What Is Multiple Sclerosis-Related Fatigue?

As the above case shows, fatigue can be a difficult concept to communicate from both the provider’s and the patient’s standpoint.
Because “fatigue” is a common lay term, there can be a wide variation in the way that patients understand it, as well as in the way they understand related terms such as depression, weakness, deconditioning, tiredness, pain, and motivation. As diagnosing fatigue relies heavily on patient self-reporting, providers’ recognition of fatigue can be limited by patients’ inability to describe their symptoms accurately. At the same time, providers’ own poor understanding of fatigue can contribute to a failure to diagnose fatigue. Providers are generally not trained to diagnose or even look for fatigue, and they usually underestimate its importance.

Because the word “fatigue” is laden with ambiguity, when patients come to physicians with complaints of fatigue, it is essential for physicians to determine accurately what patients mean by this complaint. It is equally important for providers to recognize when fatigue is present in cases where patients do not specifically complain of the symptom. Fatigue as a symptom incorporates a number of different concepts that have been applied and studied in a range of contexts. Some of the more common associations with the word fatigue include:

- Physical tiredness;
- Mental tiredness;
- Lack of motivation;
- Difficulty concentrating;
- Inability to complete tasks;
- Feelings of depression;
- Feelings of anxiety;
- Failure to feel refreshed after sleep;
- Overall muscle weakness;
- Weakness in certain muscle groups;
- Poor performance at home or work;
- Performance that fails to meet prior expectations;
- Pain or physical discomfort; and
- Sleep difficulties.

One of the most challenging issues in defining fatigue is that there are few, if any, objective criteria that can aid physicians in observing fatigue for themselves. Other than certain cases of muscle weakness, which can be quantified through neuromuscular testing, the definition of fatigue relies heavily on the patient’s experience and the information that he or she can provide. Therefore, providers must always be respectful of patients’ descriptions of their fatigue.
Insufficient work has been performed in the area of defining fatigue. This is a little disappointing and is also surprising, given both the pervasiveness of fatigue in the MS population and its effects on daily functioning. Multiple sclerosis-related fatigue has been shown to be both highly prevalent and long lasting. More than 40% of 85 MS patients in one study reported feeling fatigued on every day of the month (Figure 1).7

**Defining MS-Related Fatigue**

A variety of investigations have ascribed different definitions to MS-related fatigue, including a feeling of tiredness that is out of proportion to the level of exertion, a feeling of weakness, the lack of capacity to generate sufficient muscle force,1,2 or the lack of ability to sustain mental performance.8 In 1998, the Multiple Sclerosis Council for Clinical Practice Guidelines published a consensus definition of fatigue. The Council, which was composed of a wide variety of MS providers, including neurologists, psychologists, rehabilitation therapists, and MS nurses, defined fatigue as:

*A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.*9
The Council cited a number of advantages in this definition of fatigue, including the fact that it is a generalized definition that is easily understandable by MS patients as well as providers. Observing that the severity of fatigue may wax or wane depending on circumstances (e.g., physical exertion, the presence of infection, or hot weather), the Council separated chronic fatigue from acute fatigue. Under the Council’s definition, chronic persistent fatigue was defined as:

- Fatigue that is present for any amount of time on 50% of the days for more than 6 weeks.
- Fatigue that limits functional activities or quality of life.

Acute fatigue was defined as:

- New or a significant increase in feelings of fatigue in the previous 6 weeks.
- Fatigue that limits functional activities or quality of life.

In addition to distinguishing between acute and chronic fatigue, providers should distinguish between fatigue that results from other MS symptoms (e.g., poor sleep, pain) and fatigue that is primarily due to the MS itself. Not infrequently, fatigue has multiple causes in the same individual. Strong lines of evidence suggest that fatigue is a primary disorder, directly related to the underlying pathophysiologic processes of MS itself, including immune dysregulation, inflammation, neuronal dysfunction, and demyelination. Factors that support the concept of fatigue as an inherent component of MS include: 1) the marked association between MS fatigue and heat; 2) the fact that fatigue may precede disease relapses or be a prominent symptom within a relapse; and 3) the observation that fatigue may be the first presenting symptom of MS.10 When fatigue occurs secondary to other MS-related factors, frequent culprits are deconditioning, pain, poor sleep, and agents used to treat other symptoms of MS (e.g., muscle relaxants, anticonvulsants, and interferon betas).

It is also important for the provider to distinguish between “normal” and “abnormal” fatigue. Everyone feels fatigued at some point, and the problem is not necessarily related to MS. As many as 23% of the general population have experienced persistent fatigue at some point.11 It is likely that fatigue appears along a continuum, in much the same way that blood pressure does, with some patients experiencing low levels of fatigue, some extremely high levels, and the remainder feeling “normal” levels (Figure 2).12 The challenge to providers, therefore, is to determine not only when fatigue is present, but when it is pathologic. It has been suggested...
that fatigue in normal individuals can be distinguished from MS-related fatigue based on the fact that MS-related fatigue:

- Worsens with heat;
- Prevents sustained physical activity;
- Interferes with physical functioning;
- Interferes with role performance;
- Emerges easily;
- Causes frequent problems; and
- Interferes with meeting one’s responsibilities.\(^{10}\)

### Epidemiology and Impact of Fatigue in the MS Population

A variety of surveys and clinical studies have shown that fatigue is a major symptom, and highly prevalent in a number of disorders, including chronic fatigue syndrome, systemic lupus erythematosus, epilepsy, Parkinson’s disease, and cancer. Much of what we have learned about fatigue over the past 2 decades, however, is attributable to work in the field of MS.\(^{13}\) Fatigue in MS was not readily recognized or discussed before the early 1980s. In 1984, a seminal study on MS symptoms in 656 MS patients

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showed that fatigue was the single most commonly reported symptom, cited by 78% of patients.\textsuperscript{14} The prevalence of fatigue was higher than “typical” MS symptoms such as difficulty in balance, tremor, gait disturbances, weakness, tingling/numbness, and bowel/bladder difficulties (Table 1).\textsuperscript{14} The finding at this time was relatively novel; as based on the prior literature, the researchers did not expect fatigue to be a frequent symptom. Twenty-two percent of the patients reported that fatigue caused them to reduce their level of physical activity, 14% said it required them to have more rest, and 10% said that it forced them to quit work.\textsuperscript{14}

Since that time, a number of studies have confirmed and expanded on the epidemiology of fatigue in the MS population and its potential associations with demographic characteristics, disease subtype, level of disability, emotional status, and other symptoms of MS. Fatigue has consistently been ranked among the most prevalent and disabling MS symptoms. In a 1997 United Kingdom MS Society survey of 233 persons with MS, 86% of patients reported symptoms of fatigue, more than balance problems (73%), muscle weakness (69%), and bladder/bowel problems

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No ADL Difficulty (%)</th>
<th>Producing ADL Difficulty (%)</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>56</td>
</tr>
<tr>
<td>Balance problems</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>Weakness/paralysis</td>
<td>18</td>
<td>45</td>
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<tr>
<td>Numbness/tingling/other sensory</td>
<td>39</td>
<td>24</td>
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<tr>
<td>disturbance</td>
<td></td>
<td></td>
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<tr>
<td>Bladder problems</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>Increased muscle tension (spasticity)</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Bowel problems</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Difficulty remembering</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Depression</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Pain</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Laugh or cry easily (emotional lability)</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Double or blurred vision, partial or</td>
<td>14</td>
<td>16</td>
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<tr>
<td>complete blindness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaking tremor</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Speech and/or communication difficulties</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Difficulty solving problems</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

ADL = activities of daily living.

Two thirds of MS patients have rated fatigue as one of the three worst symptoms of their disease. It commonly occurs as the principal presenting symptom of the disease.

Multiple sclerosis-related fatigue has also been contrasted with the fatigue experienced by either healthy adults or individuals with other medical disorders. The fatigue associated with MS is unique from that of healthy individuals in its disabling effect on activities of daily living, including carrying out physical activities and meeting one’s responsibilities, as well as in its severity and frequency. Qualitatively, MS-related fatigue is different from the fatigue associated with other medical conditions because of its aggravation by heat.

Part of the difficulty in recognizing fatigue in the MS patient is the fact that it does not correlate well with demographic characteristics, the clinical form of MS, or other MS signs and symptoms. For example, fatigue has not been found to correlate closely with either age or Expanded Disability Status Scale (EDSS) score, and does not correlate with the level of disease activity as found on MRI. In addition, there does not appear to be an association between fatigue and gender in MS patients. The lack of association with these factors makes fatigue difficult to predict.

Nevertheless, fatigue has been found to be associated with perceived general and mental health, and to have a substantial impact on activities. For example, fatigue has been shown to be a frequent cause of unemployment in MS patients. It also limits social relationships and the ability to engage in self-care activities, and generally limits the patient’s ability to perform tasks requiring physical effort. Fatigue may worsen some of the other symptoms of MS. Some data have suggested that fatigue may be associated with older age and progressive forms of MS, as opposed to relapsing forms. In one epidemiologic study of 368 individuals with MS from Norway, fatigue showed a significant inverse correlation with years of education and, for patients with progressive MS, positively correlated with age and disease duration. Sleep disorders also are associated with fatigue. Fatigue has been shown to be associated with overall decrements in quality of life on instruments that include assessments of health, job activity, housing, finances, and family and friendships. The patient’s sense of control over his or her symptoms also has been shown to be significantly associated with fatigue (Figure 3).

One of the most consistent associations that has been observed is the association between fatigue and affective disorders, including depression and anxiety. Studies have shown that anxiety and depression both
Conclusions

The symptom of fatigue in the MS patient is one that incorporates a number of concepts, including weakness, tiredness, lack of motivation, affective disorders, pain, and sleepiness. Providers must be aware of all of these facets of fatigue, and any of these complaints should raise the index of
suspicion for MS-related fatigue. Publication of a consensus definition of MS-related fatigue has increased focus on this symptom. Because of the high prevalence of fatigue in MS patients, the presence of fatigue should be suspected unless and until it is specifically ruled out. Fatigue in MS is poorly related to disease type, disability level, gender, age, and imaging findings on MRI. Therefore, the provider must rely heavily on the patient's self-report in the diagnosis.

References