Title: Sleep abnormalities in multiple sclerosis

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Title Page

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Abstract

Purpose of review: This review summarizes the most well documented sleep disorders seen in patients with Multiple Sclerosis (MS), with a special focus on the impact on quality of life.

Recent findings: Sleep abnormalities in patients with MS are a multifactorial and relatively complex issue affecting approximately 60% of the patients while the pathophysiology of these symptoms is not fully understood. Circadian rhythm disorders and increased levels of Pro-inflammatory Cytokines have been recognized as potential players in affecting sleep homeostasis in MS patients. Medication related side effects such as in immunotherapy and other factors such as lesion load can contribute to the disruption of normal sleep patterns.

Summary: Most frequently encountered sleep disorders are insomnia, sleep-related movement disorders, sleep-related breathing disorders and circadian rhythm disorders affecting both adults and paediatric MS populations. Aetiology still remains unknown with treatment options focusing on behavioural cognitive therapy, life style modification including improvement in sleep hygiene as well as melatonin supplementation. Given MS prevalence is still rising affecting millions of people, more personalized medicine applications should possibly form the key approach for improving patients' quality of life and quality years.

Keywords

Immune-mediated diseases; quality of life; melatonin; fatigue; survival; circadian

Introduction

Good sleep is pivotal to maintaining a critical level of physical, mental, and emotional well-being[1, 2], including optimal cognitive functioning[3]. At any given time, 50% of the general population are affected with one or more sleep problems such as difficulty in falling or staying asleep, staying awake, or adhering to a consistent sleep/wake schedule [4]. Chronic deprivation of quality sleep can increase the activity of the sympathetic nervous system leading to the disruption of the circadian clock affecting the whole body including the brain [5] and the cardiovascular systems' health [6]. This is concerning due to the fact that adequate sleep quality and quantity is required for the maintenance of mental and physical well-being, especially in those living with a chronic disease. The underlying pathophysiology of sleep disorders often seen in various neuropsychiatric disorders still remain blurred, however, it seems that many clinical variables and mechanistic pathways are actively involved.

Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative demyelinating disease of the central nervous system defined by a wide range of symptoms and signs that disrupt physical, cognitive, emotional, and social functioning.MS affects 2.6 women for every man with the condition[7, 8], while it has been estimated that at least 2.3 million individuals worldwide suffer from the disease [9]. MS is among the most common causes of neurological disability in young adults [10, 9]. The exact aetiology or causes of the disease still remains unknown, however, various traditional and non-traditional factors have been proposed as contributors such as genetic, environmental and immunological [11, 10]. What is more evident is the pathophysiology of MS which is characterized by chronic inflammation, disruption of the blood–brain barrier and immune cell infiltration into the CNS. This combination of abnormalities compromise the myelin sheath of neurons, leading to gliosis and axonal loss[12].

MS patients manifest signs such as abnormal gait, tremors, visual problems, bladder and bowel incontinence, numbness/tingling in extremities, chronic pain, spasticity, abnormal somatic sensations, sexual dysfunction, and speech disturbances [8]. Symptoms of the disease include fatigue, depression, sleep disturbance, and cognitive decline, while mental and physical fatigue is considered one of the most devastating symptoms, affecting more than 50% of the patients [13]. The impact of MS's symptomatology on patients' quality of life (QoL) is detrimental [14], with two-thirds of the sufferers reporting that pain prevented activities, impaired mobility and imposed limitations in social aspects of life [8, 15].

Sleep abnormalities are very common among patients diagnosed with MS and still remain under-recognized and inadequately addressed. Prevalence is estimated between 42–65%, whilst the wide range of reported rates mainly due to different methodological approaches and type of disorders; sleep abnormalities have been reported to be four times higher in MS compared to healthy populations [16-18]exceeding by far rates for other chronically disease patients. Poor sleep quality could have an adverse impact on patients' health and quality of life contributing even further to the overall disease burden [3, 14].The nature of sleep abnormalities has multifactorial aetiologies and is significantly dependent on illness severity and intrusiveness [19]. The inevitable impact of low quality of sleep in patients' life is documented by various symptoms such as daytime sleepiness, impairment of cognition, mood fluctuations, as well as behavioural issues affecting patient's relationship with family, friends and caretakers [20]. A significant aspect on patients' quality of life is the contribution that lack of adequate restorative sleep has in the development of mental and physical fatigue [21, 14].This link between sleep and fatigue development has been suggested to provide a sinister background on which the overall disability, which is the amalgam of all MS associated symptoms [22, 4, 1],develops, even though research on this topic is scarce within consistent findings [23-25].

The aim of the current review is to shed more light into aspects related to sleep abnormalities and how they afflict patients' quality of life and health.

Methods

A literature search was conducted through PubMed from 1962 to November 2018 using the following terms: [“Multiple Sclerosis”] AND [“Sleep”] AND [“Disorders” OR “Abnormalities”] AND [“Therapy” OR “Intervention”] AND [“Impact”]. Reviews and case reports of MS were included, but reports that did not comment on therapy or patient outcomes were excluded. Publications in a non-English language were also excluded from this systematic review. In addition other articles related to Health and Sleep Physiology were included to support our general arguments. Articles were reviewed by two independent reviewers and a total of 37 articles were selected for inclusion in the present review [4, 14, 16, 17,18, 19, 22, 23, 24, 25, 26, 29, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 42, 43, 49, 50, 51, 53, 55, 56, 61, 62, 63, 64, 66, 67, 70].

Epidemiology

Prevalence of MS

MS appears to be one of the best-studied neurological diseases and according to recent reports, prevalence and incidence have continued to increase [26].The World Health Organization reports that people with MS increased from 2.1 million in 2008 to 2.3 million in 2013 [9]. Paradoxically, MS seems to follow a geographic pattern of prevalence [8]. High prevalence zones are generally found in Canada, Northern United States, most of Northern Europe, New Zealand, Australia (south eastern), and Israel; medium zones found in southern Europe, southern United States, and northern Australia while low zones include areas such as Asia, most of Africa, and South America [27, 8]. Globally, the median estimated incidence of MS is 5.2 (range: 0.5-20.6) per 100,000 p-yrs, the median estimated prevalence of MS is 112.0 (with a range of 5.2-335) per 100,000 p-yrs, and the average disease duration was 20.2 years (range: 7.6-36.2) [8]. The Disability-Adjusted Life-Years (DALYs) for MS found to be 17 (range:14-20) per 100,000 p-yrs ranked as 13th among all neurological disorders while neurological disorders including stroke, communicable neurological diseases, and brain cancer accounted for 10.2% of global DALYs and 16.8% of all deaths in 2015 [26].

Even though genetic factors would play a pivotal role in those geographical patterns, there is still not enough evidence to explain this paradoxical phenomenon[28]. Methodological robustness among various clinical trials affects global estimates making direct comparisons between studies and countries very problematic.

Environmental factors such as sunlight exposure and vitamin D seem to play a role in the geographical prevalence pattern [29]. The ‘hygiene hypothesis’ which is related to low exposure to pathogens early in life and to the prevalence of immune-mediated diseases, seems to be a credible explanation for the increase in incidence of allergy and autoimmune diseases in industrialized countries during the last decades[30]. Helminths which are powerful modulators of the host immune system and have a protective influence in the development of MS have been suggested as a potential target for therapy of MS[30].

Sleep disorders in MS

Sleep abnormalities in patients with MS is a multifactorial and relatively complex issue, still under-recognized and inadequately addressed, leading to a “hidden epidemic”[31].The prevalence of disturbed sleep patterns in MS patient populations is approximately 62% [4] while the pathophysiology of these symptoms is not fully understood. Is still not clear whether the clinical subtype of MS is affecting the presence of RLS in the MS

population. Published data reveal that primary progressive MS patients may exhibit an increased risk for RLS compared to the other MS subtypes [32, 33]. On the other hand, other studies observed higher prevalence of RLS in Relapsing-Remitting MS [34] and in secondary progressive MS [35]. Circadian rhythm disorders and increased levels of Pro-inflammatory Cytokines have been recognized as potential players in affecting sleep homeostasis in MS patients [19]. Medication related side effects such as in immunotherapy and other factors such as lesion load can contribute to the disruption of normal sleep patterns [19]. Evidence suggests that the treatment of sleep disturbances could have beneficial impact in patients' QoL and functional status beyond improving just sleep [36] thus timely recognition and appropriate interventions need to be developed. The most common sleep abnormalities reported in MS patients are presented below itemized in aspects related to definition, prevalence, causes impact and treatment:

Insomnia

Definition: Insomnia is defined as the incapability to falling asleep (initial insomnia), interrupted sleep (middle insomnia), early morning awakening (terminal insomnia), or non-restorative sleep; there are differences between the various classification systems worldwide making the comparison between studies very challenging [37].

Prevalence: There are no large scale epidemiological studies clarifying the true prevalence of insomnia in MS but it is generally accepted that it is a common problem that affects approximately 40-50% of patients [38]. In a recent study it was reported that 42% of MS patients had difficulty in initiating sleep, 53% reported extended awakenings, and 58% reported staying awake for the rest of the time [38]. In general, persons with insomnia are at a higher risk of developing depression while the prevalence of insomnia in non-depressed MS patients is much lower compared to all MS patients (12.5%)[39].

Causes: What causes insomnia is not yet clear. Studies suggest that psychiatric disorders and restless legs are often the triggering factors to increase sleep latency in these patient population but due to the multifactorial nature of sleep disorders, such generalization need to be avoided [38].

Impact: Chronic insomnia has a debilitating effect on patients' QoL and overall health and it should be treated as efficiently as possible [40]. Patients with chronic insomnia often suffer from daytime sleepiness and fatigue affecting significantly their functional capacity and physical activity levels, jeopardizing thus further their fitness and overall cardiovascular health [4].

Treatment: Treatment options include cognitive behavioural therapy for managing stress levels and anxiety [41] while the most used prescribed medication is the 5-HT2 ligands [36]. Some studies have used melatonin as a mean of improving sleep latency with significant effect [42].

Sleep related Movement Disorders

Definition: The two most prominent sleep-related movement disorders documented in MS patients are Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorders (PLMD) [43]. RLS is mainly a wake-related disorder, characterized by an irresistible need to move the legs, usually accompanied by unpleasant sensations which begins or worsen during inactivity, especially in the evening/night, and improves or disappears by movement [44]. On the other hand, PLMD is a sleep-related condition, appearing mainly in the lower limbs and involving stereotyped involuntary movements (periodic limp movement-PLM) such as the extension of the big toe, often combined with a partial flexion of the ankle, the knee, and in some cases, the hip; those symptoms are often associated with cortical and/or autonomic arousals or with an awakening affecting significantly the patients quality of sleep [45].

Prevalence: RLS prevalence in MS patients is approximately 20%. No clear data exist for PLMD. It should be noted however that based on the literature, the majority of the RLS patients suffer from PLMD as well [43].

Causes: The aetiology of those movement disorders is not clear but available data suggest a possible dysfunction of dopaminergic, opioid, and/or iron metabolism in the central nervous system [46]. The link however between those potential contributors and the pathophysiology of MS is not fully understood. For instance, some studies support the association between RLS and iron metabolism in MS patients [47] and others not. Therefore, RLS in MS could be considered as a real secondary form of RLS which can be attributed to other factors such as CNS lesions [48] and cervical cord damage [49] and not to iron-related parameters.

Impact: Sleep-related movement disorders, especially RLS, have an enormous impact on aspects related to QoL such as sleep quality, depression, fatigue, body composition and functional capacity of MS patients [50, 51]. In addition, the impact on functional capacity and physical fitness increases the disability levels and encourages a more sedentary life style, increasing further the overall cardiovascular risk [46, 50].

Treatment: RLS is underdiagnosed and undertreated in MS populations. We should note that no specific guidelines exist in regards to the management of RLS in the MS population. Due to the high prevalence of RLS, diagnosis should be considered with a low level of suspicion while dopaminergic therapy seems to be an effective approach at the moment[22] in combination with iron infusion and/or α-2-δ ligands [36]. Regarding PLMD the current general guidelines do not recommend pharmacological therapies in PLMD without RLS. The guidelines for the idiopathic patients recommend that ‘‘clinical judgment must be used in any pharmacologic intervention in PLMD” [52].

Sleep related Breathing disorders

Definition: Breathing disorders that affect sleep include Sleep Apnea (obstructive, central or mixed) and Hypoventilation Syndrome [53]. The seriousness of the disorders is related to the fact that apneas and hypopneas are often associated with cortical arousals disturbing the natural cycle of sleep. In obstructive sleep apnea (OSA) episodes, there is a complete absence of airflow due to collapse of the upper airway. During the apnea period, diaphragmatic contractions occur until the successful opening of the obstructed airways. In central sleep apnea (CSA), there is an absence of airflow but without any respiratory effort since the problem exists at the respiratory control in the brain [53]. Hypoventilation (Alveolar) syndrome is defined as an elevation in $PaCO_2$ to levels >45 mmHg and associated with hypercapnia and hypoxaemia, which adds to the clinical manifestations and morbidity of the syndrome [54].

Prevalence: Prevalence data are not well established. Studies have reported values from 4–21% [55, 31], up to 58% of the MS patients examined for OSA [56].

Causes: Apart of the major risk factors involved such as age, gender and obesity, there are several other possibilities and potential bidirectional relations that may create a vicious cycle between sleep-related breathing disorders and MS, however, so far no studies have been conducted to characterize this specific relationship. The pathophysiological causes of OSA vary between anatomical and non-anatomical contributors [57]. The precise pathophysiological mechanisms for central apneas vary but an unstable ventilatory drive is the principal underlying mechanism which leads to a miscommunication between the respiratory control and the peripheral sensors during sleep[58].

Impact: Sleep-disordered breathing and MS have many overlapping signs and symptoms that are very difficult to separate due to the synergistic nature of them. Sleep-disordered breathing has been documented to affect QoL by causing fatigue and day sleepiness, and to be linked with neurocognitive dysfunction, depression, falls risk and cardiovascular mortality[53].

Treatment**:** Treatment of sleep-related breathing disorders in MS is not different from treatments used for the non-MS patients including lifestyle modifications such as weight loss, smoking cessation, alcohol reduction and respiratory support using the continue positive airway pressure (CPAP) [59] or bilevel positive airway pressure (BiPAP)[60]. While CPAP generally delivers a single pressure, BiPAP delivers an inhale pressure and an exhale pressure. Alternatively, various dental appliances have been used in order to maintain an open air way but occasionally surgical approaches are recommended. Treatment of sleep-related breathing disorders in MS could led to significant improvement of fatigue and tiredness [59].

Circadian Rhythm Disorders

Definition: Circadian rhythm disorder is a condition affecting the biological clock. There is a discrepancy between the internal (biological) circadian rhythm and the external 24-h environment affecting the natural cycle of sleep [61]. The most common subcategories of the disorder include the delayed sleep phase disorder (common in adolescents) and the advanced sleep phase disorder (common in the elderly)[62]

Prevalence: The prevalence of the circadian rhythm sleep disorders is not known but in a recent study they seemed to affect approximately 30% of the MS patients and to be more frequent in MS patients with severe fatigue compared to the general population [61].

Causes: Circadian rhythm sleep disorders may be due to environmental/external factors such as shift work and jet lag but in the case of MS additional internal factors have been proposed, related to the degree of demyelination of the afferent and the efferent nerve pathways from the suprachiasmatic nucleus [63, 64].

Impact: These disorders affect patients' QoL causing insomnia, hypersomnia and severe fatigue. Patients complain also of severe disturbances in social, occupational, and other important areas of functioning[61, 62].

Treatment: There are no MS-specific treatment options for circadian disorders. The classical approach includes some cognitive behavioural therapy in addition to good sleep hygiene and timed bright light exposure [36]. The

supplementation with melatonin seems to be very beneficial for the majority of the sleep disorders including circadian rhythm sleep disorders [65].

Other Sleep Disorders

Many other sleep disorders have been reported to affect MS patients but due to the lack of systematic evidence are not presented in this review. Those include narcolepsy, hypersomnia, REM sleep behaviour disorder, nocturia and other and they have been presented elsewhere [37, 66, 62, 36].

Paediatric MS and Sleep

Paediatric-onset multiple sclerosis accounts for approximately 3%–5% of all adults with MS and it is estimated that 10,000 children and adolescents in the USA have been diagnosed with the disease [67]. Sleep disorders have not been studied in paediatric MS populations but reports from 3 studies imply that they play an important role in QoL, levels of physical activity and obesity [68-70]. It's believed that health interventions that target aspects related to physical activity, diet, and sleep could have a positive impact in children's life [67].

Conclusions

Multiple sclerosis is an immune-mediated demyelinating disease of the central nervous system defined by a wide range of symptoms and signs that disrupt physical, cognitive, emotional, and social functioning.MS is among the most common causes of neurological disability in young adults affecting at least 2.3 million individuals worldwide. Sleep abnormalities are very common among MS patients affecting approximately 60% of patients but still remain under-recognized and inadequately addressed. Most frequently encountered sleep disorders are insomnia, sleep-related movement disorders, sleep-related breathing disorders and circadian rhythm disorders affecting both adults and paediatric MS populations. Aetiology still remains unknown with treatment options focusing on behavioural cognitive therapy, life style modification including improvement in sleep hygiene as well as melatonin supplementation. Even though multiple sclerosis is one of the most well studied neurological diseases, sleep problems in MS have not been adequately addressed. Given MS prevalence

is still rising affecting millions of people, more personalized medicine applications should possibly form the key approach for improving patients' quality of life and quality years.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Human and Animal Rights: This article does not contain any studies with human or animal subjects performed by any of the authors.

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