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Editorial

Sleep and Multiple Sclerosis: An Intriguing and Promising Relationship

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Multiple Sclerosis (MS) is one of the most debilitating neurodegenerative disorders, with the highest incidence of onset between the second and the fourth decade of life; it affects approximately 2.4 million people worldwide [1]. Although the etiopathogenesis of the disease has not been fully elucidated, the effects of MS on the brain are known: the appearance of focal areas of demyelination and inflammation, reactive astrogliosis, and loss of neurons and oligodendrocytes [2]. The damage to the brain and spinal cord is initiated by T-cell-mediated inflammation, and demyelination and neurodegeneration are driven by several mechanisms involving the innate and adaptive immune systems [3].

The relationship between sleep and MS is suggested by the high incidence of sleep disorders in the MS patient population: more than half (4 times higher than in the normal population) have insomnia, sleep disorders, or breathing (Sleep-Disordered Breathing, SDB) and motor disorders [4]. Empirical evidence in recent years has highlighted the fact that MS is a disease with a multifactor etiology, and this understanding has led research to focus on modifiable factors that could have an impact on the risk of developing the disease, or disease progression, and on the poor quality of life of the patient. There is still no clarity as to what causes demyelination, neuronal loss, and astrogliosis. Among the various hypotheses, the crucial role of certain cytokines that contribute to the processes of neuroinflammation, immune dysregulation, and neurodegeneration, would seem to be confirmed [5]. Sleep fits into this scenario as it is closely correlated with some of the factors involved in these pathogenic processes: the relationship between sleep and the immune system is already known, and the growing evidence linking sleep disturbances to Alzheimer's disease suggests a close relationship with neurodegenerative processes as well.

Although the literature is still developing, there are many possible 'common grounds' between sleep and MS. There is growing evidence from studies of the relationship between sleep, quality of life, and cognitive deficits in MS patient populations. It would appear that sleep disturbances may moderate or mediate cognitive dysfunction differently in MS than in normals, and a lack of good sleep quality would make patients more susceptible to cognitive fatigue [6]. From the perspective of quality of life in MS and the possible treatment of modifiable factors that would lead to the development or progression of the disease, treating sleep disorders would also mean acting, more or less directly, on cognitive difficulties. For instance, a number of studies have used sleep deprivation (SD) protocols; SD is closely associated with cognitive impairment. In particular, SD leads to abnormal microglial activity, abnormal immune and inflammatory responses, and cognitive deterioration [7].

In relation to the immune system, the focus of the connection between sleep and MS should be mainly in the active transport mechanisms of substances from the peripheral immune system to the central nervous system (CNS) via the blood brain barrier; these transport mechanisms are influenced by sleep, its disturbances, and the circadian system. Specifically, the active transport of cytokines Interleukin-1 (IL-1), Interleukin-6 (IL-6), and tumour necrosis factor (TNF) is the main contributor to sleep alterations that appear in chronic inflammatory diseases such as MS.

The importance of sleep in the development of neuroinflammation has been demonstrated, especially with regard to the role of astrocytes and microglia [8]. Again, the same cytokines, IL-1, IL-6 and TNF, that play a role in neuroinflammation also play a role in sleep regulation. In recent years, much emphasis has been placed on the neurodegeneration process in MS. Previously, it was thought that neurodegeneration occurred after neuroinflammation, but it is now quite clear that both processes are present from the earliest stages of the disease. In fact, it is possible to observe the presence of brain, spinal cord, and retinal atrophy, which involve both white and grey matter, in early stages of MS. In the context of neurodegeneration, sleep is mainly related to oxidative stress and mitochondrial damage. Recent research has emphasized the role of sleep as a kind of antioxidant that counteracts oxidative stress [9]. Furthermore, animal studies have shown an involvement of mitochondria in various aspects of the sleep-wake cycle [10]. It is possible that this is a very promising line of research that could explain a sort of vicious neurodegenerative cycle linked to oxidative stress, sleep, and the deleterious consequences of insufficient quantity or quality of sleep that exacerbate an already compromised oxidative system in MS.

Evidence of the possible link between sleep and MS also points to possible sleep-based therapeutic scenarios

aimed at improving patients' quality of life: treating sleep problems would mean acting on a modifiable factor that has a negative impact on patients' lives. The most promising studies concern the possible role of melatonin and vitamin D. These two light-dependent mediators would seem to find a meeting point in MS-related mechanisms. On the one hand, MS research over the last 10 years has shown that melatonin acts as a powerful antioxidant, immunoactive agent, and regulator of mitochondrial processes [11]. Melatonin supplementation taken by MS patients has led to improved quality of life and reduced oxidative stress and neuroinflammatory markers. On the other hand, vitamin D metabolism is present in the CNS, is involved in myelinisation, and can be influenced by several external factors, such as sun exposure, diet, and supplementation [12]. Vitamin D plays a role in neuroprotection, remyelination, and axonal degeneration in MS patients [13]. One issue regarding the possible consideration of vitamin D associated with melatonin in MS concerns the fact that melatonin production is regulated by vitamin D: abnormal vitamin D levels could lead to decreased melatonin levels leading to sleep disturbances [14]. There is also evidence that concomitant supplementation of vitamin D and melatonin would have beneficial effects (in terms of antioxidant and anti-inflammatory action) in MS patients [15], although further confirmation is needed before such therapy can be considered in clinical practice.

Given the high incidence of sleep disorders in the MS population and the possible neuroimmunological, neuroinflammatory, and neurodegenerative mechanisms that may be shared by sleep and MS, treating sleep-related disorders could help to improve some MS symptoms and, consequently, the patient's quality of life. In addition, it would certainly be useful to introduce sleep assessment into the diagnostic phase of the disease in order to direct patients towards specific treatments in the case of sleep disorders.

Certainly, sleep-hygiene education would be possible, as well as cognitive behavioural therapy for insomnia, for the promotion of healthy sleep-related behaviour, and for the suggestion of strategies to improve psychological processes and cognitive distortions that may contribute to the persistence of insomnia. Ample emphasis should be given to the evaluation and treatment of SDB, which is very frequent in MS patients and should be treated with continuous positive airway pressure (CPAP), which keeps the upper airway pervious during sleep, improves oxygen saturation during the night, and also has beneficial effects on fatigue in MS patients.

Certainly, much more research is needed to confirm a significant relationship between MS and sleep, but there is evidence that highlights the need to clarify what could be a very promising new line of research into the relationship between sleep and MS and, more generally, between sleep and neurodegenerative disease.

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SC and LDG performed the literature searches. Both authors wrote the manuscript and contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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