Fatigue Can Be Objectively Measured in Multiple Sclerosis

Multipl Sklerozda Yorgunluk Objektif Olarak Ölçülebilir

Haluk GÜMÜŞ

Department of Neurology, Selçuk University School of Medicine, Konya, Turkey

ABSTRACT

Multiple Sclerosis (MS), is a chronic inflammatory demyelinating disorder affecting the white matter in the central nervous system (CNS), seen usually among young adults (20–40 years of age). Fatigue is an important symptom that affects a large portion of the patient population. The reason for fatigue seen in MS patients is still not well-known. Fatigue is a subjective and non-specific symptom; therefore, it is quite difficult to

evaluate fatigue. This symptom has been reported in 75–87% of patients with multiple sclerosis (MS) and two-thirds of these patients indicated fatigue as one of the worst three common symptoms they experienced. In this review, objective measurement methods of fatigue which is a subjective complaint will be discussed.

Keywords: Multiple sclerosis, fatigue, measurement

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INTRODUCTION

Multiple sclerosis (MS) is a progressive and disabling neurologic disease resulting from immune-mediated damage in the central nervous system (CNS). It differs among people in its clinical manifestations (e.g. motor, sensory visual and autonomic systems) (1).

Multiple sclerosis (MS) is a disease with many signs and symptoms, including tremor, spasticity, weakness, vision problems, and difficulties in walking. However, individuals with MS might be surprised to know that the most common symptom of MS is fatigue. Often described as an overwhelming sense of physical or mental tiredness, fatigue has a major impact on quality of life, interfering with activities of daily living, exercise, and the ability to cope with other MS symptoms. According to some studies, over 90% of individuals with MS suffer from fatigue, and over three quarters consider it to be one of their three most troublesome symptoms (2).

Fatigue is defined as a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities. (3) The definitive cause of fatigue in MS is currently unknown, however, it is postulated that MS-related fatigue may result from centrally mediated processes characterized by MS itself, such as demyelination and axonal loss in the CNS or immune actions (Primary fatigue) or from MS-related complications (trigeminal neuralgia, spasms, psychological issues, etc.), musculo-skeletal problems (pain, posture, gait anomalies, etc.), sleep problems and medications (Secondary fatigue) (4). Many studies attempted to explain fatigue from different pathophysiological mechanisms.

Most of these studies concentrated on the disease mechanisms that could explain primary fatigue. Different devices or techniques, such as magnetic resonance imaging (MRI), functional MRI, positron emission tomography and electrophysiological measurements, combined with self-reported fatigue questionnaires, have been used to study the mechanism of primary fatigue. Various anatomical brain areas have been found having associations with MS fatigue. Comparably fewer studies explained fatigue from another perspective. They focused on secondary fatigue, and tried to find fatigue contributors besides the disease mechanisms. It has been proven that sleep disorder, severe pain, use of medication, and some psychological factors such as depression, anxiety and stress may contribute to fatigue in MS. However, whether other primary or secondary factors are related to MS fatigue is still unclear, and unexplained fatigue is very often simply considered as primary fatigue (5).

In general, fatigue is a poorly defined construct and hence difficult to measure. The MS International Federation recognized two types of fatigue in pwMS, namely: physical or motor fatigue (muscle weakness, slurred speech, unable to perform daily tasks, etc.) and cognitive fatigue (deterioration of cognitive function such as, reduced reaction time response, alertness during the day, difficulty in thinking, concentration, memory, recall, word finding, etc.). Further, fatigue can be acute (newly occurring in the past 6 weeks) or chronic (lasting longer than 6 weeks) (6, 7). In contrast to fatigue in normal people, MS-related fatigue has distinctive characteristics, including: occurs on a daily basis; worse as day progresses; aggravated by heat and humidity; comes on more easily and suddenly; more severe than normal fatigue; and more likely to interfere with role performance and physical functioning. Clinically, fatigue may manifest as exhaustion, lack of energy, increased somnolence, or worsening of MS

symptoms and activity, and heat typically can exacerbate symptoms. The mechanism for fatigue in MS is not known and several different factors are believed to contribute to fatigue (8).

Although the negative impact of fatigue on individuals with MS is clear, the underlying causes of fatigue have not yet been fully defined. Many factors may underlie the occurrence of MS-related fatigue, including factors related to the nervous system damage caused by MS and factors related to the immune or endocrine systems. There are also many conditions that contribute to fatigue but may not be direct causes. These contributing factors include a lack of physical conditioning and the medications used to treat MS symptoms such as stiffness, sleep disorders, and psychological factors (9).

Part of what makes MS-related fatigue so difficult to identify and define is that it does not appear to be associated with many of the other symptoms or characteristics of MS. Studies have shown that the presence or severity of MS fatigue is not related to the individual's gender. It is also not closely related to age or level of neurologic impairment: many individuals with MS who have low levels of impairment on the Expanded Disability Status Scale (EDSS, the most common way of measuring neurologic impairment) have similar levels of fatigue to those with high EDSS scores. Fatigue is not related to how long a person has had MS, as newly diagnosed people with MS can have fatigue as severe as those who have had MS for many years (10).

Several factors are believed to be related to primary MS fatigue (so-named because these factors are directly related to the underlying disease process of MS itself). One of the most common theories is that fatigue is related to the damage that occurs to the CNS in MS. MS is characterized by damage to the nervous system related to inflammation and demyelination (the destruction of the fatty sheaths that surround nerves). Many of the nerve cells themselves are also destroyed. The damage to the nerves interferes with conduction of the electrical signals that control movement and cognitive functioning (3).

The fact that MS fatigue is so sensitive to heat supports the theory that interference with nerve conduction is at least partially responsible for fatigue. Individuals with MS feel noticeably more tired in hot, humid weather, and are also at risk for "overheating" during exercise. This overheating may be caused by the increased work that the nervous system must perform to generate activity. Finding ways to avoid heat-related fatigue is important, because it can create an aversion to exercise that will lead to even worse fatigue over the long term. Fatigue may also be related to decreased functioning, or hypometabolism, in certain areas of the brain (10).

This fatigue may be related to activation of the immune system after the interferon betas are injected (glatiramer acetate, which is a noninterferon immunomodulator used to treat MS exacerbations, does not cause this fatigue reaction). In addition to the primary or major causes of fatigue, there are a number of secondary contributors, so-named because they are not caused directly by the underlying disease process itself, but rather by some other factor related to the disease. Some of these factors include mood disorders, the medications used to treat other symptoms of MS, deconditioning, pain due to stiffness or damaged nerves, and sleep disturbances. There is clearly some overlap between depression and fatigue in MS (11). The medications used to treat other symptoms of MS, such as spasticity and pain, may have side effects that include fatigue. As mentioned above, the interferon therapies used in MS can cause severe fatigue as a side effect, although often this occurs only during the initial months of therapy. Medications such as pain relievers and muscle relaxants can cause sedation, which contributes to fatigue. Pain related to other symptoms of MS, such as spasticity, can also

make people less likely to want to engage in physical activity and can contribute to deconditioning. In addition, pain and movement disorders can significantly interfere with sleep, leaving people with less energy to cope with fatigue. Chronic stress depletes cortisol, a hormone secreted by the body's adrenal glands. Chronically low cortisol levels can cause a state of fatigue. Although this has been studied more in other disorders, such as chronic fatigue syndrome, it is possible that such hormone "dysregulation" plays a role in fatigue in the person with MS (9).

Diagnosis a physician or nurse will respond to your symptoms of fatigue by asking you additional questions and performing certain evaluations. The types of information they will collect include: your health history and the health history of your family; a physical examination and laboratory tests to rule out diseases other than MS that may be causing or contributing to your fatigue; a medication/drug use history; and possibly the use of one or more questionnaires (commonly referred to as fatigue assessment scales) to determine the severity of your fatigue and its effect on your ability to function in daily activities (12). A history of depression, anxiety, panic attacks, or other related conditions can also contribute to feelings of fatigue, it is important to provide as much information as possible about your mood. Signs and symptoms that suggest depression include a persistent feeling of depressed mood, loss of interest in everyday activities that you used to enjoy, a lack of motivation, persistent feelings of sadness, and recent weight loss or weight gain. If a family member has had depression or an anxiety disorder, it may be more likely that you will have depression or anxiety (10). Many of the drugs that are used to treat MS, as well as drugs that are used to treat other conditions, can cause or contribute to fatigue in the short term or long term. These are analgesic, interferon therapies, sedatives, anticonvulsants, antidepressants, antihistamines etc. Drugs (3). A number of instruments exist in MS literature for the assessment of fatigue and can be subjective (self-reported by patients) and objective (quantified by clinicians through various parameters). Subjective or patient-reported instruments are specifically designed to incorporate a patient's viewpoint and are more practical for use in clinical settings (13).

FATIGUE ASSESMENT SCALE

Several scales are available to measure fatigue. A list of commonly used subjective measures of MS-related fatigue is provided in Table 1 (14).

Several of the original fatigue scales, including some of the most widely used, were created to quantify fatigue associated with other chronic medical conditions including chronic fatigue syndrome and systemic lupus erythematosus. Some scales primarily quantify fatigue, whereas others assess the impact of fatigue on various functions. A useful comprehensive review of the various general and disease specific scales is outlined by Dittner et al. Here, we review scales most commonly used for MS patients, including instruments designed specifically for MS (15).

MODIFIED FATIGUE IMPACT SCALE

The Modified Fatigue Impact Scale (MFIS), suggested by the Multiple Sclerosis Council for clinical practice guidelines, has been a reliable tool for assessing MS fatigue. MFIS is derived from the 40-item Fatigue Impact Scale (FIS), and contains only 21 items, but offers a more multidimensional assessment: physical (pMFIS, 9 items), psychosocial (psMFIS, 2 items), and cognitive (cMFIS, 10 items) functioning. The sum of the 21 items makes the total score. MFIS is easy to use, and has other advantages such as good reproducibility and strong correlation with FIS results. The MFIS is easy to administer and focuses on the ways in which MS-related fatigue affects everyday life. As such it has high face validity for patients. The availability of the three subscales, physical, cognitive, and psychosocial functioning, may be useful to investigators interested

Table 1. Commonly used subjective measures of MS-related fatigue

Name of scale	Reference	Population	Specified fatigue subscales	No. of items	Scoring
Modified fatigue impact scale	Paralyzed Veterans of America, 1998 (4)	MS	Physical, cognitive, and psychosocial	21	1–7 (Likert scale)
Rochester fatigue diary	Schwid et al. (20)	MS	Lassitude (reduced energy)	12	0–100 (mm) visual analog scale
Fatigue descriptive scale	Iriarte et al. (21)	MS	Spontaneous mention of fatigue, antecedent conditions, frequency, impact on life	5	0–3 (Likert scale)
Fatigue impact scale	Fisk et al. (22)	MS	Physical, cognitive, psychosocial	40	0–4 (Likert scale)
Fatigue assessment instrument	Schwartz et al. (23)	MS, chronic fatigue syndrome, lupus, dysthymia, healthy	Fatigue severity, situation specificity, consequences of fatigue, responds to rest/sleep	29	1–7 (Likert scale)
Single item visual analog scale of fatigue	Krupp et al. (24)	MS, lupus, healthy	Depends on the question	1	0–100 (mm) visual analog scale
Fatigue severity scale	Krupp et al. (24)	MS, lupus, healthy	None	9	1–7 (Likert scale)
Fatigue scale for motor and cognitive functions (FSMC)	Penner et al. (25)	MS	Motor and cognition	20	1–5 (Likert scale)

in testing hypotheses concerning these different areas of function. However, the three subscales tend to correlate highly with one another, which limits their usefulness to some extent. The Modified Fatigue Impact Scale-5 item (MFIS-5)—also known as the MFIS abbreviated version—is one of over 50 available questionnaires for assessing fatigue in clinical and research practice. It is a short version of the 21-item MFIS. The MFIS derives from the Fatigue Impact Scale (FIS). Both modified versions of the FIS were developed for research purposes for multiple sclerosis (MS) patient groups. The FIS is a 40-item self-administered questionnaire and as such may prove less practical to administer in a clinic setting, than shorter questionnaires such as the MFIS and MFIS-5. The MFIS-5 measures the impact of fatigue on cognitive, physical and psychosocial function—considered by some authors to be three important subscales—in patients with MS. It does not identify cases or non-cases of fatigue, unlike the Chalder Fatigue Scale 11, that was recently reviewed in this journal. It consists of 5 of the 21 items of MFIS that most strongly correlate with the total MFIS score (12, 16, 17).

ROCHESTER FATIGUE DIARY

To improve on these features, we have developed the Rochester Fatigue Diary. It consists of a single page with 24 vertical bars for subjects to rate fatigue severity on a visual analog scale every hour for 1 day. The location of each hourly mark is translated to a 0 (maximal fatigue) to 100 (no fatigue) scale and averaged to provide a daily mean fatigue severity (18).

FATIGUE IMPACT SCALE

In 1994, a Canadian group frustrated by this limitation developed the Fatigue Impact Scale (FIS). The score reflects functional limitation due to fatigue experienced within the previous month rather than a measure of the level of fatigue. It may be used in both the clinical and the research setting in people for whom fatigue is a predominant symptom. There are 40 items, each of which is scored 0 (no problem) to 4 (extreme problem), providing a continuous scale of 0–160. It is composed of three subscales that describe how fatigue impacts upon cognitive (10 items), physical (10 items) and psychosocial functioning (10 items). Cognitive functioning concerns concentration, memory, thinking and organization of thoughts. Physical functioning reflects motivation, effort, stamina and coordination. Psychosocial functioning describes the impact of fatigue upon isolation, emotions, workload and coping. Validity as a quality of life measure has been established against the Sickness Impact Profile. External validity

has been established in the following patient groups (although it has been used in many more): patients presenting with chronic fatigue, MS, chronic obstructive pulmonary disease, primary biliary sclerosis and chronic hepatitis C infection (19, 20).

FATIGUE SEVERITY SCALE

The Fatigue Severity Scale (FSS) is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. Essentially, the FSS consists of answering a short questionnaire that requires the subject to rate his or her own level of fatigue. The obvious problem with this measure is its subjectivity. Here is an example FSS questionnaire containing nine statements that attempt to explore severity of fatigue symptoms. The subject is asked to read each statement and circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement (21).

CHALDER FATIGUE SCALE (THE FATIGUE SCALE)

One of the most well-known fatigue scales, the Chalder Fatigue Scale was created for chronic fatigue syndrome patients. This 14-item instrument quantifies fatigue intensity in terms of physical and mental domains. Each item is quantified by a numeric value on a Likert scale, and a sum score is calculated. Higher totals indicate more fatigue. Advantages of this instrument include its ease of use and brevity: it can usually be completed within 2–3 minutes. Although it has demonstrated good internal consistency in patients with chronic fatigue syndrome, MS-specific assessments of validity and consistency for this instrument are lacking (22).

NEUROLOGICAL FATIGUE INDEX (NFI-MS)

The NFI-MS is a self-administered questionnaire, which comprises 23 items, covering 4 different unidimensional subscales; physical (8 items), cognitive (4 items), relief by diurnal sleep or rest (6 items) and abnormal nocturnal sleep and sleepiness (5 items). Participants rate their agreement to the 23 items on a 4-point Likert scale (0='strongly disagree', 1='disagree', 2='agree' and 3='strongly agree'). For each of the four subscales, a total score can be calculated and a higher score indicates more fatigue. In addition, a summary NFI-MS score can be calculated, containing 10 items (7 and 3 items from the subscales physical and

cognitive, respectively). Note that no overall total score is calculated. There is a single-sentence instruction for the patient asking to consider the experience over the previous 2 weeks (23).

SUMMARY

Fatigue, a multidimensional, complex and highly subjective symptom, is one of the most frequent symptoms of MS patients. It is associated with several factors or mechanisms. Present findings indicate that fatigue is a serious problem in MS and provide a basis for future research. A multidimensional approach proves to be a valuable method for assessing fatigue, not only to characterize fatigue, but also to identify processes that may contribute to the subjective experience of fatigue. An important finding of the present study is that psychological factors, such as sense of control and focusing on bodily sensations, seem to play a role in the subjective experience of fatigue in MS.

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