Sleep Medicine 56 (2019) 90–97

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Sleep-related disorders and their relationship with MRI findings in multiple sclerosis

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ARTICLE INFO

Article history:
Received 8 July 2018
Received in revised form
8 January 2019
Accepted 10 January 2019
Available online 21 January 2019

Keywords:
Neuroimaging
Neurological disorders
Multiple sclerosis
Sleep-related disorders

ABSTRACT

Sleep-related disorders have been reported to have a higher prevalence in multiple sclerosis (MS) than in the general population. They are often undervalued for the presence of more severe physical problems and the occurrence at night, without a direct observation in common clinical practice, but if not recognized and treated they can negatively affect the quality of life causing daytime drowsiness and worsening fatigue. Sleep related disorders most commonly reported in MS are as follows: insomnia, sleep-related breathing disorders (SRBD), restless legs syndrome (RLS) and periodic limb movement disorders (PLMD). Secondary narcolepsy, REM sleep behavior disorder (RBD) and propriospinal myoclonus have been also described in some case reports or series. The purpose of this review is to correlate the more common sleep disturbances in MS patients to the involvement of specific brain regions, analyzing their relationship with MRI findings. While insomnia is usually secondary to other disabling symptoms such as nocturia or pain, SRBD, RLS, narcolepsy, RBD and propriospinal myoclonus in MS patients can be the consequence of an injury of specific central nervous system (CNS) areas. Lesions in the pontine tegmentum and the dorsal medulla have been associated with SRBD, spinal cord lesions or atrophy with RLS, bilateral lesions in the lateral hypothalamus with narcolepsy-like symptoms, lesions in the dorsal pontine tegmentum with RBD and intramedullary demyelinating plaques in spinal cord with propriospinal myoclonus. MS specialists and general neurologists should be aware of these comorbidities since neuroimaging, which is routinely performed in MS, could provide helpful clinical indications on patients with secondary sleep-related disorders and to categorize symptomatic patients who need to underdo more in-depth sleep studies.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory disorder of the CNS with a mean age at onset of 30 years, affecting women 2–3 times more often than men. MS has a highly variable course, since it can involve different areas of brain, spinal cord and optic nerves and can cause impairment in mobility, balance, sensation, sphincter, vision and cognition [1,2].

MRI is the most sensitive tool to confirm a clinical diagnosis of MS [3,4] and to exclude other possible causes. MS lesions typically appear as multifocal white matter T2-hyperintensities in characteristic CNS locations: periventricular, infratentorial, cortical –juxtacortical and spinal [5,6].

MS patients will often be suffering from comorbid common sleep disorders as does the largest part of the general population, but some sleep disturbances seem to have a prevalence rate higher than expected [7–9]. Veauthier et al., recently demonstrated the presence of sleep disorders in 74% of 66 consecutive MS patients through polysomnography (PSG) [7]. In particular, sleep-related breathing disorder (SRBD), insomnia, restless legs syndrome (RLS)

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https://doi.org/10.1016/j.sleep.2019.01.010
1389-9457/

and periodic limb movement disorder (PLMD) are reported to be more common in the MS population [7–9]. The role of processes related to the disease itself (lesions, brain atrophy) in causing these disturbances has not been clearly established yet. Additionally, these disorders are often under-investigated, under-recognized or undervalued by neurologists treating MS patients. Their evaluation and management can easily be overlooked in the common clinical practice due to the occurrence at night in the absence of diurnal signs or in the presence of severe motor symptoms. If untreated, these disturbances can negatively impact patients' quality of life. Indeed, poor sleep quality is related to a higher prevalence of fatigue and daytime drowsiness [7]. In addition, the oxidative stress induced by sleep deprivation has been related to the presence of acute relapses, exerting a toxic effect on oligodendrocytes and favoring myelin damage [10].

The objective of this review is to analyze the relationship of sleep disorders in MS patients with MRI findings, with the purpose to identify the probable alterations of specific neuroanatomical pathways.

2. Materials and methods

The bibliographic search was performed on PubMed database (last access on January 01, 2019) using the terms sleep disorders AND multiple sclerosis ($n = 512$), sleep-related breathing disorders AND multiple sclerosis ($n = 17$), restless leg syndrome AND multiple sclerosis (n = 85), periodic limb movement disorder AND multiple sclerosis ($n = 8$), narcolepsy AND multiple sclerosis ($n = 118$), REM Sleep Behavior disorder AND multiple sclerosis (n = 22), insomnia AND multiple sclerosis ($n = 147$), hypersomnia AND multiple sclerosis ($n = 101$), excessive daytime sleepiness (EDS) AND multiple sclerosis ($n = 44$), spinal myoclonus AND multiple sclerosis ($n = 11$). Abstracts were read to include only relevant articles and their references were hand-searched for potentially useful data. An additional research was performed with key words MRI AND sleep disorders (n = 1966) and only relevant articles were selected as well.

Searches were performed by FM and RG and the selection of relevant articles was shared with all Authors.

3. Results

Sleep disruption in MS is highly prevalent and affects approximately half of the patients [9,11]. Several factors can impact on sleep quality causing daytime somnolence, increased fatigue, worsening depression and a lowering in pain threshold. These factors must be distinguished by comorbid sleep disorders and include symptoms related or secondary to the disease itself (neuropathic and somatic or visceral pain, paresthesia, anxiety and stress, nocturia, muscular cramps and rigidity, anxiety and depression) or adverse effects of treatment (eg, INF-Beta-related flu-like syndrome, hypothyroidism, or corticosteroids-related insomnia) [9,12]. Tachibana et al., reported these "sleep problems" in 53,6% of MS patients [13].

Using current international diagnostic criteria [14,15], the most common sleep disorders reported in MS are as follows: insomnia, SRBD, RLS and PLMD [7,8,11].

Narcolepsy-like symptoms are rarely described in the literature as well as rapid eye movement sleep behavior disorder (RBD).

3.1. Insomnia in MS

3.1.1. Prevalence

The prevalence of insomnia in the general population ranges between 10 and 15% [11]. Several reports indicate a higher prevalence in MS. Brass et al., reported insomnia in 31,6% of 2375 using validated questionnaires [16]. Initial insomnia was found in 56,2% of patients in a larger study conducted by Stanton et al., 27,5% referred insomnia to anxiety, while 22,5% complained of pain [17]. In 72,5% of patients with middle insomnia it was related to nocturia, which was also the main explanation of early waking up (terminal insomnia - 40,4%) [17]. Similar data (53,6%) were found by Tachibana et al., in 28 MS patients consecutively studied [13]. Other neurological disorders can lead to insomnia in MS patients, mainly RLS and anecdotally propriospinal myoclonus (see below in the specific sections). In sum, approximately 30–50% of MS patients suffer from insomnia, but studies comparing the prevalence in MS with the general population are lacking.

3.1.2. Neuroanatomical pathways and MRI findings

Differently from other sleep-related disturbances in MS, the disruption of specific neuroanatomical pathways involved in the control of normal sleep functions cannot be directly associated with the onset of insomnia. Indeed, most of the cases of insomnia in MS patients are secondary to comorbid anxiety/depression or to physical symptoms causing nocturnal discomfort. These disturbances can in turn enhance negative effects of neuropsychological comorbidities on sleep quality either directly or indirectly, worsening pre-existent mood alterations. Although evidence of specific CNS alterations possibly related to primary insomnia in MS are currently lacking, nocturnal symptoms can be consequent to a focal damage in specific neuroanatomical sites. The most common nocturnal symptoms causing sleep discomfort in MS patients include nocturia and acute or chronic pain syndromes.

Nocturia related to neurogenic bladder is responsible for most cases of middle and terminal insomnia [18]. MRI findings in patients with nocturnal urinary urgency or incontinence are usually lesions involving the pons or the sacral spinal cord (Table 1). Specifically, patients with larger pontine lesions reported worse urgency incontinence. This data can be explained by an involvement of the pontine micturition center (Barrington's Nucleus) which coordinates the micturition reflex by receiving neural input from the bladder via the periaqueductal grey and from the hypothalamus, sending fibers to the sacral chord [19]. This nucleus cannot be reliably distinguished on MRI scans but plausibly larger pontine lesions can impair also the pontine storage center which is located ventrally and laterally to the pontine micturition center. The latter causes external urethral sphincter contractions via the Onuf's nucleus.

The most common paroxysmal syndromes in MS include Lhermitte's sign (26%), trigeminal neuralgia (25%) and painful tonic spasms (19%). Chronic pain occurs in about 60% of patients and generally consists in dysaesthetic extremity pain [20]. Mazhari et al., analyzed different case reports/series in order to identify MRI lesions as the origin of neuropathic pain in MS patients [21]. Spinal cord lesions (dorsal root entry zone, posterior columns and antero-lateral cervical or upper thoracic tract - from C2 to D2) were found to be related to most cases of painful chronic dysaesthetic syndromes. Pyramidal tract lesions in the brain (cerebral peduncle, internal capsule and corona radiata) or in the spine usually explain painful tonic spasms or stereotyped involuntary posturing of the limbs. Head/facial pain has been reported in relation to lesions involving: (1) the trigeminal root entry zone or the main trigeminal sensory nucleus in the brainstem (trigeminal neuralgia); (2) the posterior part of the upper cervical tract and the periacqueductal grey matter in the brainstem (migraine and other types of not well defined headache); (3) the left brachium or right dorsal pons (cluster-like headache); (4) the right antero-lateral spinal cord at C2 (occipital neuralgia); and (5) the midbrain adjacent to right third nerve fascicle (painful third nerve palsy) [21] (Table 1).

Regarding insomnia secondary to comorbid anxiety/depression, it is important to underline that causative mood disorders in MS

Table 1
Prevalence, MRI findings and supposed neuroanatomical pathways of sleep-related disorders in multiple sclerosis.

Sleep disorders	Prevalence in the general population	Prevalence in MS population	MRI findings in MS patients	Neuroanatomical pathways
Insomnia	10–15% [11]	31,6–56,2% [16,17]	- **Nocturia:**[a] lesions in pons and sacral spinal cord. - **Acute and chronic pain:**[a] (1) Spinal cord lesions (dorsal root entry zone, posterior columns and antero-lateral cervical or upper thoracic tract) =*painful chronic dysaesthetic syndromes.* (2) Pyramidal tract lesions in the brain (cerebral peduncle, internal capsula and corona radiata) or in the spine. =*painful tonic spasms.* (3) Brainstem/upper spinal cord lesions =*head/facial pain* • trigeminal root entry zone or trigeminal sensory nucleus: *trigeminal neuralgia*; • posterior part of upper cervical tract and periacqueductal grey matter: *migraine and other type of not defined headache*; • left brachium or right dorsal pons: *cluster-like headache*; • right antero-lateral spinal cord at C2: *occipital neuralgia*; • midbrain adjacent to right third nerve fascicle: *painful third nerve palsy*	- **Nocturia:**[a] pontine micturion center (Barrington's nucleus) and pontine storage center. Onuf's nucleus. - **Acute and chronic pain:**[a] sensory pathways and nuclei in brainstem and spine, pyramidal tracts and periacqueductal grey matter.
Sleep related breathing disorders (SRBD)	7,14–58,1% [25]	58–80% [25,26]	- Lesions in the pontine tegmentum and dorsal medulla. [13,30]	- Brainstem respiratory nuclei in the lower (dorsal and ventral respiratory nuclei) or upper (nucleus parabrachialis medialis) medulla and pons. - Vestibulo-cerebellar pathways in the brainstem.
Restless leg syndrome (RLS)	2,8–18,3% [34]	13,3–65,1% [35–38]	- Spinal cord lesions or atrophy *(lower fractional anisotropy)*.[47,48,53,54]	- Descending dopaminergic fibers regulating motor and sensory pathways.
Periodic limb movement disorder (PLMD)	8-10% [43]	36% [43,44]	- Infratentorial lesions (cerebellum, brainstem and spinal cord) [43]	- *Not well defined* (loss of supraspinal inhibitory influences on the pyramidal tract? Alteration of intra-spinal pathways?).
Narcolepsy	0–0,05% [68]	15 cases reported [72–81]	- Bilateral lesions in the lateral hypothalamus (3 out of 15 cases).[72,75,81]	- HCRT1 neurons in the lateral hypothalamus and their projection to the brainstem, basal forebrain, cortex and spinal cord.
REM sleep behavior disorder (RBD)	0.5% [101]	6 cases reported [84–89]	- Lesions in the dorsal pontine tegmentum (4 out of 6 cases). [84–86,88,89]	- Glutammatergic neurons in the pontine sublateral dorsal nucleus (SLD, locus subcoeruleus).
Propriospinal myoclonus (PSM)	NA	1 case reported [95]	- Intramedullary demyelinating plaques (cervical cord). [95]	- Spinal segmental motor generators corresponding to muscles involved by the jerks.

MRI = magnetic resonance imaging, **MS** = multiple sclerosis, **HCRT1** = hypocretin/orexin.
NA = not available.
[a] Nocturia and acute or chronic pain syndromes are the most common symptoms related to insomnia in MS.

usually results from a complex combination of genetic, biochemical, immunological and psychosocial factors [22]. Nevertheless, some studies demonstrated that some brain structural changes could contribute to the higher prevalence of anxiety and depression in the MS population. In particular, patients with RRMS and depression showed a reduced total brain volume and a significantly increased lesion burden at T2 MRI in comparison to patients with RRMS without depression [23]. Gray matter loss of cortical regions located bilaterally in the frontal lobes is the pattern of brain atrophy more commonly associated with depression in MS patients [24].

3.2. Sleep related breathing disorders in MS

3.2.1. Prevalence

Studies investigating the prevalence of SRBD in MS show a high result variability because of the use of different scoring systems and cut off values. In particular, the International Classification of Sleep Disorders (ICSD-3) [14] criteria for obstructive sleep apnea (OSA) include an apnea/hypopnea index (AHI) $\geq$ 5/h in the presence of daytime signs/symptoms (fatigue, depression, cognitive dysfunction) that in MS patients are highly prevalent [7] and in most of cases related to the disease itself. Kaminska et al., demonstrated a higher prevalence of OSA in MS patients in comparison to the general population [25] (58% versus 49%; odds ratio in the MS subgroup = 1,57), using the American Academy of Sleep Medicine (AASM) criteria of AHI $\geq$ 15/h or apnea or hypopnea episodes lasting 10 s associated with arousal or desaturation $\geq$ 4% [14]. The prevalence of central sleep apnea (CSA) in the MS population has been reported by Braley et al., to be about 4% in a group of 48 MS patients from a cross-sectional study with PSG [26].

3.2.2. Neuroanatomical pathways and MRI findings

The relationship between ischemic or structural lesions in the brainstem (in particular, lateral medulla oblongata) and the development of SRBD has been well documented [27–29]. As concerns MS, Tachibana et al., reported three cases of sleep apneas related to the MRI evidence of multiple lesions involving the pontine tegmentum and dorsal medulla [13]. Moreover, MS patients referred for PSG with MRI or clinical evidence of brainstem lesions showed a higher AHI in comparison to patients without signs of brainstem involvement [30] (Table 1). These results can be explained by a damage to brainstem nuclei localized in the lower (dorsal and ventral respiratory nuclei) or upper (nucleus parabrachialis medialis) medulla that generate a normal respiratory pattern. These three nuclei cooperate with vestibulo-cerebellar pathways to regulate the tonus of supraglottic, genioglossal,

pharyngolaryngeal, diaphragmatic and intercostal muscles during physiological nocturnal breathing [31,32].

Conversely, CSA prevalence was found to be related to the overall MRI lesion load and to be higher in patients with progressive subtypes [30]. This finding reflects a widespread damage of both brainstem and non-brainstem pathways that control nocturnal respiration.

3.3. RLS and PLMD in MS

3.3.1. Prevalence

Using the international RLS Study Group criteria [33], the prevalence of RLS in MS ranges from 13,3% to 65,1% with a significantly higher incidence than in the general population [34]. This higher prevalence rate can be influenced by a bias deriving from patients-filled questionnaires due to symptoms related to the disease itself (paresthesia or sensory symptoms at the legs, as observed by Rae-Grant et al., [35]) or by the inclusion of patients with comorbidities that can cause secondary RLS. Studies with such an exclusion showed a reduction ranging from one fifth to almost a half in the prevalence of RLS in the MS population due to the presence of condition related to secondary RLS or RLS-mimics [36–38]. Seven different studies showed a positive correlation between RLS, female sex and an older age in MS patients [34]. A positive family history was found in a lower proportion of MS patients with RLS (2,4–27,1%) [37–42] in respect to the idiopathic form in the general population. Moreover, RLS occurrence seems to be associated with progressive subtypes but the question of whether any of the MS forms predisposes to RLS development remains unclear as none of the published studies reached a definite conclusion. Some studies suggested that a higher score in the expanded disability status scale (EDSS) in patients with a longer disease history is related to RLS occurrence [37–43]. This observation has been explained as a common result of a more severe pathological process that simultaneously leads to the disability accrual and to the development of RLS [34].

PLMD can be considered a RLS endophenotype [43]. Similarly to RLS, PLMD seems to have a higher prevalence rate in MS patients compared to healthy subjects, although data are inferable only from small-sized studies. Ferini-Strambi et al., observed that 9 out of 25 MS patients (36%) showed a pathologically increased number of PLM, while the prevalence in the general populations ranges from 8 to 11% [43]. An increased periodic limb movement index (PLMI) was also reported by Chen et al., especially in fatigued patients (16,18 ± 14,67 versus 0,91 ± 0,49 in healthy controls) [44].

3.3.2. Neuroanatomical pathways and MRI findings

Pathophysiologically, RLS is related to a dysfunction of the dopaminergic transmission [45–47]. This alteration can derive both from a neuroanatomical damage of specific dopaminergic pathways and/or from a disturbance in dopamine metabolism secondary to decreased iron storage in the brain [46,47]. Bruno et al., observed a higher frequency and number of cervical lesions in the presence of RLS symptoms [48]. Similarly, a lower fractional anisotropy suggestive of spinal cord damage has been described by Manconi et al., in MS patients who developed RLS [49] (Table 1). The association between RLS and upper spinal cord injury had been previously reported in patients with different diseases such as transverse myelopathy, traumatic or compressive damage of the cervical spine or spondylotic myelopathy [50–54]. Three of these cases were reported by Hartmann et al. [54], one of which affected by MS. A higher MRI prevalence of spinal cord lesions was recently observed also by Minàr et al., in 52 RLS patients from a random MS population of 200 subjects [55] (Table 1). Twenty-three out of these 52 patients (44%) developed secondary RLS after MS onset. Therefore, the presence of spinal pathology was significantly associated with an increased risk of RLS development (OR = 3846) [55]. The involvement of descending dopaminergic fibers that control motor and sensory pathways could represent the neuropathological background for the appearance of RLS symptoms in MS patients. This hypothesis is supported by the efficacy of dopaminergic treatment in the cases of RLS related to spinal cord lesions [56] and by the development of a RLS-like phenotype in animal models with an experimental lesion in the A11 nucleus of the hypothalamus (which is the major source of dopamine for the spinal cord through the diencephalon-spinal pathway) [57].

A further pathogenic hypothesis suggested to explain the coexistence of MS and RLS takes into account a possible disorder of iron metabolism [34].

Imaging studies indeed showed reduced regional iron concentration in the brain of idiopathic RLS patients [58,59]. As for MS, the inflammatory process determines increased levels of cytokines that promote the intracellular retention of iron. This process leads to iron accumulation in some deep gray matter structures and in the perivascular areas of the white matter, as observed in neuroimaging studies [60]. This may produce local deficits of iron in other areas of the brain and a lack in available iron that disrupts dopamine synthesis. However, studies reporting objective data about iron dysregulation in specific brain areas of MS related RLS patients are missing.

Regarding PLMD, Clark et al., hypothesized a relationship with demyelination in the frontal lobe and right insular white matter [61]. The Authors suggested that demyelination of axons involved in motor movements could be related with PLM increase in MS patients. Other more recent observations indicate that MS patients with a higher number of PLM have a greater MRI lesion load in the infratentorial compartment, particularly in the cerebellum and brainstem [43], or in the spinal cord [62] (Table 1). Although the frequent occurrence of PLM in other brainstem degenerative disorders seems to confirm a subtentorial origin [63], the exact anatomical region involved remains unclear.

3.4. Narcolepsy and MS

3.4.1. Prevalence

To date, few cases of secondary narcolepsy in MS patients have been reported. In a recent review by Veauthier et al., the Authors collected 15 described cases of patients suffering from both the conditions [8]. CSF was examined in five out of these 15 patients and only in three out of five reduced hypocretin (HCRT1) levels were reported. However, a few studies failed to demonstrate a number of sleep onset REM periods (SOREMPS) $\geq$2 in MS patients with narcolepsy-like symptoms who showed a reduced mean sleep latency in the multiple sleep latency test (MSLT) [64–66]. Moreover, the HLA-DRB1*15:01 polymorphism seems to predispose to both MS and narcolepsy [67], whereas HCRT1 deficiency has its strongest association with other HLA loci polymorphisms (DQB1*06:02, DQA1*01:02) [68–70] that are not more prevalent in MS. Large multicentric and multi-national studies are needed to clarify whether the prevalence of narcolepsy in MS patients differs from that in the general population (0,05% in Europe and North America) [71].

3.4.2. Neuroanatomical pathways and MRI findings

HCRT1 neurons localize in the lateral hypothalamus and have widespread projection to the brainstem, basal forebrain, cortex and spinal cord [71]. Three out of the 15 published MS patients with narcolepsy-like symptoms [72–82] had a MRI positive for the presence of bilateral lesions in the hypothalamus [72,75,81] (Table 1). All of these three patients showed a reduction in HCRT1 levels in CSF and excessive daytime sleepiness (EDS) normalized after methylprednisolone therapy. Other MRI findings

in patients without evidence of hypothalamic involvement include lesions in the supratentorial white matter or upper cervical medulla, while six out of 15 patients were not investigated through MRI for the presence of hypothalamic involvement. Therefore, we cannot rule out that some of the described cases were suffering from idiopathic narcolepsy as a comorbid disorder. Similarly, symptomatic narcolepsy could derive from another autoimmune mechanism which does not imply the presence of hypothalamic lesions. Notably, a narcolepsy-like syndrome associated with bilateral hypothalamic lesions has also been reported in a different demyelinating condition, ie, neuromyelitis optica (NMO) positive for anti-aquaporin-4 antibodies [83].

3.5. RBD and MS

3.5.1. Prevalence

To our knowledge, there are only six cases of RBD described in MS patients [84–89]: Two out of six [87] were related to treatment with serotonin selective reuptake inhibitors (SSRI), which are known causative drugs, whereas the other four cases showed congruous MRI lesions [84–86,88,89]. In a recent case report, lesional RBD was the sole presenting symptom in a 38-year-old patient later diagnosed as having MS [85].

3.5.2. Neuroanatomical pathways and MRI findings

RBD is rarely related to non-synuclein structural lesions especially localized in the dorsal pons and limbic system [90]. The glutammatergic neurons in the pontine sublateral dorsal nucleus (SLD – also known as locus subcoeruleus) seem to play a key role in generating REM sleep atonia. Projections starting form this nucleus synapse on GABA and glycinergic neurons in the medullary gigantocellular nucleus and spinal inhibitory interneurons, promoting normal REM sleep atonia through the hyperpolarization of spinal motorneurons [91–94]. Lesions localized more rostrally in the mesiotemporal limbic neocortex can also indirectly provoke a dysregulation of REM sleep muscle tone. In a case series of 10 patients with lesional RBD, the dorsal pontine tegmentum and the rostral ventromedial medulla resulted the most frequently involved structure (nine out of 10 cases) [89]. One patient presented a FLAIR hyperintensity in the left caudate nucleus, hippocampus and parahippocampal gyrus in relation to voltage-gated potassium channel (VGKC) autoimmunity [89]. In MS, secondary RBD was described only in patients with MRI lesions involving the dorsal pons [84–89] (Table 1). In one patient symptoms improved with adrenocorticotropic hormone (ACTH) therapy [84], while other two cases responded to clonazepam [86,87].

3.6. Propriospinal myoclonus and MS

3.6.1. Prevalence

A rare subtype of spinal myoclonus is propriospinal myoclonus (PSM), a hyperkinetic movement disorders in which muscle jerks usually start at sleep onset in the midthoracic segments and slowly propagate up and down resulting in flexion or extension of the neck, trunk, knees and hips that impede falling asleep. The ICSD-3 classification includes PSM among the “sleep-related movement disorders” [14]. Only one case of MS-related propriospinal myoclonus (PSM) affecting the trunk and the right arm has been described by Kapoor et al., in 1992 [95]. Subsequently, only two cases of spinal segmental myoclonus have been reported [96,97], although without mention about relation to sleep.

3.6.2. Neuroanatomical pathways and MRI findings

Demyelinating plaques in the cervical spinal cord were identified in the MS case described [95]. In this patient, there was a clear

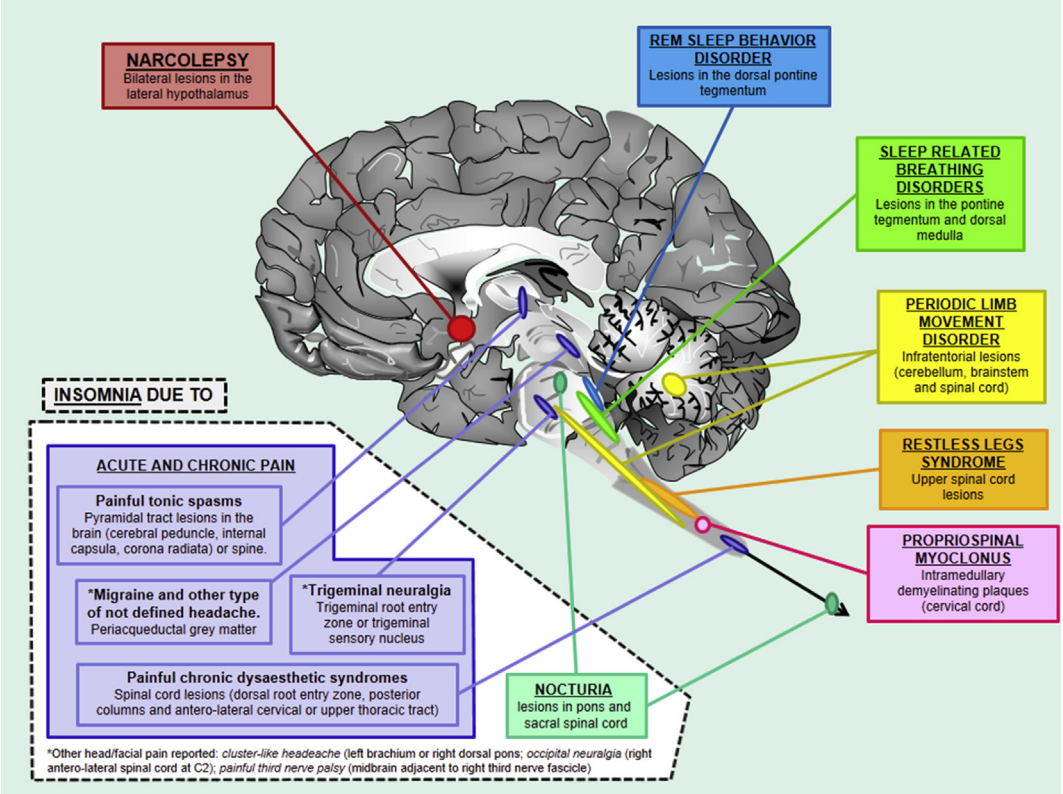

Fig. 1. Figure summarizing the localizations of the demyelinating lesions associated with sleep-related disorders in MS patients.

correspondence between the spinal motor generator level and the neuroimaging abnormalities location.

4. Conclusions

Sleep-related disorders are common in MS. In particular, insomnia, SRBD, RLS and PLMD seem to have a higher prevalence in MS than in the general population. The bidirectional relationship between fatigue, impaired quality of life and poor nocturnal sleep in MS patients requires an accurate detection of patients' likely suffering from secondary sleep disorders. Efforts to screen common sleep disturbances are crucial to start an adequate treatment, which can reduce daytime fatigue and improve patients' functions. MRI is largely used for diagnosis and follow-up in MS and a better characterization of the disrupted neuroanatomical pathways could have clinically relevant implications. Insomnia in MS is usually secondary to comorbid anxiety and depression or to nocturnal invalidating symptoms (especially nocturia and pain) easily detected clinically. There is no evidence, at present, that a focal CNS damage can cause primary insomnia. It is also important to consider that comorbid sleep disorders (eg, apnea or RLS) as well as multiple medications frequently used in MS patients, such as beta-interferon or selective serotonin reuptake inhibitors (SSRI) can directly or indirectly contribute to symptoms of insomnia. Therefore, the utility of MRI in this subgroup of patients is surely less relevant than an accurate anamnesis, a complete clinical evaluation and the use of validated questionnaires (such as the Brief Insomnia Questionnaire – BIQ) [98]. Notwithstanding, MRI can contribute to the identifications of lesions that could possibly cause insomnia-related conditions (eg, trigeminal neuralgia, painful spasms, propriospinal myoclonus). On the contrary, SRBD, RLS, PLMD in MS can be consequent to an injury of specific CNS areas, as well as narcolepsy and RBD (Fig. 1). Accordingly, MRI evidence of lesions in these specific areas can lead to investigate and diagnose these disorders in MS patients not reporting specific symptoms but more generally "fatigue" or "drowsiness". Moreover, in rare cases [84,85], lesional sleep disorders can be the sole presenting clinical manifestation and should be actively investigated through MRI in young patients without other better explanations possibly leading to a timely diagnosis and treatment of MS. A more comprehensive approach including the detection of patients with secondary sleep disturbances and the availability of imaging findings consistent with the reported sleep disturbances might provide indications about the choice and efficacy of symptomatic treatment or the use of high dose steroid treatment in the case of active lesions. Furthermore, a prompt identification of MRI findings consistent with secondary sleep disorders in MS patients could lead to a more efficient assessment of sleep quality and nocturnal symptoms through targeted questions, validated questionnaires and specific neurophysiological investigations such as polysomnography. MS, similarly to stroke, provides useful information to confirm the neuroanatomical and pathological basis of some of the commonest sleep-related disorders. It is important to underline that MS is a complex and dynamic disease characterized also by neurodegeneration and brain connectivity changes [99,100]. These factors could in turn play an important role in the dysregulation of physiological sleep pathways. Further studies are needed to better clarify the actual prevalence of lesion-related sleep disturbances and their neuroanatomical correlates. A better characterization of the association between the disruption of specific pathways and the development of secondary sleep-related disorders could help categorize symptomatic patients who need to underdo more in-depth sleep studies.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.010.

Study funding

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.01.010.

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