REVIEW ARTICLE

The characterisation of sleep and circadian rhythm in neuromyelitis optica: A review of the literature

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Abstract

Around a third of a human lifespan is spent in the essential life process of sleep. Disordered sleep is present in 15-35% of adults and is frequently underrecognized and underreported. Sleep disorders are associated with an elevated risk of hypertension, diabetes, obesity, depression, heart attack and stroke. The burden to health care associated with sleep disorders is significant and likely underestimated. Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disorder of the central nervous system characterised by devastating relapses which can result in blindness, disability, and death. Symptomatic narcolepsy is a core feature of the disease and though sleep disruption is common, it has not been systemically studied in large NMOSD cohorts. We present a literature review concerning sleep and circadian rhythm in NMOSD and offer a conceptual model of possible underlying pathophysiological mechanisms with suggestions for future research.

1. Introduction

Sleep constitutes approximately 8 hours of a typical 24-hour day, a third of a human lifespan. It is essential for optimal function during wakefulness and integral to maintaining mental and physical health. Sleep can be observed behaviourally as a vigilance state and was recognised in recent decades to comprise discrete electrophysiological states.[1,2] Sleep is a process that takes place within the brain, mediated by homeostatic and circadian mechanisms.[3]

Disordered sleep is present in 15-35% of adults and frequently underreported.[4] Disordered sleep can result in hypersomnolence, insomnia, mood disorders, poor cognitive performance and impaired social function. It has also been linked to an increased risk of cardiovascular disease, metabolic syndrome, impaired immunity, depression, and cancer.[5] The economic disease burden of sleep disorders is high. One study estimated this to amount 7.49 billion USD/year.[6] Estimates comprise direct (e.g., hospitalisation, professional, drugs) and indirect (lost productivity, premature mortality) costs and utilise different measures and models. Adopting conservative estimates with adequate controls, a European study found brain and mental disease burden (26.6% of total all cause burden) to be the largest contributor of disease morbidity burden and identified insomnia (7%) as one of the most common mental disorders.[7] Furthermore, sleep disorders may have social consequences (e.g., lower educational attainment, poorer work performance) and interfere with healthcare access for many years before diagnosis and management. This may not be accounted in economic estimates with the true extent of disease burden at risk of being underestimated.[8]

Based on the *International Classification of Sleep Disorders, Third Edition* (ICSD-3), there are approximately 80 different sleep disorders. These disorders can be broadly split into 6 major categories- sleep related breathing disorders, central disorders of hypersomnolence circadian rhythm sleep-wake disorders, parasomnias, sleep related movement disorders, and insomnia (Table 1).[9]

Sleep disorder category	Diagnoses
Insomnia	Chronic insomnia, short term insomnia, other insomnia
Sleep related breathing disorders	Obstructive sleep apnoea, central sleep apnoea, hypoxaemia disorder
Central disorders of hypersomnolence	Narcolepsy, Klein-Levin syndrome, idiopathic hypersomnia
Circadian rhythm sleep wake disorders	Advanced sleep wake phase disorder, delayed sleep wake phase disorder, irregular sleep wake phase disorder, jet lag disorder, shift work disorder
Parasomnias	NREM parasomnias, REM parasomnias, other parasomnias
Sleep related movement disorders	Restless legs syndrome, periodic limb movement disorder, myoclonus, bruxism

Other sleep disorder	Environmental factor primary reason for sleep disruption, sleep disorder due to neurological, medical condition or substance use.

Table 1. ICSD3 categories of sleep disorders. NREM; non-rapid eye movement. REM; rapid eye movement

Neuromyelitis optica spectrum disorder (NMOSD) is an antibody-mediated central nervous system disease that targets the optic nerves, spinal cord, brainstem, diencephalon, and other structures. Approximately 75% of patients have antibodies against aquaporin-4, an astrocytic protein expressed at high density in sleep related anatomical structures such as the hypothalamus, periventricular and periaqueductal grey areas. Symptomatic narcolepsy is one of the core clinical characteristics in NMOSD diagnostic criteria (IPND 2015).[10] However, many aspects of sleep and circadian rhythm in NMOSD remain uncharacterised. The overlap between sleep and NMOSD presents a unique opportunity to improve our understanding of both fields. Herein we present a review of available data concerning sleep and circadian rhythm in NMOSD alongside a model of possible underlying pathophysiological mechanisms and offer suggestions for future research.

2. Assessment of sleep

Sleep disruption may be evident through self-reported symptoms, but gauging sleep quantity and quality can be methodologically challenging. Additionally, patients with sleep disorders may present with overlapping symptoms including sleepiness, fatigue, insomnia, and symptoms suggestive of underlying sleep disorders (e.g., cataplexy, restless legs, apnoea etc.). Psychometric tools (table 2) and objective measures (table 3) may assist the identification of sleep disorders.

Qualitative sleep parameters	**Psychometric tools**
Excessive Daytime Sleepiness	Epworth Sleepiness Scale (ESS) Stanford Sleepiness Scale (SSS)
Insomnia Symptoms	Insomnia Severity Index (ISI) Brief Insomnia Questionnaire (BIQ)
Disordered sleep screen	Pittsburgh Sleep quality index (PSQI) Jenkins Sleepiness Scale (JSS)
Sleep related breathing disorders	STOP BANG questionnaire Berlin Questionnaire (Berlin-Q)
Impact of sleep on quality of life	Health related quality of life (HRQoL) Functional outcome of sleep questionnaire (FOSQ)
Fatigue	Fatigue severity scale (FSS) Functional assessment of chronic illness therapy-fatigue (FACIT-F)

Table 2. Summary of key psychometric assessment tools

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Sleep disorder category	Example Sleep Disorders	Assessment measure
Sleep related breathing disorders	Obstructive sleep apnoea, obesity hypoventilation syndrome	ESS, PSG
Insomnia	Chronic insomnia, short term insomnia	ISI, sleep diaries, actigraphy
Circadian Rhythm disorders	Advanced sleep wake phase disorder, Delayed phase sleep wake disorders, Non-24-hour sleep wake disorder	rMEQ, actigraphy, sleep diaries
Sleep related movements disorders	Periodic limb movement disorder, restless legs syndrome	IRLSSG, PSG
Parasomnias	REM sleep behaviour disorder, NREM parasomnia (sleep walking, eating etc)	RBDSQ, Video PSG
Central disorders of hypersomnolence	Narcolepsy	ESS, MSLT, PSG, HLA typing CSF orexin/hypocretin

Table 3. Psychometric and objective assessment tools employed in various sleep disorders. CSF; Cerebrospinal fluid, ESS; Epworth sleepiness Scale, HLA; Human Leukocyte Antigen, IRLSSG; International restless legs syndrome study group rating scale, ISI; Insomnia severity Index, MSLT; Multiple sleep Latency Testing, PSG; Polysomnogram, RBDSQ; REM sleep behaviour disorder questionnaire, rMEQ; Reduced Morningness-Eveningness Questionnaire.

3. Evidence of sleep disruption in NMOSD

3.1. Qualitative measures of sleep

A Chinese study of 73 NMOSD patients assessed health related quality of life (HRQoL) factors and Pittsburgh Sleep Quality Index. Poor sleep was recorded in 68% of patients and was negatively correlated with HRQoL as measured with the 54-item Multiple Sclerosis Quality of Life tool (MSQL-54, r=-0.59; p=0.000).[11] A smaller French study of 40 NMOSD patients using a language appropriate version of the MSQL-54 (SEP-59) did not find differences in sleep as compared to MS patients.[12] Although a comparison with healthy controls was not provided, sleep disorders in MS are well recognised [13, 14]; thus the finding of similar sleep subscale scores between MS and NMOSD may be significant. Collectively these studies suggest that impaired sleep impacts quality of life in NMOSD.

A retrospective observational study of 522 international NMOSD patients reported 28% of respondents had moderate to severe excessive daytime sleepiness and 35% reported moderate to severe insomnia. This study demonstrated the potential for research using online patient communities to obtain large NMOSD datasets and confirmed significant subjective sleep complaints. However, the study did not use psychometrically or clinically validated measures.[15, 16]

Perin and colleagues reported PSQI and ESS scores in a cross-sectional study of 66 NMOSD (AQP4-IgG positive=32). Poor sleep quality (PSQI>5) was present in 73% of patients and 35% reported excessive sleepiness. In the regression model, older age was associated with poor quality of sleep.[17] Contrastingly, a cross-sectional study of 39 NMOSD patients found no mean difference in PSQI and ESS scores versus gender-matched controls. In NMOSD patients, longer illness duration and higher fatigue scores were associated with increased sleep disturbance. Restless legs syndrome (RLS) was more common in NMOSD patients and higher anxiety scores predicted daytime sleepiness. There was also an association between PSQI scores and measures of depression, anxiety, and quality of life.[18]

A further prospective South Korean study found that of 25 AQP4-IgG NMOSD patients with fatigue as measured using the functional assessment of chronic illness therapy- fatigue score (FACIT-F), 71.4% had poorer sleep quality than those without fatigue (p=0.009).[19]

A Chinese study of 42 NMOSD (26 AQP4-IgG positive) patients utilising a language appropriate version of the MSQL-54 and PSQI reported poor sleep (PSQI≥6) in 64% of patients. Interestingly, there was no association with AQP4-IgG serostatus or annualised relapse rate. In regression analysis, disability, depression, and affective descriptors of pain (from the Short Form-McGill Pain Questionnaire-2) were associated with poor sleep.[20]

A South Korean study of 159 NMOSD patients and 153 matched healthy controls utilised fatigue (FSS), sleepiness (ESS) and sleep quality (PSQI) measures comparing subjects with and without RLS. FSS (p = 0.04), and PSQI (p = 0.02) scores were significantly higher in the RLS/NMOSD group than the RLS/HC group, suggesting RLS is more severe in NMOSD patients.

Collectively, these data demonstrate that sleep disruption is common in NMOSD but also highlight confounding factors that need to be considered e.g., anxiety and RLS. The use of validated questionnaires with comparable cut-off value is also an important consideration.

3.2 Quantitative and objective measures of sleep

Two Chinese prospective cross-sectional studies assessed quantitative sleep parameters in NMOSD and healthy controls. Song et al studied 33 NMOSD (70% AQP4-IgG positive) and 20 matched healthy individuals using polysomnography (PSG). NMOSD patients had reduced sleep efficiency (p=0.03), a 13-minute reduction in total sleep time (p=0.05), a 44-minute increased wake time after sleep onset (p<0.0001) and increased sleep latency. NMOSD patients spent less time in N3 deep sleep (p=<0.0001), more time in superficial N1 sleep (p=0.01) and similar periods in N2 sleep. REM sleep duration was increased (p=0.04). Decreased arousal index was also observed and was associated with increased REM during nocturnal sleep. Arousal index also correlated with higher ESS but not fatigue scores.[21] Replication of these findings in a larger cohort would be of interest and could help address factors such as the influence of AQP4-IgG serostatus as the authors highlight.

Pan et al. also reported findings in 33 NMOSD (70% AQP4-IgG) and 20 matched healthy controls. Levels of fatigue were higher in NMOSD patients and broadly correlated with PSQI (r=0.45, p=0.008) in keeping with Seok et al. findings.[19, 22] There was also a trend of association between fatigue and ESS (r=0.27, p=0.13). However, due to the study design, logistical regression could not be performed to assess other factors that may have influenced these associations.

PSG findings between NMOSD and controls were not reported. Of patients with NMOSD, those with fatigue had reduced N3 and a higher degree of sleep fragmentation suggested by a greater number of sleep stage shifts. There were no differences in wake time after sleep onset or total arousal index but as mentioned, comparison with controls for these data were not provided.[22]

In summary only one of these studies has reported PSG findings in NMOSD versus healthy controls. It is difficult to extrapolate this study's findings more widely in view of the sample size and single centre study design. Pan et al. have shown that fatigue appears to be a significant factor when assessing sleep quality mirroring findings in other studies. Larger samples sizes and addressing cofounding factors such as sedative drugs, pain, nocturia, and anxiety with regression analysis could address these limitations.

4. Insomnia in NMOSD

Insomnia is the most common of all sleep disorders. Depending on how it is measured, the prevalence of insomnia varies between 6-40%.[23] Predisposing, precipitating and perpetuating factors have been ascribed to models of hyperarousal and cognitive behaviour but the pathophysiology of insomnia is complex and remains to be understood fully.[24, 25]

Eaneff et al. reported moderate to severe insomnia in 35% of 522 NMOSD patients.[15] It was unclear in this study whether insomnia was a primary manifestation of NMOSD or secondary to other factors such as nocturia, pain, or anxiety. Indeed, in one study 62% of NMOSD patients reported sleep disruption due to urinary symptoms.[26] Treatments used in NMOSD may also exacerbate insomnia e.g., corticosteroids, antidepressants, and anticonvulsant neuropathic pain medication.[9, 27, 28]

We did not find studies of insomnia in NMOSD using validated questionnaires such as the Insomnia severity index or current diagnostic criteria (e.g., ICSD-3/ DSM-5). However, the study by Eaneff and colleagues showed that over a third of NMOSD patients report moderate to severe insomnia, justifying the need for further research.

5. Sleep related breathing disorders in NMOSD

Sleep related breathing disorders are characterised by respiratory abnormalities during sleep, categorised as obstructive sleep apnoea (OSA), central sleep apnoea, sleep related hypoventilation disorders and sleep related hypoxaemia disorders. Although these are distinct diagnostic groups, clinical features of these conditions often overlap.[9]

Severe and complicated OSA has been reported in NMOSD.[29] NMOSD patients score higher than controls on screening tools for sleep disordered breathing such as the STOP-BANG and Berlin Questionnaires.[17, 18] Barzegar et al. studied 41 NMOSD (11/28 AQP4-IgG seropositive) and 46 matched healthy controls using the STOP-BANG questionnaire. This questionnaire contains 8 sections covering the following parameters-snoring, tiredness, observed apnoea, high blood pressure, body mass index (BMI>35 kg/m^2), age (>50 years), neck circumference (male >43 cm; female >41 cm) and sex (male). A score of $\geq$3 is interpreted as a moderate to severe risk of OSA.[30] Rates of OSA were similar between NMOSD and HCs in this study, and there was modest correlation between OSA and restless legs symptoms (r^2=0.3, $p<0.05$).[11]

The study by Perin et al. also assessed NMOSD patients using the Berlin Questionnaire. This 3-category questionnaire covers snoring, fatigue, and hypertension. High risk is inferred by positive scores in 2 or more categories. Of 60

NMOSD patients (AQP4-IgG positive=32), 20 (30%) were noted to be at high risk for OSA. Sedentary behaviour (68%), smoking (36%) and alcoholism (8%) were also recorded and are factors implicated in sleep disordered breathing.[31-33] Shaygannejad et al. assessed 24 NMOSD patients. Using the STOP BANG and Berlin questionnaires they identified 2 (8%) and 5 (21%) patients at high risk of OSA respectively. An association between OSA and higher EDSS scores was noted. Importantly, this study also analysed the effect of medication, but more than half the NMOSD patients could not be classified into the pre-designated categories for analysis.[34] The wide variation in results highlights the importance of qualitatively assessing OSA in a validated and systematic manner.

Objective measures like PSG have also been used to assess OSA in NMOSD. In the prospective cross-sectional study by Song et al. PSG in 6/33 NMOSD patients demonstrated elevated apnoea hypopnoea index (AHI >5, OSA; mild=4, moderate=1 and severe=1).[21] Overall, sleep disordered breathing was more frequent in NMOSD as compared to controls (18% vs 5%; p=0.007). Pan et al. found similar AHI levels between NMOSD patients with and without fatigue (4/21 vs. 2/12). AHI did not correlate with blood oxygen levels but mean and nadir SpO2 levels were lower in NMOSD patients with fatigue (90% vs 94%; p=0.004, 87% vs. 93%; p=0.002, respectively). A modest correlation was observed between oxygen measures and fatigue. In 3 patients (who had NMOSD and fatigue) mean SpO2 was lower than 88%, and one of these patients had sleep apnoea. The mechanism for hypoxaemia was unclear as patients did not have a history of anaemia, pulmonary or cardiac disease.[22] Of note, although AQP4 is expressed in alveolar epithelium, complement regulators (CD46, CD55, and CD59) are also present and often cited as the reason for the paucity of extra-CNS manifestation in NMOSD.[35]

6. Central disorders of hypersomnolence in NMOSD

Central disorders of hypersomnolence are characterised by the irrepressible need to sleep and irrepressible episodes of daytime sleep. The experience of hypersomnolence may differ qualitatively and include persistently low vigilance and sudden onset of sleep (SOOS) attacks. These disorders include narcolepsy, Kleine-Levin syndrome, and idiopathic hypersomnia as well as where these occur with other physical, psychiatric disorders or substance use.

Narcolepsy is characterised by excessive daytime sleepiness (EDS), rapid eye movement (REM) sleep phenomena including cataplexy, hypnic hallucinations, sleep paralysis and REM sleep behaviour disorder (RBD), and fragmented nocturnal sleep.[36, 37] The diagnosis of narcolepsy is supported by PSG, MSLT and the assessment of CSF orexin/hypocretin levels (a neuropeptide which promotes wakefulness, supresses active sleep, and stabilises the wake/NREM/REM vigilance states).[38] Orexin/hypocretin is henceforth referred to as orexin.

According to the ICSD-3 diagnostic criteria, narcolepsy is classified into two types (Table 4). Narcolepsy type 1 (NT1) is differentiated from narcolepsy type 2 (NT2) by the presence of cataplexy and/or low (e.g., <110pg/mL) or absent CSF orexin levels. The clinical and MSLT requirements are the same. Cataplexy is defined as one or more episodes of sudden and brief (seconds to minutes) usually symmetrical loss of muscle tone with preserved consciousness. Attacks may be triggered by strong emotions, classically laughter. Cataplexy often results in falls (though injury is rare) and can manifest more subtly and partially with facial, neck or limb weakness. Positive motor

features may also be present such as myoclonus and tongue protrusion which are seen particularly in children. Other frequent features of narcolepsy that require recognition include psychiatric comorbidities, dream delusions, automatic behaviours (actions that are carried out without subsequent recollection), and obesity.

Narcolepsy is considered a distinct and homogenous disease entity, a "*morbus sui generis".*[39]

Low or absent CSF orexin levels are highly sensitive (87%) and specific (99%) for Type 1 narcolepsy.[38] The human leukocyte antigen HLA-DQB1* 06:02 is also found in more than 98% of cases of Type 1 narcolepsy [40, 41] and is the strongest known HLA association of any disease. However, depending on ethnicity this allele is present in around 25% of the general population limiting its specificity as a diagnostic test.[40-42]

Human narcolepsy is typified by selective hypothalamic orexinergic cell loss. An autoimmune basis for the disorder has long been suspected. Although there is strong overlap with HLA Class II, neurons express HLA Class I but not II molecules. Recently a genome wide association study (GWAS) identified a strong association with polymorphisms in the T-cell receptor α locus across multiple ethnic groups.[43, 44] Most recently orexin specific, autoreactive CD4+ and CD8+ T cells have been isolated in narcoleptic patients.[45] Newer susceptibility genes have been identified using high density genotyping including cathepsin H (CTSH) and tumour necrosis factor superfamily member 4 (TNFSF4).[46] These genes play a role in immune regulatory function through sequencing studies in rare familial cases have thus far not identified a consistent gene focus. These findings together lend credence to the hypothesis that narcolepsy is an autoimmune disorder resulting in the loss of orexinergic neurones in genetically susceptible individuals. Environmental factors have also been implicated in the pathogenesis of narcolepsy, the most convincing of which is H1N1 infection, as respective vaccination was associated a rise in the incidence of narcolepsy in 2009 and 2010. Molecular mimicry triggered by certain flu virus haemagglutinins has been postulated to account for this.[47]

The role of B-cell mediated mechanisms has also been studied but is less clear. Anti-tribbles 2 homologue 2 (TRIB2) immunoglobulin has been previously reported in narcoleptic patients but whether these are directly pathogenic in causing orexin cell loss remains uncertain.[48-50]

Narcolepsy has also been associated with rare antibody mediated CNS disorders such as NMOSD and the paraneoplastic anti- Ma2 encephalitis.

Despite these findings, conventional criteria for autoimmune disorders are not fully met and the pathophysiology of narcolepsy continues to be intensely researched and debated.[51]

A small minority (<2%) of narcolepsy patients represent familial or "symptomatic" [39] cases where features of narcolepsy occur in the context of a known underlying medical disorder, termed in ICSD-3 as "narcolepsy type 1 due to a medical condition" [9, 39]. Narcolepsy is associated with NMOSD and other causes including head trauma, hypothalamic lesions, and inherited disorders such as Niemann-Pick type C. This suggests that a variety of disease mechanisms may be associated with narcolepsy but convergence to a final common pathway involving orexin signalling is critical, though arguably not indispensable (as a proportion of narcolepsy cases have normal CSF orexin levels).

NT2, (previously termed narcolepsy without cataplexy) is likely a heterogenous disorder.

It is also associated with EDS and similar MSLT findings as NT1, but cataplexy is absent and CSF orexin levels are either unknown or above 110pg/mL. As with NT1, features such as sleep paralysis, hypnagogic/hypnopompic hallucinations, and automatic behaviour may be present. It is estimated that between 25% and 33% of patients with NT2 have low CSF orexin levels thus assessment is encouraged.[9] In cases of NT2 with NMOSD, the term Narcolepsy Type 2 due to a medical condition should be used. Other associated conditions include anti-Ma2 autoimmunity, head injuries, Prader-Willi syndrome, multiple sclerosis, myotonic dystrophy, and Parkinson's disease.

Narcolepsy Type 1
Excessive daytime sleepiness daily for ≥3 months
One or both of the following:
Cataplexy and mean sleep latency ≤8 minutes and ≥2 SOREMPs (≤15 min after sleep onset) on MSLT*. A SOREMP on preceding nocturnal PSG may replace one of the SOREMPs on MSLT
Low or absent CSF hypocretin-1 levels
Narcolepsy Type 2
Excessive daytime sleepiness and MSLT findings as above, but without cataplexy
CSF hypocretin-1 levels are unknown or are above the threshold for type 1 narcolepsy
The hypersomnolence and/or MSLT findings are not better explained by other causes, such as insufficient sleep, OSA, delayed sleep phase disorder, or the effect of medications or substances or their withdrawal.

Table 4. Adapted from ICSD-3 diagnostic criteria. *Importantly prior standardisation of sleep-wake patterns using sleep diaries and actigraphy where possible and exclusion of other sleep disorder mimics with PSG should be undertaken. Drugs that interfere with seep quality should be discontinued prior to MSLT.

Orexin cell bodies localise to the lateral hypothalamus and may be specifically targeted in NMOSD due of high AQP4 expression in the hypothalamus as well as periventricular and periaqueductal regions.[52] The first case of narcolepsy type 1 due to a medical condition in NMOSD was reported from Japan and included in a series where the authors identified 4 MS and NMOSD patients with bilateral hypothalamic lesions and reduced CSF orexin levels.[53,54] Although reports of "symptomatic narcolepsy" [54] in NMOSD are increasing, there are only 17 reported cases to date[53, 55-69]; (summarised in Table 5). It is noteworthy that narcolepsy is one of the core clinical characteristics included in the 2015 NMOSD IPND diagnostic criteria.[10]

The clinical characteristics of these cases will be expanded upon and discussed.

	Age/Sex	Ethnicity	EDS	CSF Orexin (pg/mL)	Cataplexy	ICSD3 NT1/NT2	ICSD3 NMC	AQP4-IgG	MRI HT lesion	Other features	Measures	Therapy	Outcome
Poppe et al 2005	19/F	Caucasian	+	NT	No	NA	+	NT	+	Myelitis, Bilateral Optic Neuritis	CSF	IVMTP, IVIG, PLEX	EDS resolved, Bilateral Optic Neuritis, Tetraparesis ventilator dependent
Poppe et al 2005	13/M	Haitian/FC	+	NT	No	NA	+	NT	+	Low temp		IVMTP, PLEX	NA
Carlander et al 2008	48/F	Caucasian	+	158*	No	NA	+	+	+	Dysautonomia Chiasmitis LETM	CSF	Rituximab x3	Ventilator dependent
Viegas et al 2009	17/F	Caucasian	+	NT	No	NA	+	-→+	+	High temp Hiccoughs	CSF, Brain biopsy	IVMTP IVIG Azathioprine	Death
Nozaki et al 2009	42/F	Japanese	+	191*	No	NA	+	+	+	Myelitis	CSF	IVMTP x3 PO Prednisolone	EDS Resolved
Baba et al 2009	35/F	NA	+	91	No	NT1	+	+	+	Myelitis	CSF, HLA, PSG, MSLT	High dose MTP PO Prednisolone	EDS Resolved, orexin improved
Samart et al 2010	34/F	NA	+	NT	No	NA	+	+	+	Bilateral Optic Neuritis Myelitis	CSF	High dose corticosteroids	Unknown
Nakano et al 2011	31/F	NA	+	187*	No	NA	+	+	+	SIADH Optic Neuritis, Myelitis	CSF	PO Prednisolone	EDS resolved CSF orexin increased
Sekiguchi et al 2011	41/F	NA	+	177*	No	NA	+	+	+	Anhidrosis Hypotension	CSF, MSLT	IVMTP x3 PO Prednisolone	EDS resolved CSF orexin increased
Deguchi et al 2012	36/F	Japanese	+	118*	No	NA	+	+	+	Orientation Memory disturbance	CSF, EEG	IVMTP x6 PO Prednisolone	EDS resolved memory improved CSF orexin normalised
Suzuki et al 2012	21/F	NA	+	100	No	NT1	+	+	Y	Hypotension Hypothermia, Hyponatraemia	CSF, EEG HLA, PSG	IVMTP x3 Maintenance PO prednisolone, Modafinil	Persistent EDS Memory problems Obesity
Saito et al 2014	39/F	Japanese	+	<40	No	NT1	+	-	Y	Hyperthermia, seizures weight gain, irregular menses	CSF, EEG Brain Biopsy	IVMP x3 PO Prednisolone Modafinil	Persistent severe EDS
Okuma et al 2014	41/F	Japanese	-	NT	No	NA	+	+	Y	SOOS	CSF	IVMTP x3	Resolved SOOS. No EDS

Kume et al 2015	46/F	Japanese	+	85.8	No	NT1	+	-→ +	Y	HPA dysfunction Left temporal lobe lesion	CSF, HLA	MTPx12 PO Prednisolone	SOOS & RTA post steroid taper. IVMTP & PO prednisolone Resolved EDS. CSF Orexin increased
Kallollimath et al 2018	20/F	NA	+	NT	No	NA	+	+	Y	Diplopia, seizures, ataxia hemiparesis dysphagia	CSF	Steroids Azathioprine	Improved but persistent EDS (sleep duration 22→16 hours).
Elotmani et al 2018	45/F	NA	+	NT	No	NA	+	+	Y	Nil	EEG, CSF	IVMTP x3 PO Prednisolone Mycophenolate	Resolved EDS at 1 week. Asymptomatic at 3 years
Daida et al 2020	67/F	NA	+	170*	No	NA	+	+	Y	Consciousness disorder 1 year prior	EEG, CSF	IVMTP x5, CYCL, IA, OMTP Tacrolimus Methylphenidate Modafinil	Improved but persistent EDS

Table 5: 17 reported cases of SN in NMOSD 2005-2020. CYCL= cyclophosphamide, CSF=Cerebrospinal fluid, EDS=excessive daytime sleepiness, EEG= Electroencephalogram, ESS=Epworth sleepiness score, FC= French Canadian, MRI HT lesion= Hypothalamic lesion demonstrated on MRI, IA= Immune absorption, IVIG= Intravenous immunoglobulin, IVMTP= Intravenous Methylprednisolone, MRI=magnetic resonance imaging, NA= Not available, NT= not tested, NT1= Narcolepsy type 1 according to ICSD3, NT2= Narcolepsy type 2 according to ICSD3, ON=Optic neuritis, PLEX= Plasma exchange therapy, OMTP=Oral methylprednisolone, RTA= road traffic accident, SOOS=sudden onset of sleep, *CSF orexin reduced but above absolute cut-off range of <110pg/mL.

All reported cases of narcolepsy in NMOSD demonstrated disordered arousal through hypersomnolence or sleep attacks though with absence of REM sleep phenomena (cataplexy, sleep paralysis, disrupted nocturnal sleep, hypnagogic hallucinations and RBD). REM sleep phenomena were not reported possibly due to differential expression of AQP4 in networks involved in these functions. Further studies of the narcolepsy phenotype in NMOSD may help to inform the pathophysiological mechanisms responsible.[52, 70]

The median age of reported cases was 36 years (range 19-67). Racial group was not reported in all patients, but most cases (10/17) were reported from Japan. Caucasian cases(n=3) were reported from the UK, France, and French Canada. One case from French Canada was of mixed French and Haitian ancestry. Single cases were reported from India, Morocco, and Thailand. All cases were from northern hemispheric countries; possibly implicating environmental factors.

CSF orexin levels were assessed in 10 cases and were reported(range < 40-190) according to local reference ranges but only 4 cases had levels below 110pg/mL.[53, 63, 64, 66] MSLT and PSG were utilised in 3 cases and demonstrated reduced sleep latency and sleep onset REM periods consistent with narcolepsy.[53, 61, 63] Of the 15 cases tested for AQP4-IgG, 14 were seropositive. In 2 cases AQP4-IgG seroconversion was observed though a variety of assay methodologies were used across studies. The single AQP4-IgG negative case was not subsequently re-tested.[64] HLA DQB1*0602 was only assessed in 3 patients and was negative in all cases.[53, 63, 66]

Bilateral hypothalamic lesions were present on fluid attenuated inversion recovery (FLAIR) and T2 weighted MRI sequences and showed improvement on interval imaging. Narcolepsy was a *forme fruste* of NMOSD in 2 cases though more commonly occurred following other NMOSD manifestations.[53,67] Narcolepsy was also associated with autonomic and endocrine dysfunction 8/17 (47%) of cases.[55-57, 60, 61, 63, 64, 66]

Most cases of hypersomnolence (12/17) resolved at least partially with immunotherapy though 4 cases had persistent somnolence. Symptomatic treatments including modafinil and methylphenidate were used in some cases.[63, 64, 69]

At last review 1 patient had died, 4 had severe disability (ventilator dependence and disabling hypersomnolence), and the remainder (n=12) with follow-up data had mild or no disability.

It is currently unclear what proportion of NMOSD patients have narcolepsy and as with other sleep disorders the condition may be underreported and/or underdiagnosed. It would seem reasonable to screen NMOSD patients for sleep disorders using a validated scale such as ESS in conjunction with a sleep history and if warranted proceed to further testing e.g., MSLT and CSF orexin levels, particularly if hypothalamic and/or endocrine dysfunction is present. Conversely in patients presenting with narcolepsy, we would recommend AQP4-IgG testing using a validated methodology such as the live cell-based assay.[71] In such cases where narcolepsy is the *forme fruste* of NMOSD, early immunosuppression could avert long term disability from subsequent relapses.

7. Circadian rhythm sleep-wake disorders

Circadian (from Latin "*circa diem"* meaning around a day) rhythm relates to the body's intrinsic 24-hour clock that regulates key physiological processes including the sleep-wake cycle. Circadian rhythm sleep-wake disorders (CRSWDs) occur when endogenous circadian time and exogenous 24-hour time are misaligned. This results in wake/sleep at undesirable times of day with typical symptoms including insomnia and

hypersomnolence often with impaired social function. Examples of CRSWDs include advanced, delayed, irregular and non-24-hour sleep-wake phase disorder, jet lag disorder, and shift work disorder.[9] CRSWDs are associated with mental and physical health disorders such as depression and cancer.[72, 73]
Severe visual impairment, a hallmark of NMOSD, may also result in circadian rhythm disruption due to loss of the synchronising effect of natural light through the retino-hypothalamic tracts to the suprachiasmatic nuclei.[74]
In keeping with these findings, visual impairment correlated significantly with sleep impairment (p=0.025) in the study by Chanson et al.[12] Perin and colleagues published in poster format the results of chronotype analysis using the Morningness-Eveningness questionnaire in 66 NMOSD (32 NMO IgG positive) from Brazil. Morning (47%), evening (18%) or neither (35%) chronotypes were identified.[17] To our knowledge there are no other reports analysing for chronotype or the presence of CRSWDs in NMOSD. Dedicated studies of circadian rhythm in NMOSD using sleep diaries, validated questionnaires, and objective assessment methods such as actigraphy and dim light melatonin onset (DLMO) are needed.

8. Sleep related movement disorders

Sleep related movement disorders (SRMDs) are characterised by movements that disturb sleep or its onset. They are a group of several disorders including restless legs syndrome (RLS), periodic limb movement disorder (PLMD), bruxism, myoclonus or movement disorders related to medical disorders or medication.[9]
SRMD movements are typically simple and stereotyped with the exception of RLS, where patients engage in more complex and non-stereotyped movements to address limb discomfort.
RLS and PLMD are the most common movement disorders of sleep with conservative prevalence estimates in the general population of around 5% and 4% respectively.[75, 76]
RLS symptoms include an urge to move the limbs that begins or worsens during periods of inactivity, is relieved by movement, occurs predominantly in the evening, and is not better accounted for by another disorder (e.g., venous stasis). The international restless leg syndrome study group (IRLSSG) and ICSD-3 have established international consensus diagnostic criteria for RLS.[77, 78] IRLSSG criteria includes a "specifier for clinical significance" [77] but does not include functional impairment as part of essential criteria. Conversely, the ICSD-3 criteria stipulates RLS symptoms must cause concern, distress, sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioural, or other impairments of function (though this may be omitted for research purposes).[79]
Primary RLS is a disorder of unknown aetiology; several factors may be involved including genetic, cortical-spinal excitability, iron and dopamine dependent neurotransmission.[80] Secondary RLS can occur in the context of pregnancy, medical disorders (e.g. iron deficiency anaemia, uraemia, chronic kidney disease), and chronic neurological disorders including Parkinson's disease and MS.[81, 82] Myelitis can occur in NMOSD and in our experience, patients often complain of leg restlessness as a sensorimotor symptom. RLS may be underrecognized and confounded by the sensorimotor disturbance seen in myelitis.[83]
It is also worth noting that women over the age of 35 years have double the risk of RLS as compared with men in this age range and NMOSD predominantly affects women with a median age of onset of 39 years.[84, 85]

Hyun et al. investigated the relationship between RLS and NMOSD in 159 NMOSD patients and 153 matched healthy controls using IRLSSG questionnaire and the IRLSSG severity scale with fatigue (FSS), sleepiness (ESS) and sleep quality (PSQI) measures.[86] RLS was more frequently observed (17% vs 7.8%; p=0.02) and more severe (22.6+/-10.2 vs 14.3 +/-6.9; p=0.02) using RLS severity scale in NMOSD patients as compared to HCs. RLS occurred at or after NMOSD onset in 89% of patients and was seen in the later stages of the disease (disease duration 11.0 +/-6.1 vs 8.4 +/-12.0 years; p=0.03) and those patients with greater disability scores (EDSS 4.5 (0-8) vs 3.0 (0-7.5); p=0.001) as compared to NMOSD without RLS. Although median FSS and PSQI scores were higher in NMOSD with RLS cases than healthy controls, differences with NMOSD without RLS were not statistically significant.

Barzegar and colleagues also used the IRLSSG rating scale to assess 41 NMOSD patients (11 AQP4 IgG positive) and 46 matched healthy controls. Higher RLS scores in NMOSD patients compared to healthy controls were observed with a large effect noted in the analysis.[18] Higher RLS scores were modestly associated with OSA scores (r^2=0.38) but not other measures such as sleepiness, depression, anxiety, or quality of life. The NMOSD and control groups did not differ in sleep quality, OSA risk and sleepiness.

Shaygannejad et al. assessed RLS using IRLSSG screening and severity scales in NMOSD (n=25), MS (n=359) and clinically isolated syndrome (n=112) providing a disease relevant control group for comparison. RLS was noted in 46%, 41%, and 29% of these groups respectively. A moderate to severe severity was recorded in 8/11 (73%) with RLS. A degree of correlation between RLS and ESS (r^2=0.10), fatigue (r^2=0.11), paraesthesia (r^2=0.28), StopBang (r^2=0.24) and Berlin scores (r^2=0.27) was observed when examining the total cohort. As Barzegar et al. also found, NMOSD patients with higher EDSS scores had higher RLS scores, as well as higher fatigue and OSA scores, though correlation coefficients were small. Importantly medication did not appear to impact RLS scores. In summary RLS appears common in NMOSD and is worth screening for at routine clinical assessments.

PLMD is diagnosed when periodic movements of sleep (PLMs) cause significant impairment to sleep or daytime function. In a prospective cross-sectional PSG study, Song et al identified higher rates of PLMs in NMOSD as compared to controls. The mean PLMs/h for patients with NMOSD was 20 (range 0-177) vs 2 (range 0-24) in the control group (p=0.02). Using a cut-off of >5 PLMs/h on PSG, a higher proportion of NMOSD patients experienced PLMs as compared to controls (39% vs 10%; p=0.03). There were no differences in degree of spinal cord involvement between subgroups but interestingly, 67% (10/15) NMOSD patients with PLMs had infratentorial disease suggesting a possible supraspinal origin of PLM generation. Importantly, AQP4-IgG serostatus did appear to influence the presence of PLMs and none of the NMOSD patients fulfilled RLS diagnostic criteria. There were no differences in total sleep time and arousal indexes in NMOSD patients with and without PLM.[21]

Similar to other aforementioned sleep related disorders, the study of sleep related movement disorders would benefit from large studies utilising validated psychometric and objective assessments.

9. Parasomnias

We were not able to identify studies that have specifically assessed for parasomnia in NMOSD.

10. Neuroanatomical basis of sleep disruption in NMOSD

Several distinct neuronal loci function in interconnected networks responsible in the mediation of alternate wake and REM/NREM sleep states.[87-89] Broadly, these are wake promoting monoaminergic neuronal clusters in the brainstem operating synergistically to inhibit the sleep promoting, predominantly GABAergic networks including the basal forebrain and pre-optic areas. These reciprocal processes alternate under homeostatic and circadian influences. The circuits are housed in AQP4 rich brain structures and are thus vulnerable to the AQP4-IgG mediated disease processes. We propose a schematic mechanistic model of relevant anatomical sites that may be affected by NMOSD in Figure 1.

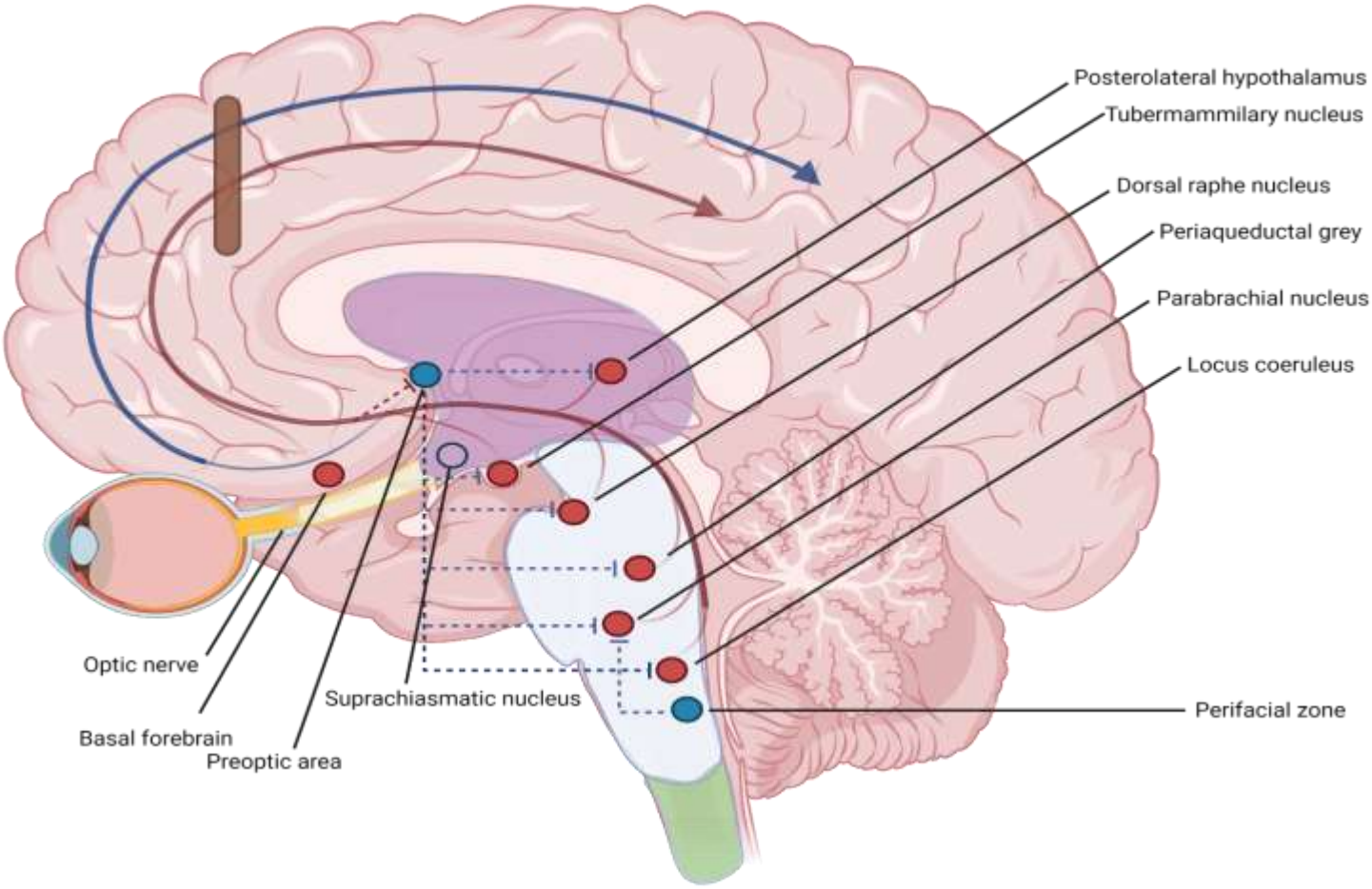

Figure 1: A simplified schematic of wake (red) and sleep (blue) promoting nuclei and pathways. Red circles and lines denote respective wake promoting nuclei and pathways. These include the locus coeruleus (noradrenaline) parabrachial nucleus (glutamate), periaqueductal grey (dopamine), dorsal raphe nucleus (serotonin), tuberomammillary nucleus (histamine), posterolateral hypothalamus (orexin) whose circuits project rostrally to the thalamus, basal forebrain, and cortex. Blue circles and lines denote the respective NREM sleep promoting nuclei and pathways and include the preoptic area (GABA and galanin) that inhibits wake promoting nuclei and the perifacial zones (GABA) that inhibit parabrachial nuclei. The neuroanatomical structures susceptible to NMOSD clinical syndromes have been colour designated. Optic neuritis and chiasmitis (yellow), symptomatic narcolepsy/diencephalic syndrome (purple), brainstem syndromes (light blue), symptomatic cerebral syndrome (brown), and transverse myelitis (green).

The effect of these lesional clinical syndromes may disrupt sleep and wake pathways with some postulated effects. Optic neuritis or chiasmitis severe enough to disrupt retino-hypothalamic signalling to the suprachiasmatic nucleus may impair light dependent entrainment and result in circadian rhythm disorders. Direct involvement of the hypothalamic structures including the suprachiasmatic nucleus and orexin containing cells in the posterolateral hypothalamus may disrupt circadian rhythm regulation and key wake promoting orexin signalling respectively. Spinal cord involvement can result in periodic limb movements and secondary restless legs syndrome. Infratentorial involvement may also contribute to sleep related movement disorders independent of cord involvement. Cerebral and brainstem lesions may affect both sleep and arousal mediating pathways though along with other regions such thalamic and periaqueductal grey (PAG), the effect of their involvement on sleep-wake states in NMOSD is unknown.

11. Conclusions

NMOSD is a rare antibody mediated inflammatory disorder and is one of only a handful of conditions in which narcolepsy is a recognised manifestation. There is an unmet need for large multicentre studies of sleep and circadian rhythm disorders in NMOSD utilising validated subjective (e.g., ISI, MEQ) and objective assessment tools (e.g., PSG, MSLT, CSF orexin levels, DLMO). Perhaps through careful study of such disorders in a disease with a relatively clear pathophysiology, inferences can be made that improve our understanding of sleep physiology and importantly improve patient care.

Though NMOSD confers direct (e.g., narcolepsy with hypothalamic lesion) and indirect (e.g., nocturia with myelitis) susceptibilities to sleep and circadian rhythm disruption, disease activity involving the visual pathways, hypothalamic orexin, suprachiasmatic nuclei, and brainstem structures may also play a role. Further studies and disease models may help to better understand the overlapping pathophysiology of NMOSD and sleep disorders.

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Image in figure 1 created by Biorender.com

References and links

1. Berry RB, R; Gamaldo, CE; Harding, SM; Lloyd, RM; Marcus, CL; Vaughn, BV for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events : Rules,Terminology and Technical Specifications*. American Academy of Sleep Medicine; 2015.
2. Rechtschaffen AKA. *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects.* . US Department of Health, Education, and Welfare Public Health Service - NIH/NIND; 1968.
3. Borbély AA. A two process model of sleep regulation. *Hum Neurobiol*. 1982;1(3):195-204.
4. Institute of Medicine CoSMR. The National Academies Collection: Reports funded by National Institutes of Health. In: Colten HA, BM, ed. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. National Academies Press, National Academy of Sciences.; 2006.
5. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep*. 2017;9:151-161. doi:10.2147/NSS.S134864
6. Hillman DR, Murphy AS, Pezzullo L. The economic cost of sleep disorders. *Sleep*. Mar 2006;29(3):299-305. doi:10.1093/sleep/29.3.299
7. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. Sep 2011;21(9):655-79. doi:10.1016/j.euroneuro.2011.07.018
8. Kjellberg PJJ. Societal, economic organisational and research aspects of sleep disorders. In: Z. Dogas PP, D. Pevernagie, ed. *Sleep Medicine Textbook*. European Sleep Research Society; 2014:487-493:chap Demographic and socioeconomic aspects of sleep disorders.
9. Sateia MJ, American Academy of Sleep M. *International classification of sleep disorders*. American Academy Of Sleep Medicine; 2014:383.
10. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. Jul 14 2015;85(2):177-89. doi:10.1212/WNL.0000000000001729
11. Shi Z, Chen H, Lian Z, Liu J, Feng H, Zhou H. Factors that impact health-related quality of life in neuromyelitis optica spectrum disorder: anxiety, disability, fatigue and depression. *J Neuroimmunol*. Apr 15 2016;293:54-58. doi:10.1016/j.jneuroim.2016.02.011
12. Chanson JB, Zephir H, Collongues N, et al. Evaluation of health-related quality of life, fatigue and depression in neuromyelitis optica. *Eur J Neurol*. Jun 2011;18(6):836-41. doi:10.1111/j.1468-1331.2010.03252.x
13. Braley TJ, Boudreau EA. Sleep Disorders in Multiple Sclerosis. *Curr Neurol Neurosci Rep*. May 2016;16(5):50. doi:10.1007/s11910-016-0649-2
14. Veauthier C. Sleep disorders in multiple sclerosis. Review. *Curr Neurol Neurosci Rep*. May 2015;15(5):21. doi:10.1007/s11910-015-0546-0
15. Eaneff S, Wang V, Hanger M, et al. Patient perspectives on neuromyelitis optica spectrum disorders: Data from the PatientsLikeMe online community. *Mult Scler Relat Disord*. Oct 2017;17:116-122. doi:10.1016/j.msard.2017.07.014
16. Moore P, Jackson C, Mutch K, et al. Patient-reported outcome measure for neuromyelitis optica: pretesting of preliminary instrument and protocol for further development in accordance with international guidelines. *BMJ Open*. Sep 30

2016;6(9):e011142. doi:10.1136/bmjopen-2016-011142
17. Perin MM; Bichuetti D. Frequency of sleep abnormalities in a Brazilian cohort of patients with Neuromyelitis Optica Spectrum Disorder. presented at: ECRTIMS; 25/10/2017 2017; Paris. https://onlinelibrary.ectrims-congress.eu/ectrims/2017/ACTRIMS-ECTRIMS2017/199455/marlia.m.m.perin.frequency.of.sleep.abnormalities.in.a.brazilian.cohort.of.html
18. Barzegar M, Sadeghi Bahmani D, Nehzat N, et al. Comparison of sleep complaints and quality of life between patients with neuromyelitis optica spectrum disorder (NMOSD) and healthy controls. *Mult Scler Relat Disord*. Jul 2019;32:81-87. doi:10.1016/j.msard.2019.04.008
19. Seok JM, Choi M, Cho EB, et al. Fatigue in patients with neuromyelitis optica spectrum disorder and its impact on quality of life. *PLoS One*. 2017;12(5):e0177230. doi:10.1371/journal.pone.0177230
20. Miao X, Shi Z, Chen H, Zhou H, Yang R. The impact of pain, anxiety and depression on sleep quality in Chinese patients with neuromyelitis optica spectrum disorders. 2017:
21. Song Y, Pan L, Fu Y, et al. Sleep abnormality in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm*. Jun 2015;2(3):e94. doi:10.1212/NXI.0000000000000094
22. Pan J, Zhao P, Cai H, et al. Hypoxemia, Sleep Disturbances, and Depression Correlated with Fatigue in Neuromyelitis Optica Spectrum Disorder. *CNS Neurosci Ther*. Jul 2015;21(7):599-606. doi:10.1111/cns.12411
23. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. Apr 2002;6(2):97-111. doi:10.1053/smrv.2002.0186
24. Spielman AJ. Assessment of insomnia. *Clinical Psychology Review*. 1986/01/01/ 1986;6(1):11-25. doi:https://doi.org/10.1016/0272-7358(86)90015-2
25. Kyle SD, Espie CA. Classification, evaluation, and pathophysiology. *Oxford Textbook of Sleep Disorders*. 2017:177.
26. Mutch K, Zhao S, Hamid S, et al. Bladder and bowel dysfunction affect quality of life. A cross sectional study of 60 patients with aquaporin-4 antibody positive Neuromyelitis Optica spectrum disorder. *Mult Scler Relat Disord*. Nov 2015;4(6):614-8. doi:10.1016/j.msard.2015.07.015
27. Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. *World Psychiatry*. 2019;18(3):337-352. doi:10.1002/wps.20674
28. Pagel JF, Parnes BL. Medications for the Treatment of Sleep Disorders: An Overview. *Prim Care Companion J Clin Psychiatry*. 2001;3(3):118-125. doi:10.4088/pcc.v03n0303
29. Dube DS, Sarinas P. SEVERE obstructive sleep apnea (osa) associated with severe secondary polycythemia and pulmonary hypertension in a patient with devic's syndrome. C*hest*. 2005;128(4):458S. doi:10.1378/chest.128.4_MeetingAbstracts.458S
30. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology*. May 2008;108(5):812-21. doi:10.1097/ALN.0b013e31816d83e4
31. Simou E, Britton J, Leonardi-Bee J. Alcohol and the risk of sleep apnoea: a systematic review and meta-analysis. *Sleep medicine*. 2018;42:38-46. doi:10.1016/j.sleep.2017.12.005
32. Krishnan V, Dixon-Williams S, Thornton JD. Where there is smoke…there is sleep apnea: exploring the relationship between smoking and sleep apnea. *Chest*.

2014;146(6):1673-1680. doi:10.1378/chest.14-0772
33. Simpson L, McArdle N, Eastwood PR, et al. Physical Inactivity Is Associated with Moderate-Severe Obstructive Sleep Apnea. *J Clin Sleep Med*. 2015;11(10):1091-1099. doi:10.5664/jcsm.5078
34. Shaygannejad V, Sadeghi Bahmani D, Soleimani P, et al. Comparison of prevalence rates of restless legs syndrome, self-assessed risks of obstructive sleep apnea, and daytime sleepiness among patients with multiple sclerosis (MS), clinically isolated syndrome (CIS) and Neuromyelitis Optica Spectrum Disorder (NMOSD). *Sleep Med*. Jun 2020;70:97-105. doi:10.1016/j.sleep.2019.11.1266
35. Kulkarni HS, Liszewski MK, Brody SL, Atkinson JP. The complement system in the airway epithelium: An overlooked host defense mechanism and therapeutic target? *J Allergy Clin Immunol*. 2018;141(5):1582-1586.e1. doi:10.1016/j.jaci.2017.11.046
36. Nishino S. Clinical and neurobiological aspects of narcolepsy. *Sleep Med*. Jun 2007;8(4):373-99. doi:10.1016/j.sleep.2007.03.008
37. Billiard M. REM sleep behavior disorder and narcolepsy. *CNS Neurol Disord Drug Targets*. Aug 2009;8(4):264-70. doi:10.2174/187152709788921690
38. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol*. Oct 2002;59(10):1553-62. doi:10.1001/archneur.59.10.1553
39. Lammers GJ. Narcolepsy with cataplexy. In: Ferini-Strambi SCaL, ed. *Oxford Textbook of Sleep Disorders*. Oxford University Press; 2017:chap 14.
40. Rogers AE, Meehan J, Guilleminault C, Grumet FC, Mignot E. HLA DR15 (DR2) and DQB1*0602 typing studies in 188 narcoleptic patients with cataplexy. *Neurology*. Jun 1997;48(6):1550-6. doi:10.1212/wnl.48.6.1550
41. Tafti M, Hor H, Dauvilliers Y, et al. DQB1 locus alone explains most of the risk and protection in narcolepsy with cataplexy in Europe. *Sleep*. Jan 1 2014;37(1):19-25. doi:10.5665/sleep.3300
42. Mignot E, Hayduk R, Black J, Grumet FC, Guilleminault C. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. *Sleep*. Nov 1997;20(11):1012-20.
43. Hallmayer J, Faraco J, Lin L, et al. Narcolepsy is strongly associated with the T-cell receptor alpha locus. *Nat Genet*. Jun 2009;41(6):708-11. doi:10.1038/ng.372
44. Han F, Faraco J, Dong XS, et al. Genome wide analysis of narcolepsy in China implicates novel immune loci and reveals changes in association prior to versus after the 2009 H1N1 influenza pandemic. *PLoS Genet*. Oct 2013;9(10):e1003880. doi:10.1371/journal.pgen.1003880
45. Latorre D, Kallweit U, Armentani E, et al. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature*. 2018/10/01 2018;562(7725):63-68. doi:10.1038/s41586-018-0540-1
46. Faraco J, Lin L, Kornum BR, et al. ImmunoChip study implicates antigen presentation to T cells in narcolepsy. *PLoS Genet*. 2013;9(2):e1003270. doi:10.1371/journal.pgen.1003270
47. Luo G, Ambati A, Lin L, et al. Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. *Proceedings of the National Academy of Sciences*. 2018;115(52):E12323. doi:10.1073/pnas.1818150116
48. Cvetkovic-Lopes V, Bayer L, Dorsaz S, et al. Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. *J Clin Invest*. Mar 2010;120(3):713-9. doi:10.1172/JCI41366
49. Kawashima M, Lin L, Tanaka S, et al. Anti-Tribbles homolog 2 (TRIB2)

autoantibodies in narcolepsy are associated with recent onset of cataplexy. *Sleep*. Jul 2010;33(7):869-74. doi:10.1093/sleep/33.7.869
50. Lim AS, Scammell TE. The trouble with Tribbles: do antibodies against TRIB2 cause narcolepsy? *Sleep*. Jul 2010;33(7):857-8. doi:10.1093/sleep/33.7.857
51. Archelos JJ, Hartung HP. Pathogenetic role of autoantibodies in neurological diseases. *Trends Neurosci*. Jul 2000;23(7):317-27. doi:10.1016/s0166-2236(00)01575-7
52. Pittock SJ, Weinshenker BG, Lucchinetti CF, Wingerchuk DM, Corboy JR, Lennon VA. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. *Arch Neurol*. Jul 2006;63(7):964-8. doi:10.1001/archneur.63.7.964
53. Baba T, Nakashima I, Kanbayashi T, et al. Narcolepsy as an initial manifestation of neuromyelitis optica with anti-aquaporin-4 antibody. *J Neurol*. Feb 2009;256(2):287-8. doi:10.1007/s00415-009-0139-4
54. Kanbayashi T, Shimohata T, Nakashima I, et al. Symptomatic narcolepsy in patients with neuromyelitis optica and multiple sclerosis: new neurochemical and immunological implications. *Arch Neurol*. Dec 2009;66(12):1563-6. doi:10.1001/archneurol.2009.264
55. Poppe AY, Lapierre Y, Melancon D, et al. Neuromyelitis optica with hypothalamic involvement. *Mult Scler*. Oct 2005;11(5):617-21. doi:10.1191/1352458505ms1200cr
56. Carlander B, Vincent T, Le Floch A, Pageot N, Camu W, Dauvilliers Y. Hypocretinergic dysfunction in neuromyelitis optica with coma-like episodes. *J Neurol Neurosurg Psychiatry*. Mar 2008;79(3):333-4. doi:10.1136/jnnp.2007.135228
57. Viegas S, Weir A, Esiri M, et al. Symptomatic, radiological and pathological involvement of the hypothalamus in neuromyelitis optica. *J Neurol Neurosurg Psychiatry*. Jun 2009;80(6):679-82. doi:10.1136/jnnp.2008.157693
58. Nozaki H, Shimohata T, Kanbayashi T, et al. A patient with anti-aquaporin 4 antibody who presented with recurrent hypersomnia, reduced orexin (hypocretin) level, and symmetrical hypothalamic lesions. *Sleep Med*. Feb 2009;10(2):253-5. doi:10.1016/j.sleep.2007.11.022
59. Samart K, Phanthumchinda K. Neuromyelitis optica with hypothalamic involvement: a case report. *J Med Assoc Thai*. Apr 2010;93(4):505-9.
60. Nakano T, Fujimoto T, Fukuda Y, Takahashi T, Kanbayashi T. [Neuromyelitis optica with syndrome of inappropriate secretion of antidiuretic hormone and hypersomnia associated with bilateral hypothalamic lesions: a case report]. *Rinsho Shinkeigaku*. Aug 2011;51(8):599-602. doi:10.5692/clinicalneurol.51.599
61. Sekiguchi T, Ishibashi S, Kubodera T, et al. Anhidrosis associated with hypothalamic lesions related to anti-aquaporin 4 autoantibody. *J Neurol*. Dec 2011;258(12):2293-5. doi:10.1007/s00415-011-6112-z
62. Deguchi K, Kono S, Deguchi S, et al. A patient with anti-aquaporin 4 antibody presenting hypersomnolence as the initial symptom and symmetrical hypothalamic lesions. *J Neurol Sci*. Jan 15 2012;312(1-2):18-20. doi:10.1016/j.jns.2011.08.031
63. Suzuki K, Nakamura T, Hashimoto K, et al. Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: a case report and literature review. *Arch Neurol*. Oct 2012;69(10):1355-9. doi:10.1001/archneurol.2012.300
64. Saito N, Inoue M, Hasuo K, Kanbayashi T, Murayama S, Takeuchi S. [A 39 years old woman responding to modafinil with bilateral hypothalamic lesion associated

with hyperthermia and hypersomnia: a case report]. *Rinsho Shinkeigaku*. 2014;54(7):550-5. doi:10.5692/clinicalneurol.54.550
65. Okuma H, Matsumura K, Hatanaka Y, Saito F, Sonoo M. Sudden onset of sleep due to hypothalamic lesions in neuromyelitis optica spectrum disorder positive for anti-aquaporin-4 antibody. *Mult Scler*. Sep 2014;20(10):1407-8. doi:10.1177/1352458514540359
66. Kume K, Deguchi K, Ikeda K, et al. Neuromyelitis optica spectrum disorder presenting with repeated hypersomnia due to involvement of the hypothalamus and hypothalamus-amygdala linkage. *Mult Scler*. Jun 2015;21(7):960-2. doi:10.1177/1352458515569100
67. Kallollimath P, Gujjar A, Patil M. Symptomatic Narcolepsy as a Presenting Feature of Neuromyelitis Optica. *Ann Indian Acad Neurol*. Apr-Jun 2018;21(2):156-158. doi:10.4103/aian.AIAN_74_18
68. El Otmani H, Abdulhakeem Z, El Moutawakil B, Rafai MA. Hypersomnia as an isolated symptom of neuromyelitis optica. *Intern Med J*. Dec 2018;48(12):1546-1547. doi:10.1111/imj.14118
69. Daida K, Ogaki K, Hayashida A, et al. Somnolence Preceded the Development of a Subthalamic Lesion in Neuromyelitis Optica Spectrum Disorder. *Intern Med*. Feb 15 2020;59(4):577-579. doi:10.2169/internalmedicine.2947-19
70. Kanbayashi T, Sagawa Y, Takemura F, et al. The pathophysiologic basis of secondary narcolepsy and hypersomnia. *Curr Neurol Neurosci Rep*. Apr 2011;11(2):235-41. doi:10.1007/s11910-011-0178-y
71. Waters P, Reindl M, Saiz A, et al. Multicentre comparison of a diagnostic assay: aquaporin-4 antibodies in neuromyelitis optica. *J Neurol Neurosurg Psychiatry*. Sep 2016;87(9):1005-15. doi:10.1136/jnnp-2015-312601
72. Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol*. 2008;23(7):571-585. doi:10.1002/hup.964
73. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*. Dec 2007;8(12):1065-6. doi:10.1016/s1470-2045(07)70373-x
74. Lockley SW, Arendt J, Skene DJ. Visual impairment and circadian rhythm disorders. *Dialogues Clin Neurosci*. 2007;9(3):301-314. doi:10.31887/DCNS.2007.9.3/slockley
75. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res*. Jul 2002;53(1):547-54. doi:10.1016/s0022-3999(02)00443-9
76. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med*. Mar 2003;4(2):121-32. doi:10.1016/s1389-9457(02)00258-7
77. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. *Sleep Med*. Aug 2014;15(8):860-73. doi:10.1016/j.sleep.2014.03.025
78. Ito E, Inoue Y. [The International Classification of Sleep Disorders, third edition. American Academy of Sleep Medicine. Includes bibliographies and index]. *Nihon Rinsho*. Jun 2015;73(6):916-23.
79. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. Nov 2014;146(5):1387-1394. doi:10.1378/chest.14-0970
80. Allen RP. Restless Leg Syndrome/Willis-Ekbom Disease Pathophysiology. *Sleep Med Clin*. Sep

2015;10(3):207-14, xi. doi:10.1016/j.jsmc.2015.05.022
81. Manconi M, Rocca MA, Ferini-Strambi L, et al. Restless legs syndrome is a common finding in multiple sclerosis and correlates with cervical cord damage. *Mult Scler*. Jan 2008;14(1):86-93. doi:10.1177/1352458507080734
82. Manconi M, Fabbrini M, Bonanni E, et al. High prevalence of restless legs syndrome in multiple sclerosis. *Eur J Neurol*. May 2007;14(5):534-9. doi:10.1111/j.1468-1331.2007.01740.x
83. Brown LK, Heffner JE, Obbens EA. Transverse myelitis associated with restless legs syndrome and periodic movements of sleep responsive to an oral dopaminergic agent but not to intrathecal baclofen. *Sleep*. Aug 1 2000;23(5):591-4.
84. Manconi M, Ulfberg J, Berger K, et al. When gender matters: restless legs syndrome. Report of the "RLS and woman" workshop endorsed by the European RLS Study Group. *Sleep Med Rev*. Aug 2012;16(4):297-307. doi:10.1016/j.smrv.2011.08.006
85. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. Sep 2007;6(9):805-15. doi:10.1016/s1474-4422(07)70216-8
86. Hyun JW, Kim SH, Jeong IH, et al. Increased frequency and severity of restless legs syndrome in patients with neuromyelitis optica spectrum disorder. *Sleep Med*. Jan 2016;17:121-3. doi:10.1016/j.sleep.2015.08.023
87. Lu J, Sherman D, Devor M, Saper CB. A putative flip-flop switch for control of REM sleep. *Nature*. Jun 1 2006;441(7093):589-94. doi:10.1038/nature04767
88. Horner RL, Peever JH. Brain Circuitry Controlling Sleep and Wakefulness. *Continuum (Minneap Minn)*. Aug 2017;23(4, Sleep Neurology):955-972. doi:10.1212/con.0000000000000495
89. Schneider L. Neurobiology and Neuroprotective Benefits of Sleep. *Continuum (Minneap Minn)*. Aug 2020;26(4):848-870. doi:10.1212/con.0000000000000878

