinical trials for fatigue agents will need to be designed to include and address specific biologically distinct fatigue phenotypes, lest the impact of a therapeutic agent be washed out by overly broad inclusion criteria. Moving away from a singular concept of “MS fatigue” may be an important next step in this direction.

Declaration of Conflicting Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.C.K.: Consulting or advisory work with Biogen, EMD Serono, Genentech, Genzyme, Mallinckrodt, MedDay, Novartis, Teva, and TG Therapeutics, and non-promotional speaking with Biogen, EMD Serono, Genentech, and Novartis. J.F.S.: Consulting or advisory work with Biogen and Genzyme.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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