Fatigue in Multiple Sclerosis

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Abstract

Fatigue is an important, under-recognized, and complex problem in multiple sclerosis (MS). There are several interacting causes of this fatigue and most will respond to treatment. Factors identified as contributing to the overall problem include disease process related fatigue, fatigue related to intercurrent infection, iatrogenic fatigue (caused by medications), fatigue of handicap, lack of energy related to depression, and fatigue due to disordered or disrupted sleep. Management of fatigue is a multidisciplinary process. Effective treatment requires analysis of the contributing factors in each patient and treatment or management of those factors.

Introduction

Fatigue: "A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities."

- Fatigue guideline of the Multiple Sclerosis Council for Clinical Practice Guidelines

Fatigue is the Single Most Common Complaint of MS Patients
Different people mean different things by the term fatigue. We all think we know what the term means but there are many different causes and aspects of fatigue in MS. Despite the difficulty in defining it precisely, the complaint is so universal in MS that, in the author's opinion, the absence of significant fatigue casts doubt on the diagnosis.

Fatigue Is Subjective
Despite the fact that fatigue interferes with both work and play, it is subjective and therefore invisible. A spouse or co-worker cannot see it. As a result, fatigue often causes problems with relationships socially, in the family, and on the job. Unfortunately, we know all too little about the most important cause of fatigue, which is MS disease-related fatigue. We can isolate a number of factors that contribute to fatigue, many of which are amenable to treatment. In addition, we do have some empiric therapies that help disease-related fatigue in some patients.

Fatigue can be categorized as follows:

- Multiple sclerosis disease process related fatigue
- Fatigue related to intercurrent infection
- Iatrogenic fatigue (caused by medications)
- Fatigue of handicap
Fatigue due to disordered or disrupted sleep patterns
Fatigue associated with depression
Nerve fiber fatigue

It is important to be aware that several different causes and types of fatigue may co-exist, and usually do.

**Disease Process Related Fatigue**

Fatigue related to the disease process is the most important and least understood cause of fatigue in MS. It is typically at its worst in the early- to mid-afternoon, is usually absent or mild in the morning, and often improves in the evening. It appears to mirror the normal diurnal temperature variation of the body, which is at its lowest around 2:00 AM to 3:00 am, and peaks in mid-afternoon. It impairs executive and decision-making functions as well as general energy level. Fatigue severity is worse in individuals with more active disease. Indeed, severe fatigue, in the absence of new symptoms, suggests the presence of magnetic resonance imaging (MRI) activity. Fatigue is worse in those with higher expanded disability status scale (EDSS) scores.5

MS disease related fatigue is thought to relate to the continuing inflammatory process in the brain and the associated secretion of lymphokines and cytokines (substances secreted by the immune system as part of the inflammatory process). We know that inflammatory processes cause fatigue in other disorders. When influenza occurs, the exhaustion and fatigue are not directly caused by the virus but are a part of the body's response to the infection. Symptoms of viral infection usually do not occur until the body starts to fight the infection. It is the release of substances that form part of the immune response to the infection that causes fatigue. We do not know which of the numerous lymphokines and cytokines released as part of the immune response are most responsible for fatigue in any of these conditions, but they are the most likely source of disease related fatigue. Fatigue similar to MS fatigue also is seen in other autoimmune disorders such as lupus5 and rheumatoid arthritis.6 Fatigue related to infection can be regarded as a signal from the immune system to the nervous system telling the individual to slow down and rest while the immune systems fights the infection.

Suppression of the immune response with immunomodulatory drugs may explain the improvement in fatigue that can be seen with high dose steroid treatment or as a delayed effect of interferon treatment in MS. We also have seen improvement in fatigue with immunosuppressive therapies, though it does not appear to be a universal response to any of these therapies. It is a topic that should be investigated in future clinical trials.

**Fatigue Due To Intercurrent Infection**

Intercurrent infection contributes to fatigue, but this type of fatigue is usually transient, clearing after the infection clears. It is worse if there is a fever. Cure of the infection eliminates this contribution to fatigue. When there is an acute worsening of fatigue, we should look for infection or for new MS symptoms, because fatigue increases with either. Clinically silent infections in MS patients are most often found in the urinary tract.

**Iatrogenic Fatigue**

This term comes from the Greek iatro for physician and gennan to produce and thus refers to physician-caused fatigue. A substantial number of medications widely used in MS can cause or aggravate fatigue. Drugs such as benzodiazepines and tricyclic antidepressants used to aid sleep may cause sedation and drowsiness the following day. The clinical practice guideline for fatigue in multiple sclerosis provides a long list of medications that can cause or aggravate fatigue and are commonly used in MS. These include analgesics, anticonvulsants, antihistamines, antihypertensives, muscle relaxants, and many others.1 In assessing fatigue, it is often useful to question the patient regarding any changes in medication made at the onset or worsening of fatigue to ascertain whether or not medication is contributing to the problem.
Fatigue Of Handicap
Fatigue of handicap is fatigue that results from the extra effort and energy required to compensate for a handicap. Metabolic studies have shown that a person with a spastic gait can expend twice as much energy walking as a normal individual. Individuals with weak muscles will use a different set of muscles to compensate for the weakness and overwork those muscles that are still functioning, leading to increased fatigue. This can perhaps be best understood by thinking back to the last time you twisted an ankle and had to use crutches; by the time the day was over, you probably felt that your arms were ready to fall off. Alternatively, try to do the dishes or prepare a meal with an arm in a sling. Using only one hand for simple routine process takes a surprising amount of extra time and energy.

Fatigue Due To Disordered Or Disrupted Sleep Patterns
Disrupted sleep is very common in MS. Periodic limb movements, urinary frequency and even sleep apnea can cause significant sleep disruption in MS. Sleep deprivation is a well-recognized and frequent cause of fatigue. Older individuals, particularly those who are overweight, can develop sleep apnea with drowsiness and confusion during the day. Formal sleep studies in MS patients show a variety of disrupted sleep patterns. These include sleep apnea, periodic limb movements, and altered respiratory patterns due to involvement of parts of the brainstem controlling sleep. Additionally, depression often causes individuals to awaken in the middle of the night and then lie awake for hours. Add frequent awakenings due to urinary frequency and urgency and it is easy to see how many different elements contribute to sleep problems and why disrupted sleep is such a problem for many MS patients.

Fatigue Associated With Depression
Depressed individuals usually do not complain of fatigue in particular; but because of lack of interest and of motivation, they do not have the energy to do even the daily routine. This does not show up as fatigue on fatigue scales, but the lack of interest and complaints may be interpreted by others as fatigue. Additionally, disrupted sleep due to depression may increase fatigue. Depressed individuals often have little trouble going to sleep but awaken in the middle of the night and can't go back to sleep. Careful questioning regarding mood and sleep patterns is helpful in making the diagnosis of depression.

It is important to realize that there are occasional MS patients with lability of affective expression (or, in the extreme, pathological laughing and weeping) in whom depression may be hidden. The external expression of mood either reflects the current situation and emotional milieu or is a perverted expression of the internal affective state. It may bear little or no relationship to the patient's underlying feelings. In such patients, internal affective state is not visible to the casual observer, though it may be recognized by family members. Pathological laughing can coexist with depression, and both the depression and the pathological laughing or lability are responsive to antidepressants.

Nerve Fiber Fatigue
Nerve fiber fatigue in MS is a distinct problem not usually thought of as "fatigue" and rarely covered in discussions of fatigue in MS. Nevertheless, it is an important element that severely affects function and contributes significantly to perceived fatigue. Nerve fiber fatigue has its own distinct characteristics and a diurnal variation similar to disease related fatigue. It is seen in most MS patients and increases as the disease progresses. Nerve fiber fatigue is an activity and/or temperature related failure of the demyelinated nerve fibers to conduct impulses. Even Charcot, who wrote the classical description of MS in the 1860s, knew that demyelinated fibers could conduct. He stated that MS: "very rarely issues in complete blindness. This is peculiarly worthy of notice especially if you remember that patches of sclerosis have been found after death occupying the whole thickness of the nerve trunks in the optic nerves in cases, where during life, an enfeeblement of sight simply had been noted. This apparent disproportion between the symptom and the lesion constitutes one of the most powerful arguments that can
be invoked to show that the functional continuity of the nerve tubes is not absolutely interrupted.\textsuperscript{10}

The literature regarding conduction failure in demyelinated nerves is extensive. During an exacerbation, conduction fails in the nerves as they are demyelinated; however, over time, conduction in most of the surviving fibers is restored. The causes of the acute conduction failure during demyelination are not completely understood but include: damage to the nodal sodium channel,\textsuperscript{11,12} virtual absence of sodium channels from the internodal membrane,\textsuperscript{13} and increased membrane capacitance in the demyelinated region.\textsuperscript{14} The role, if any, of alterations in the extracellular fluid composition in the inflamed area is unclear. There is reasonably good evidence that the nodal membrane is damaged by lysolecithin and other detergent lysolipids generated from myelin by enzymes present in the inflammatory exudate. Various enzymes are released by inflammatory cells, including a variety of proteases, lipases, neuraminidase, phosphatases, and glycosidases. Of these, phospholipase appears to produce the most rapid and extensive damage to myelin. Phospholipase also specifically destroys sodium channels as measured by saxitoxin binding.\textsuperscript{11,12} Once the acute inflammatory response is over, repair processes take over and nerve conduction resumes.

The internodal membrane normally contains very few sodium channels.\textsuperscript{15,16} Indeed, if sodium channels of a myelinated fiber were evenly distributed over the length of the fiber, the density would be much less than half that in most unmyelinated fibers and would be too few to support conduction.\textsuperscript{17} For continuous conduction to develop in a demyelinated axon, additional sodium channels must be inserted into the axonal membrane. This is a prerequisite for the restoration of continuous conduction along a demyelinated fiber, but this alone will not ensure that conduction will occur.

Increased membrane capacitance and the resulting increase in capacitative charge on the demyelinated axolemma results in an increase in the amount of current required to depolarize the membrane to threshold. The current, which must pass down the axon from the myelinated region, is normally insufficient to discharge the demyelinated membrane to threshold. This can be most easily understood if you regard the axolemma and myelin as the dielectric of a tubular capacitor with the extracellular fluid and axoplasm serving as the plates (Figure 1). Since capacitance is inversely proportional to the distance between the two plates of a capacitor, the capacitance of a demyelinated fiber is many times that of a myelinated fiber, where numerous layers of myelin membrane separate the axoplasm and the extracellular space.

\textbf{Figure 1.} Diagrammatic representation of the capacitative charge on a cross section of a myelinated axon (1A) and of a demyelinated axon (1B). In 1A, the myelin separates the negatively charged axoplasm from the positively charged extracellular milieu so the charge on the membrane is very small and little current is needed to depolarize it. In 1B, there is no myelin to separate the charges, and, because they are only about 10-12 nm apart, the capacitative charge is quite large. It is so large that the current coming down the axon from the myelinated segments cannot discharge it and conduction block occurs.
The current passing along the last myelinated segment to a demyelinated segment comes mainly from the last node, which in a large fiber is as much as 12 mm away (Figure 2). This is insufficient to depolarize the demyelinated membrane to threshold. Thus, conduction fails at the junction of the myelinated and demyelinated segments even if the number of sodium channels in the demyelinated membrane has increased enough to support continuous conduction (Figure 2C). In the electrophysiologic literature, this conduction problem is termed *impedance mismatch*.

*Figure 2. Diagram illustrating restoration of conduction following demyelination. In (A), a wave of depolarization reaches the node on the left. A transient outward depolarizing current results in opening of sodium channels and the initiation of an inward sodium current shown in (B), which depolarizes the next node. In (C), the depolarizing current is diffused by the large capacitative charge on the demyelinated membrane, which also is inexcitable because there are not enough sodium channels in the newly demyelinated membrane to support conduction. In (D), remyelination has occurred with thin myelin and short internodes. These nodes depolarize almost simultaneously. The additive effect of the current from several adjacent nodes then depolarizes the unmyelinated membrane in (E), resulting in continuous conduction. This is because, as part of the recovery process, enough sodium channels have been added to the demyelinated membrane to support continuous conduction. Note that a great deal more sodium enters the fiber with each impulse in D and E, which results in a marked increase in energy requirement per impulse—one cause of nerve fiber fatigue with conduction failures.*

Conduction block is overcome by remyelination at the plaque margins (Figure 2D and 2E) and by an increase in the number of sodium channels in the demyelinated membrane. The new myelin has very short internodes, which allow summation of the current from several nodes. Thus, there is an increase in the sodium current, which overcomes the impedance mismatch and initiates continuous conduction in the demyelinated nerve. This has several consequences:

1. The amount of sodium entering the nerve with each impulse is markedly increased. Thus, when the nerves are very active, the sodium pump cannot keep up with the high rates of sodium entry resulting in flooding of the nerve fiber with sodium and conduction failure.
2. Recovery time between impulses is prolonged so that many impulses drop out during fast trains of impulses.
3. The fibers become temperature sensitive.

The temperature sensitivity results from the low safety margin for conduction and the sodium channel response to temperature. When a nerve impulse triggers a node, essentially all of the sodium channels open and sodium pours in, depolarizing the membrane. The rate at which the
sodium channels close is very temperature dependent. With an increase in temperature, they close faster, decreasing the time in which the current can flow and thus decreasing the total current, causing failure of conduction. Cooling has the opposite effect, increasing the time the channels are open and improving conduction.

Experimental studies of demyelinated fibers show temperature sensitivity such that a rise in temperature of as little as 0.5°C above normal will cause conduction failure in some fibers. It is this nerve fiber fatigue that accounts for the problem many MS patients have in walking more than short distances and causes heat sensitivity. When nerve fiber fatigue occurs and the fibers stop conducting, the legs simply will not move until the nerve fibers are rested enough to begin conducting again. Nerve fiber fatigue is worst during the early stages of recovery from an attack. You may see patients who can make a particular movement only once or twice initially; but over the next several days, they will be able to repeat the movement more and more often—sometimes with a return to near normal function.

**Treatment**

**Treatment of Fatigue in MS**

From the foregoing, it is apparent that the management of fatigue is complex and multifaceted. There often are multiple contributing factors and treatment depends on the causes. The fatigue guideline published by the Multiple Sclerosis Council for Clinical Practice Guidelines contains an algorithm for the management of fatigue, which is very useful in managing fatigue and fatigue related problems.

Disease related fatigue often responds to drug therapy with amantadine. Although some have recommended pemoline, it did not prove helpful in a properly controlled trial. Preliminary data has suggested that high dose aspirin may be useful in fatigue management, but this requires confirmation in a larger controlled trial. There are anecdotal reports of improvement of MS fatigue with the newer serotonin reuptake inhibitor type antidepressants such as fluoxetine (Prozac) or sertraline (Zoloft), but these have not been studied in a properly controlled trial. A number of anecdotal reports describe fatigue lifting after several months of treatment with interfero. This is a very gradual process and frequently individuals are unaware of the change until it is brought to their attention. When fatigue relates to an acute attack, treatment of the attack with steroids will, in many cases, improve the fatigue.

There are several additional strategies that may be helpful in management of disease related fatigue. These include periodic rest and scheduling strategies, so that more difficult tasks are done early in the day when fatigue is less. A fatigue diary may be helpful in analyzing the problem and working out strategies to minimize the impact of fatigue. A team approach can be very helpful.

Fatigue brought on by infection is best addressed by treating the infection. A search for infection, particularly urinary tract infection, should be carried out if there is a sudden worsening of fatigue in an MS patient. If fever is present, use of acetaminophen (Tylenol) or aspirin to bring the fever down will also help. In severely disabled patients, the increased weakness that accompanies fever will add to the fatigue and disability.

Iatrogenic fatigue is best dealt with by identifying the offending medication and, if possible, discontinuing it or substituting a medication that is less likely to cause fatigue. If in doubt, most medications can be discontinued temporarily to see if they are contributing to the fatigue.

Fatigue of handicap can be helped by conditioning exercises and by the use of adaptive equipment. Physical and occupational therapists are particularly helpful with this modality.
Conditioning exercises, gait training, and appropriate equipment can reduce the effort involved in normal activities. Occupational therapists can suggest modifications in the home and work environment to improve efficiency and reduce the effort involved in daily tasks. Use of appropriate equipment and adaptive devices also can reduce the abnormal stress and strain on muscles and joints, reducing fatigue.

Management of fatigue due to disrupted sleep depends on analyzing and correcting the sleep disturbance. If the problem is an overactive bladder, anticholinergic medications to relax a spastic bladder and/or DDAVP (Desmopressin) to inhibit urine secretion can be quite helpful. If the problem is early morning awakening, (whether or not the patient is depressed), tricyclic antidepressants often help. If the problem is periodic limb movements or myoclonic jerks, benzodiazepines may prove useful. Formal sleep studies can be very useful and should be performed if the problem does not respond to simple measures. This becomes increasingly important in older overweight patients where sleep apnea is likely to be a problem. In such cases, continuous positive airway pressure (C-PAP) may be needed to keep the airway open. Correcting sleep disruption will usually produce quite a significant improvement in fatigue and often in mood.

Fatigue related to depression requires management of the depression, which may involve both medication and measures to deal with underlying problems contributing to the depression. Options include counseling by a psychiatrist, psychologist, or social worker, but other health professionals may be helpful in the management of problems that may be contributing to the depression and worry.

Nerve fiber fatigue is often physically limiting and is markedly influenced by body core temperature. A cool environment may help, particularly during physical activity. Studies show that individuals can exercise longer with appropriate cooling. Some individuals claim that a cold swim will allow them to function better for hours. It not only lowers the core temperature but causes cooling and vasoconstriction in the extremities. These then serve as heat sinks to keep the individual's body temperature down for some time. Drugs like 4-aminopyridine (4-AP) have been shown to be helpful in some individuals in controlled trials; however, 4-AP has a very narrow safety margin, and seizures and cardiac arrhythmia occur with even modest overdoses. For this reason, even though it can be obtained from compounding pharmacists, it has found limited use. It has a short shelf life and potency of the preparations that have been tested has been highly variable, which compounds the problem of a narrow safety margin. Most physicians have been reluctant to use it because of the risks involved.

**Summary**

Fatigue in MS is complex and multifaceted and treatment should be multifaceted. Fatigue plays a major role in MS related disability and appropriate management can significantly improve function. Disease process related fatigue is poorly understood but is a major contributor to the overwhelming and often disabling sense of fatigue experienced by many MS patients. Analysis of the components contributing to the fatigue state can lead to more effective therapy in the individual patient but additional research on disease process related fatigue and its relationship to autoimmunity is sorely needed. Only with a better understanding of the mechanisms of disease related fatigue will we be able to develop more effective therapies.
References