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COMPREHENSIVE REVIEW/REVUE GÉNÉRALE

Fatigue in multiple sclerosis — Insights into evaluation and management

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Summary Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, characterized by the accumulation of numerous neurological symptoms and signs throughout its course. Fatigue is one of the most distressing complaints that MS patients may experience over their lifetime. In spite of its high prevalence, the pathophysiology of MS fatigue is far from being fully elucidated and a constellation of mechanisms seems implicated in this setting. Several factors could contribute to its development and/or exacerbation, and this requires a careful workup in order to search for all possible underlying causes, such as sleep disturbances, endocrine dysfunction and mood disorders, to cite a few. The aim of this review is to revisit the definition of MS fatigue, provide an overview of its pathophysiology, and reappraise its clinical, structural and functional correlates. Additionally, we discuss the available assessment tools, as well as the various management strategies including pharmacological and non-pharmacological interventions. Special emphasis will be placed on the role of noninvasive brain stimulation techniques in this field. Finally, we propose a ''road map'' to facilitate the diagnosis and guide the therapeutic regimens of this multifactorial and multidimensional construct.

MOTS CLÉS
Échelle ;
Évaluation ;
Fatigue ;

Résumé La sclérose en plaques (SEP) est une maladie inflammatoire et neurodégénérative du système nerveux central, caractérisée par l'accumulation de nombreux symptômes et signes neurologiques au cours de son évolution. La fatigue reste l'un des problèmes les plus invalidants des patients SEP. Malgré sa fréquence, la physiopathologie de la fatigue est loin d'être entièrement comprise et un nombre de mécanismes semblent être impliqués dans la génération de ce

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symptôme. Plusieurs facteurs pourraient contribuer au développement et/ou à l'exacerbation de la fatigue dans la SEP, ceci nécessite une prise en charge assez globale afin de déterminer les éventuelles causes sous-jacentes, parmi lesquelles on trouve les pathologies du sommeil, les troubles de l'humeur, les maladies endocriniennes, etc. Le but de cette revue est de revisiter la définition de la fatigue dans la SEP, discuter sa physiopathologie, et réévaluer ses corrélats cliniques, anatomiques et physiologiques. De plus, on discutera des principaux outils d'évaluation diagnostiques ainsi que des diverses stratégies thérapeutiques, pharmacologiques et non pharmacologiques. Un accent particulier sera mis sur les techniques de stimulation non invasive et leur place dans ce domaine. On proposera également « une feuille de route » afin de faciliter la démarche diagnostique et la prise en charge thérapeutique de ce problème multidimensionnel et multifactoriel.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) that constitutes the second most common cause of handicap in young adults [39]. Although most patients suffer from recurrent relapses in the initial phase of the illness, they would ultimately face a progressive neurological decline: an unavoidable fate in the vast majority of cases [39]. Throughout the disease course, various symptoms and signs would accumulate, among which fatigue remains particularly disabling and very challenging for the medical community to manage. Since the pioneering work of Freal et al. in 1984, MS fatigue continues to attract the attention of scientists and caregivers [67]. Although Kurtzke did not include fatigue in his famous scale [108], Freal et al. reported, for the first time, that 78% of MS patients they surveyed complained of fatigue and considered it their most annoying symptom [67]. Following these surprising findings, growing literature has proven that fatigue is frequently encountered in the MS population, with 75%—90% of patients reporting it at some point in time [59,103,115]. Importantly, MS fatigue can occur at all stages of the disease [99,104], profoundly alters quality of life, impacts work performance and affects social and family interactions [59].

Despite the high prevalence and debilitating nature of the symptom, its underlying mechanisms are still far from being fully understood. In this regard, studies have highlighted the role of various structural, functional, and immunological factors [61,62,82,116,179,188,205]. In addition, several limitations in fatigue measurement exist, since its evaluation mainly relies on a handful of subjective instruments that were chosen as primary outcomes in the majority of trials. The situation is further complicated by the lack of efficient and satisfactory management protocols. Therefore, in-depth comprehension of the underlying causes and implementation of new therapeutic strategies appear mandatory.

In this review, we aim to:

- define fatigue and present its available classification;
- briefly reappraise its pathophysiological mechanisms;
- suggest a screening/diagnostic approach for daily practice;
- and finally discuss the available treatments, with a particular emphasis on the pharmacological and innovative interventions, namely non-invasive brain stimulation.

Other treatment modalities such as exercise and cognitive behavioural therapies are discussed elsewhere and therefore are beyond the scope of the current work [84,232]. For this purpose, a systematic research was conducted according to PRISMA guidelines [133]. First, computerized databases indexed in peer-reviewed journals (*PubMed*, *Medline*, and *Scopus*) were consulted between January and October 2016 aiming to identify articles in English and French languages addressing MS fatigue. We combined the following research terms: multiple sclerosis, MS, fatigue, fatigue severity scale, FSS, modified fatigue impact scale, MFIS, evaluation, treatment, management, therapy, axonal loss, inflammation, neurodegeneration, brain atrophy, pathophysiology, imaging, MRI, transcranial direct current stimulation, tDCS, transcranial magnetic stimulation, TMS, noninvasive brain stimulation, NIBS, disability and disease duration. In addition, a second research was conducted combining the names of treatments derived from the first research. Finally, the references of the selected studies were scanned independently by both co-authors in order to look for additional relevant sources.

Definition and classification of multiple sclerosis fatigue

Before discussing the various work-up strategies, it is essential and even crucial to set an agreement on fatigue definition. Indeed, there is no clear consensus in this context, and fatigue description varies among patients, scientists and caregivers. While patients refer to fatigue as ''excessive tiredness'', ''malaise'' or ''weakness'' [102], this symptom is observed from another perspective by researchers and physicians. For instance, some authors look at fatigue as having its origin in the CNS, namely in the upper motor neurons [241], or resulting from reduced muscular activation following an intensive exercise [68]. Others consider fatigue subsequent to a lack of self-motivation [27] or consequent to a subjective decrease in mental/physical energy [11].

Interestingly, a clearer and more practical definition has been offered by the work of Mills and Young [131]. Here,