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Editorial

The Place of tDCS in the Management of Fatigue in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, characterized by demyelination and neurodegeneration. Its treatment consists mainly of immunomodulatory, immunosuppressive and symptomatic drugs. MS patients can suffer from various symptoms, among which fatigue remains one of the most debilitating and difficult to manage. Despite all the available data in this field, MS fatigue is still a challenging symptom for patients and physicians, since it is usually hard to identify and describe and even tough to treat. Therefore, clarifying it would be the cornerstone of an ideal management. Here, we will briefly reappraise the definitions of fatigue from different scopes. The symptom will be considered from semiological and etiological perspectives. We will also revisit its pathophysiological mechanisms. The available pharmaceutical and alternative therapies will be cited in this context, and a special emphasis will be placed on the potential role of noninvasive brain stimulation techniques, namely transcranial direct current stimulation, as a promising tool in the management of MS fatigue.

Keywords: *Fatigue; MS Fatigue; Multiple Sclerosis; Non-Invasive Brain Stimulation; tDCS; Transcranial Direct Current Stimulation*

Abbreviations

MS: Multiple Sclerosis; tDCS: Transcranial Direct Current Stimulation

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, characterized by demyelination and neurodegeneration. Its treatment consists mainly of immunomodulatory, immunosuppressive and symptomatic drugs.MS patients usually suffer from various symptoms, among which fatigue remains one of the most debilitating and difficult to manage [1,2]. Fatigue can occur at any time throughout MS course regardless of the disease characteristics (such as MS type, degree of disability or disease duration). It can be triggered and/or exacerbated by many factors, namely humid or hot environment, infections, motor or cognitive tasks [1]. Most importantly, MS fatigue has drastic impacts on professional performance, family life, and interpersonal interactions.

A major obstacle that may face the medical team resides in the patients' difficulty to precisely define the symptom, which they often perceive as 'weakness', 'excessive tiredness' or 'lack of motivation' [1,2]. This renders fatigue diagnosis hard to be disentangled from that of other concomitant motor and mood symptoms. In this perspective, confirming the presence of MS fatigue requires a detailed description of the symptom per se, in order to provide an optimal management and a better quality of life. Different approaches could be taken when it comes to symptom definition [2]. This will be discussed in the following paragraph.

Current knowledge on multiple sclerosis fatigue

In terms of semiology, fatigue could be classified as either a 'trait' or a 'state' which respectively refers to (i) a persistent sensation of

fatigue that is always present regardless of task performance or (ii) a reversible decline in performance during or following the exertion of motor or cognitive tasks [1,2]. It should be noted here that both conditions could coexist in a given patient, and some authors refer to them by using the terms of 'fatigue' and 'fatigability', respectively.

Etiologically speaking, one should differentiate between primary and secondary MS fatigue. In fact, primary fatigue results from the pathophysiological mechanisms of the disease itself. This includes the inflammatory medium, demyelination and neurodegeneration; all of which can lead to the disturbance of several cortico-subcortical circuits. These networks are parts of the so-called 'cortico-striato-thalamo-cortical loop' of MS fatigue [1]. However, before attributing the symptom to a primary cause, physicians should keep in mind that MS fatigue could be the consequence of several factors. The latter mainly consist of endocrinopathies, sleep and mood disorders, vitamins deficiencies, anemia, and medications side effects [2].

Based on these facts altogether, setting good therapeutic strategies appears crucial. Managing MS fatigue was the subject of a bunch of studies which have investigated the potential effects of different molecules (i.e. modafinil, carnitine, pemoline, potassium channel blockers, aspirin, antidepressants, vitamins, etc.) [2]. However, some of them were majorly limited by their modest efficacy (i.e. amantadine) and others were faced by serious side-effects (i.e. pemoline) [2].

Aside from pharmacological interventions, some alternative therapies such as cryostimulation, exercise, and cognitive behavioral therapies have been also tried in this context and yielded inconsistent outcomes [2].

Transcranial direct current stimulation in multiple sclerosis fatigue

Nowadays, noninvasive brain stimulation techniques are being tested for their efficacy in different neuropsychiatric settings. Among these techniques stands the transcranial direct current stimulation (tDCS). By delivering a weak current of 1 - 2 mA over different cortical sites, tDCS modulate the resting membrane potentials of targeted neurons and could improve the function of different brain networks such as those involved in MS fatigue. In this perspective, a few sham-controlled double-blind randomized trials have tried to ameliorate MS fatigue by targeting prefrontal [3,4], somatosensory [5,6] ormotor cortices [7]. All of these areas have been incriminated in the aforementioned MS fatigue loop. These trials adapted a crossover design and consisted of five consecutive daily 20-minute sessions of anodal tDCS. While most of them have documented positive outcomes, a discrepancy has been found between the two studies that applied left prefrontal tDCS. This might be due to the lower current intensity adopted in the negative trial [4] versus that chosen in the positive one (1 mA vs 2 mA) [3].

Conclusion

In summary, tDCS seems to be a promising tool for managing MS fatigue. Its non-invasiveness and safety profile provide an additional rational for its use. However, the beneficial effects should be replicated in large-scale studies before it could be translated in regular clinical practice.

Conflict of Interest

Moussa A. Chalah has no conflict of interest. Samar S. Ayache declares having received travel grants or compensation from Genzyme, Biogen, Novartis and Roche.

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