

## **DOES MS RELATED FATIGUE REFLECT A SLEEP DISORDER? NO**

**Cris S. Constantinescu**; Radu Tanasescu

*Division of Clinical Neuroscience, School of Medicine, University of Nottingham, UK*

The question, the way it is formulated, with no reference to special situation of group of people with MS-related fatigue, requires an emphatic: "No" for an answer. Had it included special qualifiers, for example, had it been formulated "Does MS-related fatigue reflect a sleep disorder in some cases?" the answer, like the question, could have been more differentiated. But these debates are binary, and the possibilities for an answer are binary, so it is logical to answer: "No". From a logical perspective, our task could be reduced to demonstrating that there are people with MS related fatigue who do not have a sleep disorder, a fact that has been documented in many publications. However, we will elaborate our answer a little more, to justify our position in this debate.

First, we need to reflect on the meaning of the word "reflect" in this context. Without much doubt, the most accurate sense of this word in the title of the debate is that MS-related fatigue is caused by a sleep disorder. We could give many examples of the use of the word reflect to mean causation. For MS purposes, it is logically similar to "brain atrophy on MRI in MS reflects neurodegeneration". If we agree this is the meaning, implying that MS-related fatigue is caused by a sleep disorder, our argument here is that we need to distinguish between association and causation. Indeed, work by our group, the group of Prof Paul, and others, has clearly shown a correlation between sleep disorders, or simply sleepiness, and fatigue in MS. However, this does not mean, and our review of some date will show that it is not possible, that this association is causal.

Another aspect of the title to be discussed is the generalizability of the relationship between fatigue and sleep disorder, beyond MS. This is important as fatigue is one of the main symptoms for which people seek medical attention. The attractiveness of this plays well in the hands of those on the "yes" side of the debate, as it may lead to a fast, intuitive positive answer. One does not need to be a neurologist to agree that if one does not sleep well, or does not sleep enough, one will be tired. We have all experienced sleep-deprivation induced fatigue. However, we should be aware of the logical fallacy of affirming the consequent. Moreover, we all probably accept and state repeatedly that MS-related fatigue is has something specific about it, it is part of the disease entity itself, and is not the same as the routine fatigue of someone who just hasn't slept enough, or even of a patient with another disease entity with fatigue such as cancer, chronic fatigue syndrome, Parkinson's disease and many others.

An important aspect, which no doubt will be addressed by the other side of the debate, is the definition of MS-related fatigue. Although there are consensus definitions, and it is a frequent symptom in MS, it is still difficult to grasp the unitary concept of MS fatigue. There are several levels of fatigue (primary, secondary and tertiary) several dimensions (physical and cognitive), time-dependent features (i.e. fatigue-as-state versus dynamic fatigue or fatigability) and long lists of symptoms with which it should not be confused. These include depression, chronic pain, anxiety, and, importantly, primary or secondary sleep disorders.

Specialists in sleep disorders insist that sleepiness, and sleep propensity should not be confused with fatigue. Therefore, sleepiness, while it correlates with fatigue, does not substitute (or is not reflected) in fatigue entirely.

Up to 97% of people with MS report fatigue, and roughly 40% of people with MS report some type of sleep disorder or have objective evidence of sleep study abnormalities such as the multiple sleep latency test (MSLT). This implies that there are more patients with MS with fatigue than patients with MS with sleep disorder of any type or with sleepiness.

It is true that sleep disorders in MS are better documented now than they were in the past, not least due to the excellent efforts of Professor Paul's group. As a consequence the proportion of patients with sleep disorders in MS is increasing, but these are still considerably outnumbered by patients with MS and fatigue. In fact, in our previous studies comparing MS patients with and without fatigue, it proved difficult to recruit the latter group; and in an

unpublished study of differences in gene expression profiling, non-fatigued MS patients were more similar to healthy controls than to their fatigued counterparts. This suggests that fatigue in MS is indeed part of the MS entity itself, and is almost universally present. This cannot be said about sleep disorders.

We will present some of the studies to prove the higher proportion of fatigue than of sleep disorder in MS. While many of these papers show a correlation between fatigue and sleepiness/sleep disorder, let us not confuse correlation for causation (or subsequence for consequence, as the late MS neurologist W Ian McDonald often used to say, quoting Dr Johnson). Moreover, there are many other aspects of MS that correlate with fatigue, and we cannot argue, by the same token, that MS fatigue reflects them.

An argument can be made that, if sleep disorder were a causal determinant of MS fatigue, improvement of MS fatigue would follow successful treatment of the sleep conditions. This has been proven and to some extent does indicate that a subgroup of MS patients with fatigue have an underlying sleep problem as the main determinant of fatigue. But by the same token, treatment of depression in MS or of walking dysfunction has improved fatigue, and again we need not make any causal inferences from these results.

Along similar lines, it is clear that some drugs used to treat MS fatigue are drugs for sleep disorders, such as methylphenidate or modafinil. However, we have shown that modafinil produced the same effects in MS patients regardless of fatigue, and in non-fatigued healthy volunteers. Also, amantadine, serotonin or noradrenalin reuptake inhibitors, fampridine, aspirin, which also have positive effects in MS fatigue, are primarily used for other indications, and we cannot infer that MS fatigue therefore reflects parkinsonism, depression, walking disturbance, or platelet dysfunction, respectively.

We therefore would urge the readers and listeners to agree with the answer “No” to the title question as formulated.