Editorial

Journal of Clinical & Experimental Immunology

Fatigue in Multiple Sclerosis: Current Concepts and Future Challenges

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Submitted: 26 Sep 2016; **Accepted**: 27 Sep 2016; **Published**: 29 Sep 2016

Keywords
Multiple sclerosis; Fatigue; Cytokines; Synaptotoxicity; tDCS.

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Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). During the disease process, affected patients can experience sensory, motor, cognitive and emotional symptoms. Fatigue is also a common and debilitating complain that can affect up to 75% of MS patients at some point during their life [1]. By definition, it is a reversible subjective lack of mental and/or physical energy that can alter normal functioning. The symptom severity can fluctuate in a way that it is usually higher at the end of the day, and during hot or humid environment [1].

Clinically, there is a common consensus to classify fatigue as 'primary' or 'secondary'. While the former is due to MS related pathological changes in gray and white matters; the latter could be the result of various concomitant factors that occur in the disease context, such as infection, endocrine dysfunction, anemia, psychiatric comorbidities, sleep disorders, and medications side-effects [1].

From an etiological perspective, no single underlying mechanism can account for the symptom occurrence which makes scientists and physicians consider a multifactorial contribution to its pathophysiology. The tremendous advances in neuroimaging have revealed dysfunction in many cerebral regions that could have a key role in MS fatigue. These cerebral hubs are mainly composed of fronto-parietal cortices, thalami and basal ganglia; and constitute the so-called 'cortico-striato-thalamo-cortical fatigue loop' [1]. Moreover, physiological and immunological studies have supported the contributory role of neuroinflammation to the occurrence of neurotransmitters imbalance and subsequently synaptotoxity and neurodegeneration which seem to be linked to MS fatigue. Particularly, inflammatory cytokines such as interleukin 1-beta, interleukin 6, tumor necrosis factor alpha, and interferon gamma seem to be associated with MS fatigue [1].

From a clinical scope, it is quite challenging to screen or diagnose MS fatigue, an issue that might be due to several reasons. On the one hand, patients find it difficult to describe the symptom that they usually refer to as 'malaise', 'weakness', 'lack of energy', and 'excessive tiredness'. On the other hand, the physicians need to rule out several conditions prior to setting the right diagnosis. Adding to this reality, the available scales are very heterogeneous in their abilities to detect MS fatigue. For instance, while the 21-item Modified Fatigue Impact Scale has physical, cognitive and psychosocial dimensions; the 7-item Fatigue Severity Scale mainly evaluates the physical component. Additionally, the Visual Analogue Scale assesses the perceived fatigue on a scale of 0 to 100 mm and remains limited by its unidimensional nature that may not consider the complexity of the symptom [1]. Admitting the subjective nature of the aforementioned scales, some objective tasks have been proposed as cognitive correlates of MS fatigue, mainly the ones evaluating alertness.

Although MS fatigue is a very prevalent and debilitating symptom, the available therapeutic options are limited by their poor outcomes and multiple side effects. These include psychostimulants and dopaminergic drugs, aerobic exercises, cooling therapies and psychotherapies, among others. Currently there is a growing interest in studying the effects of non-invasive brain stimulation techniques on various neuropsychiatric symptoms, particularly in MS [1-3]. Among them, transcranial direct current stimulation (tDCS) is the most appealing one, since it is very simple to use, not expensive and has a good safety profile with minimal to no side effects. It consists of applying a direct current via sponge electrodes at low intensity (1-2 mA) over different cortical areas. Several trials have investigated the tDCS efficacy in MS fatigue [3-7]. Some of them have yielded promising outcomes that remains to be replicated in future studies before drawing any conclusion [4,6,7].

In addition, upcoming tDCS protocols should be extended to large samples and over long period of time in order to understand the long-term after effects of this intervention. Furthermore, a better understanding of its underlying mechanism would benefit from a multidisciplinary approach combining imaging, immunological and physiological modalities in this interesting context.

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