Fatigue is one of the most common and disabling symptoms of multiple sclerosis (MS). Not only does fatigue affect up to 87% of patients with MS but as many as 40% of patients with MS regard fatigue to be their most disabling symptom. Although several therapies have shown some promise in the treatment of fatigue in patients with MS, the lack of a truly effective treatment for this symptom may be due to the underlying pathophysiology for MS fatigue still being debated.

Many factors can contribute to fatigue experienced by patients with MS. In addition to the underlying disease process, factors such as depression, deconditioning, hypothyroidism, anemia, and medications can all contribute to fatigue in patients with MS, making the study of this phenomenon quite complex. Although fatigue in patients with MS can be worsened owing to depression and poor sleep habits, there are several clinical clues to suggest that MS fatigue is related to the underlying pathophysiology of the disease. First, similar to the Uthoff phenomenon, MS fatigue is strongly temperature dependent. It often occurs as an episode, similar to other MS exacerbations, and may even precede typical MS relapses. While most neurologists experienced in the management of patients with MS recognize fatigue as a major component of the disease, many other physicians often dismiss complaints of fatigue. Many psychological symptoms as well as physiological complaints are often described by the patient in terms of fatigue. Because complaints of fatigue are often difficult to define and many patients with MS describe a lack of physical energy, it has been difficult to deal with MS fatigue in terms of its underlying cause.

In thinking about central nervous system conduction in patients with MS, clearly there is clinical evidence to suggest upper motor neuron dysfunction (eg, hyperactive reflexes and impaired movement). Measurement of central motor conduction time is longer in patients with MS, which is not surprising considering the utility of evoked potentials in the diagnosis of MS. Thus, clinical and electrophysiological evidence of demyelination seemed like a reasonable explanation for the development of frequency-dependent conduction block and subsequent fatigue. This could also provide a physiological basis for the heat-sensitive fatigue experienced by many patients with MS.

Interestingly, when transcranial magnetic stimulation has been used to examine the primary motor pathways of a limb undergoing fatigue, there was no difference in response for patients with MS vs control subjects. Thus, it appears that there is not always an abnormality of intracortical excitability to explain the fatigue experienced by patients with MS. However, one could consider that the methodology was examining large-diameter, fast-conducting fibers, which might not necessarily be the same fibers activating pathways in which the patient is experiencing fatigue. Thus, while patients with MS are thought to experience central fatigue, there has been little evidence to suggest that this fatigue is the result of increased central motor dysfunction due to frequency-dependent conduction block.

Another possibility for the fatigue in patients with MS was that inflammatory mediators being produced in the central nervous system as part of the inflammatory process were recognized by receptors that interpreted the inflammatory stimuli as fatigue. Cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF) and IL-6 are known to have widespread systemic effects and when administered to humans are associated with the feeling of fatigue. In patients with rheumatoid arthritis, active inflammation has been shown to correlate with fatigue. Because these cytokines are also produced as part of the inflammatory process in MS, they would play a role in the fatigue experienced by some patients with MS, particularly when in association with an acute exacerbation. However, a study that tried to correlate MS fatigue with inflammatory activity such as serum C-reactive protein or gadolinium-enhancing lesions on magnetic resonance images had little success in demonstrating an association. Interestingly, this study did show that patients with primary progressive MS have lower fatigue scores as assessed by the Fatigue Severity Scale, suggesting that less inflammation in this subgroup of patients may be playing a role in their reduced fatigue.

In this issue, Tartaglia et al have used magnetic resonance imaging to examine the relationship between axo-
nal injury and fatigue in patients with MS. According to their study, there does not appear to be any association between fatigue and levels of clinical disability. Lesion load using conventional magnetic resonance imaging measures also does not seem to correlate with levels of fatigue experienced by patients with MS. This would suggest that the level of fatigue in MS is not due to disability or disease burden.

Using proton magnetic resonance spectroscopy, the authors evaluated the relationship between the N-acetylaspartate creatine ratio and MS fatigue. Consistent with other studies, Kurtzke Expanded Disability Status Scale score, T2 lesion volume, and other variables did not correlate with MS fatigue. However, they did observe a statistically significant relationship between the Fatigue Severity Scale score and the N-acetylaspartate-creatine ratio. The implication of this finding is that rather than trying to explain fatigue solely on the basis of conduction block or inflammatory mediators, axonal injury may be an important contributor to the development of MS fatigue. This measurement of axonal injury might explain the increased complexity in cortical activity measured in patients with MS executing a voluntary movement and also experiencing fatigue.

Not surprisingly, the same arguments that are now being made for the early treatment of MS can now be made as the best strategy to reduce MS-related fatigue. Since neuronal injury can start at the earliest stages of MS, this can also be the mechanism for the development of fatigue in some patients with MS at this stage of the disease.

It is also quite likely that all of the mechanisms discussed earlier may contribute to MS-related fatigue and that their relative contribution to the overall clinical picture varies in each individual patient. However, recognizing that diffuse axonal injury may also contribute to this very common and significant symptom in MS does provide new insight into the pathophysiology of this very complex disorder. Hopefully, as implied by Tartaglia et al, neuroprotective strategies will not only benefit patients with MS in terms of the overall pathologic process but may also provide significant benefit to this troubling symptom of fatigue.

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