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Sleep Disorders in Multiple Sclerosis

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Abstract

Patients with multiple sclerosis (MS) have multiple causes of poor sleep and potential triggers may relate to MS-related symptoms, co-morbidities and adverse effects from medication. Sleep disorders may occur independently of demographic factors, gender and clinical condition. The real frequency of sleep disturbances in MS and their impact on the patients' quality of life are unknown. The prevalence of sleep problems in the population with MS ranges between 47 and 62% and is more frequent in women, as well as having a higher risk of mortality. High psychological burden has been associated with poor sleep and with increased risk of co-morbid conditions such as heart disease, obesity, dyslipidemia and diabetes, which may have a profound impact on long-term health. The poor sleeping patients with MS were more likely to report fatigue and sleepiness. Insomnia is present in mood disorders, restless leg syndrome (RLS), pain, nocturia and obstructive sleep apnea (OSA), in patients with MS. All the symptoms are intermixed, and it is not possible to discern the precipitating factor or the perpetuating factor. Clinicians should routinely ask about sleep when forming a comprehensive care plan for patients with MS. Sleep specialty referrals should be considered for management of conditions that require polysomnography (PSG) diagnosis.

Keywords: sleep disorders, insomnia, sleepiness, fatigue, respiratory disorders during sleep, cognitive impairment, cognitive behavioral therapy, multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that is increasingly prevalent in young adults. Patients with MS have multiple causes of poor sleep, and potential triggers may be related to MS-related symptoms, co-morbidities and adverse effects from drug therapy.

Major sleep disorders have been reported to be associated with numerous co-morbid conditions, including heart disease, obesity, stroke and diabetes [1].

The poor sleepers among patients with MS are more likely to report fatigue (one of the most frequent symptoms in MS) and pain (a co-morbid condition to MS-related fatigue but is confounded by depression and medication for treating pain or pain-induced sleep disorder) [1].

All the symptoms are intermixed, and it is not possible to discern the precipitating factor and the perpetuating factor. In this respect, sleepiness and fatigue may converge in some situations [1].

Insomnia is present in mood disorders (depression and anxiety), restless leg syndrome (RLS), pain, nocturia and others [1]. RLS is also an important cause of pain in patients with MS. Sleep disorders may occur independently of demographic factors such as gender and clinical-demographic factors. High psychological burden has been said to be independently associated with poor sleep patients with increased risk of co-morbid conditions such as heart disease, obesity and diabetes, which may have a profound impact on long-term health. The reverse situation is also possible.

The frequency of sleep disturbances in MS and their impact on the patients' quality of life are unknown. The prevalence of sleep problems in the MS population ranges from 47 to 62%, with a higher prevalence in women [2–5]. Sex hormones and genetic mechanisms, psychosocial factors, certain physical factors that disrupt sleep, such as pain or bladder dysfunction may contribute to sleep differences between women and men [5].

Obstructive sleep apnea (OSA), RLS and chronic insomnia in particular are frequent problems in the MS population, and play a key role in the development of debilitating fatigue and other poor functional outcomes in MS. Yet, despite their impact, sleep disorders in MS remain critically under-recognized in most clinical settings. A recommended approach to the fatigued patient with MS is also highlighted [6].

Sleep disorders during the course of MS may be secondary to numerous symptoms arising from the disease itself or can be primary with a common biological link. In either of the two cases, a bidirectional relationship exists between these co-morbid conditions [7].

Sleep disturbances have been associated with increased risk of mortality, cardiac disease, obesity and diabetes [8] and can contribute to the depression, pain and fatigue symptoms that are commonly seen in MS patients, which are often disabling [3, 9].

Sleep disorders are under-recognized in persons with MS. These sleep disorders can contribute significantly to fatigue, other daytime dysfunction and poor quality of life. A systematic, practical approach that takes into account clinical features of MS is recommended to enhance recognition of these conditions and facilitate appropriate treatment. Clinicians caring for patients with MS should routinely screen for sleep disturbances and initiate diagnostic workups, if clinically indicated.

Sleep specialty referrals should be considered for management of conditions that require polysomnography (PSG) diagnosis, for complex patients who present a diagnostic challenge and for patients who do not respond to first-line treatments. Clinicians should also routinely ask about sleep when forming a comprehensive care plan for patients with MS.

2. Effect or influence of multiple sclerosis in sleep disorders

2.1. Insomnia

Sleeplessness or insomnia is an inability to fall asleep or to stay asleep as long as desired. Insomnia is described as a complaint of prolonged sleep-onset latency, disturbance of sleep maintenance or the experience of non-refreshing sleep [10]. Episodic insomnia can usually be traced to an acute psychological stressor or an environmental change. Chronic insomnia may be related to a combination of factors including depression, poor sleep hygiene, learned sleeplessness, sleep-disordered breathing, nocturia, drugs or extrinsic factors such as noise [6, 11].

Patients with MS face a high risk of insomnia of around 40% [6] compared to roughly 10–15% in the general population [12]. Awakening too early in the morning is the most common symptom (58%) [13].

Primary symptoms of MS that can condition the onset of insomnia are neurogenic bladder (nocturia), spasticity, sexual dysfunction, neuropathic pain, paroxysmal phenomena, depression and anxiety [7].

Insomnia affects daytime activities, because of fatigue, mood disturbances (depression and anxiety), attention, concentration and memory impairment [7]. Higher fatigue scores have also been found to correlate with insomnia, especially middle insomnia [13].

2.1.1. Diagnostic approach

Patients with insomnia may complain of difficulty falling asleep, difficulty staying asleep or waking up sooner than desired [10]. There are screening tools to identify such patients.

The Pittsburgh Sleep Quality Index (PSQI) measures seven domains: subjective sleep quality, latency, duration, habitual efficiency, disturbances, use of sleep medication and daytime dysfunction over the last month. Each of these seven domains is self-rated by the individuals. The score of each question is based on a scale from 0 to 3, in which a score of 3 demonstrates the negative extreme on the Likert Scale. A global sum of 5 or greater indicates a poor sleeper (sensitivity of almost 100% for insomnia) [14, 15].

Insomnia Severity Index (ISI): a seven item questionnaire designed to assess the nature, severity, and impact of insomnia in adults. Scores >15 reflect moderate clinical insomnia. It is also a useful tool to monitor the effects of insomnia interventions [6].

Athens Insomnia Scale (AIS): a psychometric instrument designed for quantifying sleep difficulty. It consists of eight items: the first five pertain to sleep induction, awakenings during the night, final awakening, total sleep duration and sleep quality; while the last three refer to well-being, functioning capacity and sleepiness during the day. Either the entire eight-item scale (AIS-8) or the brief five-item version (AIS-5), which contains only the first five items, can be used. The score of each question is based on a scale from 0 to 3, where a score of 3 indicates the negative or normal extreme on the Likert Scale. A cut-off score of ≥ 6 on the AIS is used to establish the diagnosis of insomnia [16].

2.1.2. Management

After detecting insomnia, amelioration of any precipitating causes of insomnia is a cardinal step in its management. Medications or substances that may contribute to insomnia should be reduced or discontinued, if possible, there should be a check on which drugs the patient is taking (medications used to alleviate MS-related symptoms, including over-the-counter medications).

Selective serotonin reuptake inhibitors, while helpful for depressive symptoms, may worsen insomnia.

Stimulants and wake-promoting agents, which are commonly used for fatigue, may interfere with sleep initiation if taken during the late afternoon or early evening hours.

Antihistamines, which are used as sleep aids by up to 25% of patients with MS, have the potential to worsen RLS, and thereby worsen sleep-onset insomnia [6].

Co-morbid symptoms must be identified and treated: neuropathic pain (tricyclic antidepressants and the α -2- δ ligand pregabalin), spasticity (baclofen or tizanidine) and urinary urgency (anticholinergics) [6].

Cognitive behavioral therapy (CBT) is an innovative psychotherapy approach. CBT treatment could reduce anxiety and depression by changing thoughts and beliefs and consequently reduce the symptoms of insomnia [6, 17].

Pharmacological therapies can be considered if more conservative strategies have been exhausted or are not fully effective: benzodiazepines, benzodiazepine agonists, melatonin receptor agonists and orexin receptor antagonists.

2.2. Hypersomnia

Excessive daytime sleepiness (EDS)/excessive daytime drowsiness disrupt daily performance.

Hypersomnia may be due to acute thalamus injuries, mental disorders, especially depressive symptoms, sleep deprivation or as a consequence of received treatments.

2.2.1. Diagnostic approach

The Epworth Sleepiness Scale (ESS) is a screening tool that assesses sleepiness and has eight items. ESS values equal to or greater than 10 indicate excessive daytime sleepiness (EDS), and in this case, patients should undergo polygraphy or PSG (screening for sleep apnea) [18].

All fatigued patients should be asked about sleepiness and fill in the Epworth Sleepiness Scale (ESS) as these are not always associated with sleepiness.

Magnetic resonance imaging (MRI) should be performed because of the need to identify structural lesions in the brain.

2.2.2. Management

After detecting hypersomnia, the physician should check for any medications involved and withdraw them if possible, treat acute lesions of multiple sclerosis with corticosteroids,

indicate adequate sleep hygiene and assess whether specific treatment is needed to improve daily performance.

2.3. Restless leg syndrome

The four main criteria for diagnosis of RLS are: (1) unpleasant sensations in the legs; (2) worsening of the symptoms during rest; (3) relief of the symptoms by movement and (4) exacerbation of the symptoms in the evening or at night [19].

The periodic limb movement disorder (PLMD) includes repetitive periodic shaking episodes lasting between 0.5 and 5 seconds that occur during sleep every 20–40 seconds; mainly in the legs, but sometimes in the arms.

RLS and PLMD are motor disorders of sleep considered separate clinical entities, both conditions have the potential to cause disrupted sleep, share similar pathogenesis and have an increased prevalence among persons with MS. PLMD also frequently occur in the absence of RLS.

Most RLS patients (80–90%) have periodic leg movements PLM during sleep. They can cause arousals or micro-arousals leading to non-refreshing sleep, daytime sleepiness and fatigue. The prevalence of RLS in the general population ranges from 1 to 12% [20]. The prevalence of RLS in MS patients is two to five times higher than in the general population [21–24].

Differentiating RLS from other sensory and motor symptoms of MS can be difficult, as MS patients frequently suffer from spasms, dysesthesia, paraesthesia and spasticity in the legs, which worsen with immobility [25].

Predictive factors for RLS in MS patients include: older age, longer disease duration, progressive primary forms, greater disability as measured by the Expanded Disability Status Scale (EDSS), especially in the pyramidal and sensory subscales and shaking of the legs before onset of sleep [26]. Furthermore, RLS symptoms are more severe when associated with MS than when not associated with MS.

MS patients with RLS have more cervical cord lesions than those patients without RLS. These lesions possibly disrupt the ascending and descending pathways with cerebrospinal disconnection leading to these symptoms [10].

Primary RLS is a genetic form of RLS with autosomal dominant transmission [27]. Four genes have been associated with this syndrome [28] but no crossing over of those involved in MS [10].

Pathogenesis of RLS and PRLS shows dysfunction of downstream dopaminergic pathways, namely diencephalospinal and reticulospinal pathways, that project to the spinal cord. These pathways, *via* dopaminergic transmission, are responsible for the suppression of sensory inputs and motor excitability, and are susceptible to damage from diseases affecting the spinal cord. Impaired iron metabolism is also thought to contribute to the pathogenesis of RLS, as iron is a cofactor for a rate-limiting step in the synthesis of dopamine [6, 10].

Certain medications used in the management of persons with MS, such as antiemetic drugs, antipsychotic dopamine antagonists, antidepressants and antihistamines can also cause or worsen RLS [6, 10].

2.3.1. Diagnostic approach

Many descriptors can be used by patients to describe the restless sensation, including creeping, crawling, itching, burning, tightening, tingling or pain.

Symptoms of leg tightness relieved by voluntary movement suggest RLS, whereas involuntary spasms, even if a circadian component is endorsed, suggest spasticity. Rhythmic involuntary movements triggered by stretching or certain leg positions suggest clonus.

The Restless Legs Syndrome Diagnostic Index (RLS-DI) is a 10-item questionnaire. Scores range from -22 (no RLS) to $+20$ (definite RLS). A score of $+11$ yields 93.0% sensitivity and 96.1% specificity to accurately diagnose RLS [6].

Diagnosis of PLMD requires overnight PSG to assess for the presence of leg movements [6, 10].

The RLS Rating Scale is a useful tool to track treatment response and is a 10-item self-administered scale. Scores of 11–20 reflect moderate RLS.

2.3.2. Management

Iron supplementation should be implemented for a ferritin level of less than 50 ng/ml.

Reduction or discontinuation of medications and substances that can cause or worsen RLS or PLMD (dopamine antagonists, lithium, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, antihistamines, tricyclic antidepressants, alcohol, tobacco and caffeine) is recommended.

Dopamine agonists (pramipexole, ropinirole and rotigotine), and the α -2- δ ligand gabapentin and anticonvulsants are first-line treatments.

Benzodiazepines and opioid agents (oxycodone and methadone) are second line treatments.

Treatment for refractory RLS, or augmentation in response to dopaminergic therapy, is also likely to be optimized by sleep specialty care [6].

2.4. Respiratory disorders during sleep

Sleep-disordered breathing is characterized by episodes of nocturnal hypopnea and apnea resulting in a reduction or a cessation of airflow in the upper airway.

Patients with sleep-disordered breathing may complain of “fatigue,” decreased concentration, mood changes, erectile dysfunction, nocturia and mood changes, all these complaints are similar to those experienced in MS [29].

2.4.1. Apnea and hypopnea

Apneas and hypopneas may be caused by a collapse of the tissues and muscles in the pharynx (obstructive apnea/hypopnea) or a failure in the medullary respiratory signal (central apnea/hypopnea) [10].

Maintenance of upper airway patency during sleep requires an increase in pharyngeal tone that is primarily mediated by efferent motor output from cranial nerves X and XII to the palatal and genioglossus muscles, respectively. This process is largely influenced by afferent sensory input from pressure receptors in the upper airway, peripheral chemoreceptors in the aortic and carotid bodies, and brainstem respiratory generators. Pathophysiological processes that disrupt these tightly regulated brainstem pathways have the potential to impair nocturnal respiration. The medullary reticular formation is responsible for controlling automatic breathing during sleep [10].

Causative factors include obesity, craniofacial abnormalities, enlarged tonsils, congestive heart disease and degenerative central nervous system (CNS) disorders, to name a few [10].

Such apnea and hypopnea episodes may lead to nocturnal hypoxemia, frequent awakenings and daytime somnolence. When the apneas are associated with respiratory effort, the term obstructive apnea is used, and central apnea is used when there is a lack of respiratory effort [10].

Central sleep apnea is diagnosed when more of 50% of the events are central in patients with both central and obstructive apneas.

2.4.2. Obstructive sleep apnea

Obstructive sleep apnea is characterized by repeated episodes of upper airway obstruction and hypoxia during sleep [6].

The incidence of OSA in patients with MS is 2–21% and is one of the most common respiratory disorders [10].

Patients with MS who have a diagnosis of OSA and those at an elevated risk of OSA have increased fatigue and diminished quality life compared with undiagnosed or low-risk patients [6].

Sleepiness is primarily a result of acutely or chronically reduced sleep time, or poor sleep quality. Apnea severity may correlate with impaired cognition in MS [6].

2.4.2.1. Diagnostic approach

Questions must be asked about symptoms of snoring, pauses in breathing witnessed by a bed partner, gasping or choking upon awakening, non-restorative sleep, excessive daytime hypersomnolence or fatigue, cognitive disturbances and nighttime awakenings, any of which may arise in part from underlying OSA [6].

Dysarthria or dysphagia, obesity, increased neck circumference, crowded oropharyngeal inlet, retrognathia, or micrognathia are common physical exam findings [6].

The STOP-Bang questionnaire is a screening tool consisting of eight questions and measures that form the acronym snoring, tired, observed apnea, Blood Pressure-Body Mass Index, age, neck circumference and gender. Scores of 3 or higher indicate an elevated risk of OSA [6].

A full-night PSG is necessary to demonstrate the presence of obstructive respiratory events during sleep to confirm the diagnosis of OSA. These events may be partial (hypopneas) or

complete (apneas), but must demonstrate evidence of a reduction in airflow during sleep, despite continued effort to breathe [6].

2.4.2.2. Management

Management strategies for sleep-disordered breathing should take into account the patient's primary apnea subtype, apnea severity, co-morbidities and behaviors, and other MS-specific symptoms or limitations. Guidance by a sleep medicine physician is often helpful [6]. Discontinuation of medication, such as opiates, antispasmodics or CNS depressants medications [6].

Positive airway pressure (PAP) therapy is delivered by a mechanical device and mask to splint the upper airway open during sleep. Supplemental oxygen, bi-level PAP and adaptive servo ventilation are other improvements that these devices have [6].

Oral appliances work by repositioning the mandible in the anterior and inferior position [6]. By improving nocturnal oxygen saturation and sleep quality, PAP therapy effectively reduces fatigue and can be effective in the treatment of depression. This is especially important given the link between fatigue and depression in MS [6, 18].

Disease-modifying therapy use, in particular emerged as a strong predictor of *reduced* apnea severity, raising interesting possibilities about the role of local and/or systemic inflammation in OSA [6].

2.4.3. Central sleep apnea

Central sleep apnea (CSA) is rare, and the prevalence is unclear in the general population. CSA involves repeated complete or partial reduction of airflow, caused by an intermittent lack of respiratory effort by failure in the medullary respiratory signal [10].

While the prevalence of CSA is less than that of OSA, patients with CNS disorders that affect pontine and medullary respiratory generators, including MS, may be at increased risk for this condition as well even nocturnal death (Ondine's curse) [6, 10].

CNS and brain stem-related nocturnal respiratory abnormalities such as central sleep apnea, paroxysmal hyperventilation, hypoventilation, respiratory muscle weakness and respiratory arrest have all been described and should be considered in this patient population in the evaluation of symptoms of daytime somnolence, increased fatigue and non-refreshing sleep [11].

2.4.3.1. Diagnostic approach

In patients with symptoms of daytime somnolence, increased fatigue and non-refreshing sleep, the physician must ask about nocturnal respiratory abnormalities [11] and look for evidence of reduction in airflow in the absence of respiratory effort in an overnight PSG.

In patients with both central and obstructive apneas, central sleep apnea is diagnosed when more than 50% of the events are central. The coexistence of OSA or CSA and MS has been described by several authors [2, 10, 30].

2.4.3.2. Management

In the cases of central sleep apnea not symptomatic or central sleep apnea during sleep-wake transition (20% of central sleep apnea cases resolve spontaneously) observation is recommended.

In other cases, PAP treatment, adaptive servo ventilation, oxygen, added dead space, carbon dioxide inhalation and overdrive atrial pacing are needed.

2.4.4. Nocturnal urinary disorders

Sleep disturbance is associated with outcomes such as increased risk of falls and mortality. Nocturia may both precipitate poor sleep and perpetuate insomnia (awakenings associated with nocturia may themselves be perpetuating factors) [31].

Overactive bladder (OAB) syndrome is a condition that accompanies urgency (a significant factor for sleep disruption), with or without incontinence, frequently with increased daytime frequency and nocturia [32]).

Nocturia is defined by the International Continence Society as the complaint that an individual has to wake at night one or more times to void. It reflects the relationship between the amount of urine produced while asleep, and the storage by the bladder of urine received. Nocturia is a symptom rather than a disease and causative categories have been proposed and is the most common storage symptom in the general population [32].

Nocturia can occur as part of lower urinary tract dysfunction (LUTD), notably in overactive bladder syndrome (OAB). Nocturia can also occur in association with other forms of LUTD, such as bladder outlet obstruction or chronic pelvic pain syndrome [33].

Nocturia is due to nocturnal polyuria, a decreased nocturnal bladder capacity or a mixture of the two. Various duplicating factors for nocturia have been reported, including pathological conditions such as diabetes, LUTD, cardiovascular disease, primary sleep disorders and sleep apnea [32].

Nocturia is a feature of systemic conditions affecting water and salt balance, leading to excessive production of urine at all times (global polyuria) or primarily at night (nocturnal polyuria), so that nocturia can be a systemic symptom such as cardiovascular, endocrine and renal disease can affect water and salt homeostasis, leading to an increased rate of urine production [33].

Nocturia can significantly influence quality of life, efficiency, vigor and awareness of health, primarily due to sleep disruption.

2.4.4.1. Diagnostic approach

Asking how many times the patient wakes up at night because of nocturia, whether urinary urgency exists and the characteristics of urination, quantity of fluid intakes, physical exercise, medication being taken, etc. is also necessary *for the diagnosis of urinary problems*.

The use of specific questionnaires such as the PSQ, ISI and ASI for the diagnosis of insomnia or the ESS for the diurnal hypersomnia helps the physician to approach the functional repercussion of the problem.

The study occasionally needs to be completed with ultrasound studies, urodynamics, MRI and urinary sediment to identify LUTD or OAB problems.

2.4.4.2. Management

Interventions targeting nocturia may potentially improve sleep quality [31].

Hygienic measures such as reduced fluid intake at the end of the evening and frequently going to the bathroom during the day can help. Adequate treatment of co-morbid conditions such as diabetes mellitus, congestive heart failure or sleep apnea requires direct intervention for improvement nocturia.

Anticholinergics, mirabegron, α -blockers, 5- α reductase inhibitors, oral phosphodiesterase-5 inhibitors, desmopressin, diuretics, sleep-promoting agents and phytotherapy are used to treat urinary problems [33]. Half of MS patients with moderate to severe overactive bladder symptoms are treated with an anticholinergic medication [18].

Antimuscarinic drugs (Solifenacin), the most appropriate treatment for OAB, inhibited bladder stimulation may originate a decrease of drive to the brain stem, improve urination urgency and frequency and effectively reduce involuntary contractions and increase bladder capacity in patients with storage symptoms. The night time dosing of antimuscarinic drugs may improve tolerance compared to daytime dosing [32].

Antidiuretic therapy using clinician-directed dose titration has been reported to be more effective than placebo in terms of reduced nocturnal voiding frequency and duration of undisturbed sleep [33].

Nocturia severity improvement contributes to overall improvements in health-related quality of life [33].

The impact of treatment for nocturia in MS fatigue is unknown [18]. Non-pharmacological therapies such as cognitive behavioral therapy for nocturia (CBT-N) act on the abovementioned perpetuating factors. Sleep restriction entails reducing the excessive time in bed (a common occurrence in insomnia) and thereby improves sleep efficiency.

3. Effect of the quality of sleep in multiple sclerosis

Sleep disturbances have been associated with increased risk of mortality, cardiac disease, obesity and diabetes [8] and can contribute to the depression, pain and fatigue symptoms that are commonly seen in MS patients, which are often disabling [3, 9, 10].

3.1. Fatigue

Fatigue is defined as a subjective lack of physical or mental energy perceived by the patients or their caregivers which interferes with desired activities of daily living and it is the most frequent symptom in MS [18].

Between 80 and 97% [6] of patients report chronic fatigue, and more than 33% of patients rate this symptom as the most disabling [34–36].

Fatigue may occur at any stage of the disease and can even precede MS onset by several years. Fatigue affects the social and professional capabilities of patients, is a major reason for early retirement, reduced employment and is considered to be one of the main causes of impaired quality of life among MS patients, regardless of depression or disability [18].

Fatigue starts early in the morning and increases during the day. The perception of fatigue is exacerbated with environmental temperature and humidity [25], with age, [36] greater EDSS, mental or physical activity, infections and food ingestion [37].

Fatigue also deteriorates cognitive domains, such as information processing, memory and attention, [35] and it has significant socioeconomic consequences, including loss of work hours and in some instances, loss of employment, as well as family relationships and leisure time [36].

Fatigue is a symptom in MS patients and may have multi-factorial causes such as immunologic abnormalities (pro-inflammatory cytokines such as $\text{INF-}\alpha$), endocrine influences (cortisol and dehydroepiandrosterone (DHEA)), axonal loss, altered patterns of cerebral activation, sleep disorders (RLS, chronic insomnia, sleep-disordered breathing and altered sleep microstructure), depression and medications used to treat MS symptoms or immunomodulatory and immunosuppressive treatments [7, 38, 39].

“Primary” fatigue is related to the pathological changes of the disease itself, and results from a spectrum where one pole is the inability to generate the force required to perform the task due to a failure of force production at the muscle level “*peripheral fatigue*”; and the other pole is the inability to sustain the required neural drive to muscle because of supraspinal, spinal and even peripheral nerve contribution “*central fatigue*.”

“Central fatigue” can be the result of both cognitive and physical exertion and can reflect either a subjective sensation (fatigue) or an objective change in performance (fatigability) [37]. Dopamine imbalance plays a major role in developing fatigue. Central fatigue is a failure of the non-motor functions of the basal ganglia.

The subjective feeling of fatigue is related to inflammation and increased levels of cytokines such as interleukin-1 (IL-1), IL-6 and TNF-alpha [40].

“Secondary” fatigue attributed to mimicking symptoms, co-morbid sleep, irritable bowel syndrome, migraine, mood disorders, depression and anxiety and medication side effects [36, 37]. Persons with secondary fatigue report greater levels of fatigue than those with isolated primary fatigue [36].

There is a great variability in MS lesions from extensive areas of destruction during MS attacks, healing processes of and neuroplasticity. The clinical manifestations of fatigue do not seem to exclusively depend on the structural damage, but rather on the balance between restorative and inflammatory/degenerative processes and the rupture of the neural network [37].

In this respect, there is evidence that supports these hypotheses, linking fatigue with structural or functional abnormalities (atrophy in the thalamus, corpus callosum, cortical gray matter

regions: superior frontal and inferior parietal gyrus, parietal lobe) within various brain networks (the cortico-subcortical circuit as a substrate for MS fatigue and the involvement of a “fronto-striatal network”), greater activation of the premotor area ipsilateral to the movement with functional MRI (fMRI), decreased N-acetylaspartate-creatine ratio (NAA/Cr) as a marker of axonal dysfunction. Resting-state fMRI studies show changes in functional connectivity (FC) of the basal ganglia including reward processing and motivation. In addition to motor functions, the abovementioned aspects are involved in the pathophysiology of fatigue [18].

3.1.1. Diagnostic approach

Patients with MS report being fatigued very often, sometimes it is just the feeling of lack of energy but in others it interferes with their work or their daily life. There are tools that help quantify the degree of fatigue which are described below.

Severity Scale (FSS): is a self-administered questionnaire with nine items (questions) investigating the severity of fatigue in different situations during the previous week. Grading of each item ranges from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement and the final score represents the mean value of the 9 items. A total score of less than 36 suggests that you may not be suffering from fatigue [24].

Modified Fatigue Impact Scale (MFIS): The full-length MFIS consists of 21 items (total score 0–84, 38 as a cutoff to discriminate fatigued from non-fatigued individuals) while the abbreviated version has 5 items (0–20.). The abbreviated version can be used if time is limited but the full-length version has the advantage of generating physical, cognitive and psychosocial functioning subscales. The MFIS is one of the components of the MS quality life inventory [37].

MS patients, regardless of their fatigue level, have a significantly high frequency of RLS, higher Epworth sleepiness scale (ESS) scores, and higher PSQI scores. The time in bed, wake time after sleep onset %, total arousal index, limb movement arousal index and periodic limb movement arousal index are abnormal. The sleep efficiency index and sleep continuity index are lower in fatigued MS patients than non-fatigued MS patients. The PSQI results also suggest more disrupted sleep in fatigued MS patients. For all of the reasons above, quality of sleep studies should be performed with fatigued MS patients.

Once the patient has been identified with fatigue, it is necessary to investigate whether other co-morbidities are present (depression, anxiety, sleep disturbance, diabetes, heart disease, obesity, anemia, thyroid disease and nocturnal urinary disorders), what factors influence perpetuating fatigue and what situations can be modified in their lifestyle [6].

3.1.2. Management

Interventions targeting fatigue may potentially improve sleep quality and quality of life [31].

Pharmacological interventions are also reviewed and if there is evidence that a drug is involved in fatigue, it should be suppressed or the dose decreased [18]. Disease-modifying treatments (DMTs) are generally used to reduce relapses and progression and they occasionally cause an increase in fatigue, and in these circumstances it is important to change the medication for another DMTs [40].

Hygienic measures such as energy conservation programs, specific rehabilitation interventions physical (endurance, resistance, aerobic and combined training), aquatic therapy, cooling therapies, Tai chi, stretching, mindfulness-based interventions, yoga, acupuncture, progressive muscle relaxation and sleep hygiene advice (dependent on the nature of the sleep disorder) are more effective than pharmacological interventions [41].

Adequate treatment of co-morbid conditions such as diabetes mellitus, congestive heart failure, obesity, sleep apnea and other sleep disorders, depression and anxiety with pharmacological, psychological, behavioral and educational interventions is recommended [40, 41]. Pharmacological interventions for fatigue that are effective for reducing fatigue in patients with MS include amantadine, pemoline, prokarin (1 pilot study, side effects not reported), modafinil and pemoline combined with aspirin are efficacious for reducing fatigue in patients with multiple sclerosis. Carnitine has a discreet effectiveness. In general, the risk benefit of the drugs used for fatigue makes their recommendation be evaluated in each patient, highlighting them to the amantadine [37, 41]. Aminopyridines and coenzyme Q10 have an effect on fatigue by improving nerve conduction.

Nowadays, non-invasive brain stimulation (NIBS) techniques are gaining interest in the treatment of MS fatigue [37].

Promotion of health behaviors such as quitting smoking, physical activity (a high level of physical activity was borderline significantly associated with a decrease in co-morbidity) [42] and healthy eating may prevent some co-morbidities which were slow to show improvement in fatigue after the intervention, but they are effective [36].

3.2. Cognition

Cognitive impairment is a frequent feature of MS affecting up to 65% of patients [43] at both the earlier and later stages of the disease [44] and it tends to worsen over time [45].

MS negatively affects several aspects of cognitive functions, including attention, information processing [46], learning and memory, executive function and visuospatial abilities [47], having an important impact on quality of life [48], employment status [49], daily functioning, independence [50] and participation in social activities [51, 52].

Several factors have a negative influence on cognition in MS patients, such as depression [53], fatigue and sleep disturbances. Proper sleep is important for memory consolidation [54], and sleep deprivation has been related to impaired functioning in various cognitive domains [55].

Sleep disturbance causes a decrease in sustained attention [56], interferes with information processing and executive functioning [52]. Sleep disturbed patients reported higher levels of subjective cognitive problems compared to patients with normal sleep [52].

OSA and sleep disturbance are significantly associated with diminished visual memory, verbal memory, executive function (as reflected by response inhibition), attention, processing speed and working memory [52].

Excessive daytime sleepiness can lead to poor attention, poor memory, mood disturbances and increased risk of accidents [29].

In subjects with insomnia, a functional magnetic resonance imaging (fMRI) showed hypoactivation of the medial and inferior prefrontal areas during a cognitive task, in relation to the control subjects, which returned to normal values after treatment. Insomnia or superficial sleep produces less activation of the hippocampus and less connectivity is observed in the thalamus than in the control subjects. Damage to the hippocampus and thalamus (e.g., lesions and atrophy) in MS is associated with worse cognition. In controls, both regions may be related to sleep and cognition [52].

MS patients performed worse on all cognitive tests compared to controls. MS patients had less normalized gray matter (GM) volume, normalized white matter (WM) volume, hippocampal volume and thalamic volume. The hippocampus and thalamus showed increased functional connectivity (FC) in patients compared to controls, but lower FC was observed in patients with sleep disturbances (32%) [52].

3.2.1. Diagnostic approach

Neuropsychological manifestations can even be detected in patients during early stages of the disease. The Brief Repeatable Battery-Neuropsychology (BRB-N) [57] test was developed as a short and sensitive test to identify disturbances of cognitive domains in MS patients. The BRB-N has become the most widely used neuropsychological battery for MS, [58] and it is now being applied in clinical trials to monitor cognitive changes.

Different cognitive impairment criteria have been used: <1.0 SD, <1.5 SD and <2.0 SD in one, two or three subtests of the battery, respectively [59, 60].

3.2.2. Management

Strategies to optimize sleep could improve cognitive function in patients with MS.

In the case of insomnia, relaxation techniques such as autogenic training or progressive muscle relaxation can help the patient fall asleep earlier and have a longer sleep. But they do not improve sleep, so it has no sleep recovery effect. Behavioral therapies can improve sleep, but not prolong it. A combination of relaxation techniques and behavior therapy could be the most appropriate therapy for certain sleep disorders.

The general strategies for insomnia treatment include aspects of sleep hygiene such as extensions of night time in bed and frequent naps during the day. Pharmacological treatment is usually administered with stimulants such as amphetamines, methylphenidates, pemoline and modafinil [61].

As regards sleep hygiene, it is often necessary to make some lifestyle changes such as dinner should not be too late, nor too spicy or copious, maintain a regular sleep schedule, do not spend too much time in bed other than bedtime, do not drink caffeinated beverages such as coffee, black tea or cola, or caffeine medications, 4–6 hours before bedtime, do not smoke before going to bed or during the night, try to get enough rest and darken the bedroom, ventilate the bedroom, the temperature should not exceed 18° , do not do any physically demanding sport immediately before sleep because otherwise it will stimulate too much circulation, do not drink alcohol before going to bed or avoid sleeping too much during the day.

Patients with fatigue should organize daily routine and workloads. The physician also needs to improve the efficiency of information processing and working memory in these patients with fatigue [40].

Anxiety, depression, difficulty in sleeping and fatigue may have an impact on cognitive problems. If a person with MS experiences these symptoms and has problems with memory and cognition, they need to be provided with assessment and treatment (occupational therapist and neuropsychologist).

The concept of mental toughness (MT) has recently been recognized for its psychological importance not just in coping with stress but also for its association with increased physical activity (PA), and for its impact on both stress and objective sleep quality. MT consists of four key factors such as control (of own life and emotions), commitment, challenge and confidence (in own abilities and in other people); thus covering a range of cognitive-emotional processes closely involved in coping with stress, emotions, unexpected events and social setting [62].

3.3. Depression

Patients who suffer from problematic sleep and/or fatigue (with or without anxiety) may be more likely to experience higher depressive symptoms [63].

Depression is a mental illness that causes feelings of sadness and loss of hope, changes in sleeping and eating habits, loss of interest in your usual activities and pains that have no physical explanation.

3.3.1. Diagnostic approach

A trans-diagnostic approach to symptoms may be more effective than targeting each symptom separately, such as depression treatment or pain treatment alone. Trans-diagnostic models explain how multiple co-morbid symptoms or disorders develop rather than create disorder or symptom specific models [63].

3.3.2. Management

A trans-diagnostic treatment is an intervention that targets a range of diagnoses or problems through the use of treatment strategies targeting psychological processes that are common across disorders. It may be useful to consider all five factors such as depression, pain, anxiety, sleep and fatigue in designing a treatment plan. Treatments for the constellation of biopsychosocial concerns affecting many people living with MS.

The beneficial effects on depression of CBT targeting insomnia highlight a need for a comprehensive assessment of multiple concerns such as depression, anxiety, sleep problems or fatigue when treating people with MS who report higher levels of pain [63].

3.4. Trigger for an acute multiple sclerosis exacerbation

The mechanism by which sleep disorders trigger an acute MS relapse might be multi-factorial. Normal sleeping plays an important role in maintaining the normal function of the immune

system. Various studies have shown that sleep disorders are associated with elevated serum levels of pro-inflammatory cytokines and markers of oxidative stress [15].

The circadian regulation of cytokine output produces a daily rhythm in the inflammatory profile, with a pro-inflammatory state occurring at night. Disrupted sleep can interfere with this pattern leading to prolonged periods of inflammation throughout the day, thereby exacerbating symptoms. Furthermore, the circadian rhythmicity of key components of the immune system has been shown to be dysregulated in MS patients [64].

The central circadian pacemaker, located in the hypothalamic suprachiasmatic nuclei, is responsible for regulating the timing and expression of various circadian rhythms [65].

Sleep dysfunction and disruption in the circadian system alter the synchrony between these transcriptional and translational feedback loops, resulting in increased cellular permeability, which is thought to be an important underlying mechanism for initiating the inflammatory cascades causing a disease flare. In addition, the presence of pro-inflammatory cytokines has been proven to suppress the activity of circadian genes [65].

Melatonin is produced by the pineal gland that regulates circadian and seasonal rhythms. Secretion of melatonin is suppressed during daylight and enhanced during the night, promotes sleep by reducing sleep latency, decreasing wake time and increasing overall sleep quality [65].

Melatonin promotes anti-inflammatory states: it inhibits nitric oxide production, nuclear factor- κ B activation and tumor necrosis factor- α , it reduces COX-2 expression and matrix metalloproteinase activity (modulating apoptosis) [65].

Circadian sleep disorders are common in MS patients and could be linked to a disruption in melatonin production, which is important in sleep-wake cycle regulation. Melatonin helps dampen the overactive immune system and low levels are associated with relapse [64].

According to studies on an animal model, sleep deprivation is associated with an accelerated autoantibody production rate and increases oxidative stress (toxic effect on oligodendrocytes causing oligodendrocyte death and myelin damage). Chronic sleep deprivation breaks down blood-brain barrier (BBB) thereby increasing permeability [15].

Sleep disorders also result in an elevated serum concentration of interleukin-6 (IL-6), which further activates polyclonal B cells and triggers an autoimmune reaction. The serum concentration of IL-6 is significantly associated with the number of relapses in female patients with relapsing-remitting multiple sclerosis (RRMS) [15]. In the study of Sahraian et al. [15], the group in relapse had worse scores of global PSQI for the previous month than remission group (87.5% were poor quality sleepers). Age, gender, EDSS and disease duration did not associate with sleep quality in either group.

4. Co-morbidity condition

Co-morbidities have been shown to affect MS progression, time to initiation of the disease-modifying therapy (DMT), as well as treatment compliance, which may be related to the increased mortality of these patients as compared to the general population.

Co-morbidities can negatively impact sleep in MS patients, which can, in turn, lead to a worsening of symptoms, especially fatigue and pain.

Patients with sleep disorders are at risk of co-occurrence of other problems like vascular diseases, obesity and diabetes that would threaten the health of patients in the long term [17].

Circadian disruptions occur in shift workers and appear to contribute to hypertension, diabetes, breast cancer, lung cancer and elevated prostate-specific antigen. Shift work entails changes in diet, exercise and tobacco use, which can confound circadian rhythm and sleep disturbance studies [65].

4.1. Narcolepsy

Narcolepsy is classified as a chronic sleep disorder associated with sleep attacks and other features attributed to abnormalities of rapid eye movement sleep, such as hypnagogic/hypnopompic hallucinations, cataplexy, sleep paralysis and disrupted nocturnal sleep. The usual PSG features include a mean sleep latency of less than or equal to 8 minutes and two or more sleep onset rapid eye movement periods [6]. There is a high variability in the prevalence across different geographic areas, which is thought to be related to differences between the populations and current study methods [10].

Narcolepsy is estimated to affect 0.02–0.05% of the general population, the overall prevalence of narcolepsy among persons with MS is unknown [6, 10].

There are two subtypes of primary narcolepsy which are described below.

Narcolepsy type 1 (immune-mediated loss of hypocretin-secreting cells in the lateral hypothalamus) [6, 10] is characterized by the presence of cataplexy (a reliable clinical marker for hypocretin deficiency) and hypocretin deficiency in CSF (<110 pg./dl).

Narcolepsy type 2: normal hypocretin levels [6, 10].

The secondary causes of narcolepsy show that MS is the fourth most common cause of narcolepsy after inherited disorders, CNS tumors and brain injury, and it has been found that 12% of the cases of secondary narcolepsy were due to MS [6, 10, 66].

In terms of genetics, 95% of narcoleptic patients and 50–60% of MS patients are positive for DR2 haplotype. The human leukocyte antigen (HLA) DQB1*0602, a known genetic risk factor for narcolepsy, also influences the presence and severity of MS. Therefore, both diseases are closely related to the same genes of the human leukocyte antigen (HLA) system, which is the basis for labeling for most autoimmune diseases. This relationship suggests that similar autoimmune factors may be at work in the development of each disorder and might be partially responsible for symptoms of fatigue and sleepiness [6, 10, 67].

The aforementioned findings merit further attention given the potential impact of sleep disorders on the health and quality of life of MS patients [10].

4.1.1. Diagnostic approach

A diagnosis of narcolepsy requires PSG and CSF hypocretin assays (only performed at a few academic institutions).

Narcolepsy cannot be established in the presence of concomitant OSA, insufficient sleep, shift work or another circadian sleep disorder [10].

In such cases, adequate treatment of concomitant sleep disorders must be confirmed prior to the multiple sleep latency testing.

The usual PSG features include a mean sleep latency of less than or equal to 8 minutes and two or more sleep onset rapid eye movement periods [6].

It is necessary to perform MRI studies to rule out secondary causes of narcolepsy [6].

4.1.2. Management

Patients with suspected narcolepsy are usually referred for diagnosis and management by sleep specialists: wake-promoting agents or stimulants may be used to increase wakefulness and vigilance.

Sodium oxybate (an endogenous metabolite of gamma-aminobutyric acid (GABA) may be used in selected cases.

REM-suppressing antidepressants may be useful for cataplexy and sleep paralysis.

In cases of secondary narcolepsy when new hypothalamic lesions are identified, a trial of high-dose steroids should be considered [6].

4.2. Overweight and obesity

Being overweight is having more body fat than is optimally healthy. The degree to which a person is overweight is generally described by the body mass index (BMI). Overweight is defined as a BMI above or equal to 25 and below 30.

Obesity is defined as a BMI over 30. The prevalence of overweight and obesity in patients with multiple sclerosis ranges from 19 to 55%. These differences are due to the distinct prevalence in the general population, differences in geographic origin, population type (military veterans or hospital users) and/or age group. It is notable that the American population has the highest numbers of obesity. Besides which, it is worth mentioning the different methodology used, including overweight with obesity in some studies [42, 68].

Spanish data (NARCOMS study) have shown that overweight people with MS had lower general and mental health scores compared to those with normal weight and found no differences in other quality of life scales of the SF-36 [69].

Depression levels were higher in the overweight versus normal weight MS Spanish patients. This finding is due to pathophysiological mechanisms common to both depression and obesity, given that chronic low-grade pro-inflammatory states can generate various abnormalities in different neural networks [69].

BMI was significantly related to levels of disability, with obese participants 1.4 times more likely to have moderate/severe disability while controlling for age, gender, time since diagnosis and number of co-morbidities. As the BMI increases, the number of co-morbidities

increases with higher odds for disability and prior relapse and lower health-related quality of life [42].

Central obesity, as defined by increased waist circumference, absolute waist circumference >102 cm in men and >88 cm in women or waist-hip ratio (the circumference of the waist divided by that of the hips) of >0.9 for men and >0.85 for women, is often indicative of metabolic syndrome, and is suggested to be a more potent risk factor (cardiovascular disease, Alzheimer's diseases and type 2 diabetes) than body mass index alone.

4.2.1. Diagnostic approach

Weight, height, BMI = weight (kg)/height (m²), waist circumference and waist-hip ratio.

4.2.2. Management

Patients who are overweight and obese are usually referred for diagnosis and management by a multidisciplinary team such as specialist nutritionist, physiotherapists, surgeons and neuropsychologists.

Gradual weight loss and gentle physical exercise and stretching are recommended. Small meals and small amounts of food, low in animal fats and fresh fruits. Bariatric surgery may be necessary in severe cases of obesity.

Co-morbidities have been shown to be associated with increased hospitalization, rate of progression to disability, decreased quality of life and increased mortality risk which is why they have to be properly treated [42].

Adverse health behavior including being overweight and obese, smoking and sedentary behavior are common in people with MS [42]. These behaviors can be modified and may significantly change the level of health. Health professionals should be focused on achieving these behavioral changes in patients with MS.

5. Influence of the treatment of multiple sclerosis in sleep

The therapeutic approach to multiple sclerosis involves pharmacological, rehabilitative, psychological, lifestyle modifying interventions, etc. These can be used independently or coordinated with each other with a holistic view. This approach involves changes in the structure of sleep, which are not always beneficial.

5.1. Treatment of relapses

Therapeutic options to treat MS relapses include oral glucocorticosteroids [70, 71] or their intravenous administration at a high dose as first line and therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIG) as second line treatments in glucocorticosteroids unresponsive patients [72], corticotrophin injection and Acthar [73].

The action mechanisms of glucocorticosteroids in the immune system are pleiotropic, induced apoptosis of peripheral blood leucocytes and down-regulation of T-cell activity delayed for 7–10 days after a 5-day course of administration [72].

TPE is the removal of circulating antibodies, cytokines, immune complexes and complementary factors, all of which are assumed to be involved in immune-mediated neuroinflammation.

IVIg reduces or prevents the activation of inflammatory cells and alters antibody responses.

Optimal treatment of relapses increases the chance of limiting or avoiding residual deficits which have been related to the progression of disability in MS [72].

Sleep disturbance (insomnia) might be one of the side effects of corticosteroid therapy during an acute exacerbation in MS. Benzodiazepines are useful during these periods [74].

5.2. Disease-modifying therapies

Interferons are DMTs that produce major alterations of sleep, mainly by the flulike reaction, fever, headache, alteration of the mood and fatigue. It is imperative to treat these effects to improve the patient's quality of life including finding what time is best to administer the treatment. The monoclonal antibody Natalizumab could reduce fatigue [37].

5.3. Symptomatic treatment

Specific treatment of symptoms of MS manifestations occasionally interferes with sleep quality, leading to insomnia or drowsiness. The treatments the patient is receiving need to be reviewed in the event of any sleep disturbance.

Selective serotonin reuptake inhibitors, while helpful for depressive symptoms, may worsen insomnia. Stimulants and wake-promoting agents, which are commonly used for fatigue, may interfere with sleep initiation if taken during the late afternoon or early evening hours. Antihistamines, which are used as sleep aids by up to 25% of patients with MS, have the potential to worsen RLS, and thereby worsen sleep-onset insomnia.

Patients suffering from fatigue symptoms are often treated with antidepressants due to the strong association between depression and fatigue. Modafinil, amantadine and aminopyridine are known as fatigue treatment options, although the physician must monitor the real effect on sleep and adjust the administration schedules so as not to mask the effect on fatigue.

Medications used to alleviate MS-related symptoms, including over-the-counter medications, also have the potential to interfere with sleep. Given the high frequency use of these medications in this population, the physician should carefully consider screening for these medications and assessing possible effects on sleep.

5.3.1. Management

The first approach includes reviewing the list of drugs being taken by the patient and adjusting doses or suspending them if necessary to avoid interference with other situations of the patient. In this respect, the multidisciplinary approach to the patient is important.

6. Conclusions

Sleep disorders in patients with MS are frequently underdiagnosed. Clinicians caring for patients with MS should routinely screen for sleep disturbances.

All the symptoms are related, many of them share the same pathophysiology where it is not possible to identify the precipitating factor and the perpetuating factor. Sleep disturbances increase the risk of mortality, co-morbidities (cardiac disease, obesity and diabetes) and can contribute to the depression, pain, cognitive impairment and fatigue symptoms which are disabling and worsen the prognosis of multiple sclerosis.

The therapeutic approach to sleep disorders in MS involves pharmacological, rehabilitative, physical, psychological, educational and lifestyle modification interventions. These can be used independently in combination, with combined therapies being more effective.

The list of drugs being taken by the patient should always be reviewed and doses should be adjusted or suspended if necessary to avoid interference with sleep disorders.

Conflict of interest

Montserrat González Platas and María Yaiza Pérez Martín report no conflicts of interest concerning the manuscript.

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