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

Authors
Elhadd KT¹, Healy S¹, Gibbons E¹, Linaker S¹, Kelly P¹, Manuel A² Huda S¹

Affiliations
¹The Walton Centre NHS Foundation Trust
²Aintree University Hospitals Foundation Trust

Correspondence
Elhadd KT
Email: Kariem.Elhadd@thewaltoncentre.nhs.uk

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.\textsuperscript{1,2} Sleep is a process that takes place within the brain, mediated by homeostatic and circadian mechanisms.\textsuperscript{3}

Disordered sleep is present in 15-35\% of adults and frequently underreported.\textsuperscript{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.\textsuperscript{5} The economic disease burden of sleep disorders is high. One study estimated this to amount 7.49 billion USD/year.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{9}

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

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

Table 2. Summary of key psychometric assessment tools
### Table 3. Psychometric and objective assessment tools employed in various sleep disorders.

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

**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. Contrasting, 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. 

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). 

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. 

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. 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. 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.\textsuperscript{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 confounding 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\%.\textsuperscript{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.\textsuperscript{24, 25} Eaneff et al. reported moderate to severe insomnia in 35\% of 522 NMOSD patients.\textsuperscript{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.\textsuperscript{26} Treatments used in NMOSD may also exacerbate insomnia e.g., corticosteroids, antidepressants, and anticonvulsant neuropathic pain medication.\textsuperscript{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.\textsuperscript{9} Severe and complicated OSA has been reported in NMOSD.\textsuperscript{29} NMOSD patients score higher than controls on screening tools for sleep disordered breathing such as the STOP-BANG and Berlin Questionnaires.\textsuperscript{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\textsuperscript{2}), age (>50 years), neck circumference (male >43 cm; female >41 cm) and sex (male). A score of \textguillemotleft 3\textguillemotright is interpreted as a moderate to severe risk of OSA.\textsuperscript{30} Rates of OSA were similar between NMOSD and HCs in this study, and there was modest correlation between OSA and restless legs symptoms ($r^2=0.3$, $p<0.05$).\textsuperscript{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.

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. 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). 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 hypoaxemia was unclear as patients did not have a history of anaemia, pulmonary or cardiac disease.

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.

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. The diagnosis of narcolepsy is supported by PSG, MSLT and the assessment of CSF orexin/hypocretin levels (a neuropeptide which promotes wakefulness, suppresses active sleep, and stabilises the wake/NREM/REM vigilance states). 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

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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”.

Low or absent CSF orexin levels are highly sensitive (87%) and specific (99%) for Type 1 narcolepsy. The human leukocyte antigen HLA-DQB1* 06:02 is also found in more than 98% of cases of Type 1 narcolepsy 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.

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. Most recently orexin specific, autoreactive CD4+ and CD8+ T cells have been isolated in narcoleptic patients. Newer susceptibility genes have been identified using high density genotyping including cathepsin H (CTSH) and tumour necrosis factor superfamily member 4 (TNFSF4). 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.

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.

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.

A small minority (<2%) of narcolepsy patients represent familial or “symptomatic” 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”. 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. 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.

<table>
<thead>
<tr>
<th>Narcolepsy Type 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive daytime sleepiness daily for ≥3 months</td>
</tr>
<tr>
<td>One or both of the following:</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Low or absent CSF hypocretin-1 levels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Narcolepsy Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive daytime sleepiness and MSLT findings as above, but without cataplexy</td>
</tr>
<tr>
<td>CSF hypocretin-1 levels are unknown or are above the threshold for type 1 narcolepsy</td>
</tr>
<tr>
<td>The hypersomnoleance 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.</td>
</tr>
</tbody>
</table>

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 sleep 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. 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. Although reports of “symptomatic narcolepsy” in NMOSD are increasing, there are only 17 reported cases to date (summarised in Table 5). It is noteworthy that narcolepsy is one of the core clinical characteristics included in the 2015 NMOSD IPND diagnostic criteria. The clinical characteristics of these cases will be expanded upon and discussed.

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<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Ethnicity</th>
<th>EDS</th>
<th>CSF Orexin (pg/mL)</th>
<th>Cataplexy</th>
<th>ICSD NT1/NT2</th>
<th>ICSD3 NMC</th>
<th>AQP4-IgG</th>
<th>MRI HT lesion</th>
<th>Other features</th>
<th>Measures</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poppe et al 2005</td>
<td>19/F</td>
<td>Caucasian</td>
<td>+</td>
<td>NT</td>
<td>No</td>
<td>NA</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>Myelitis, Bilateral Optic Neuritis</td>
<td>CSF</td>
<td>IVMTP, IVIG, PLEX</td>
</tr>
<tr>
<td>Poppe et al 2005</td>
<td>13/M</td>
<td>Haitian/FC</td>
<td>+</td>
<td>NT</td>
<td>No</td>
<td>NA</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>Low temp</td>
<td>CSF</td>
<td>IVMTP, PLEX</td>
</tr>
<tr>
<td>Carlander et al 2008</td>
<td>48/F</td>
<td>Caucasian</td>
<td>+</td>
<td>158*</td>
<td>No</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Dysautonomia, Chiasmitis, LETM</td>
<td>CSF</td>
<td>Rituximab x3</td>
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<tr>
<td>Viegas et al 2009</td>
<td>17/F</td>
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<td>+</td>
<td>NT</td>
<td>No</td>
<td>NA</td>
<td>+</td>
<td>-→+</td>
<td>+</td>
<td>High temp, Hiccoughs</td>
<td>CSF, Brain biopsy</td>
<td>IVMTP, IVIG Azathioprine</td>
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<tr>
<td>Nozaki et al 2009</td>
<td>42/F</td>
<td>Japanese</td>
<td>+</td>
<td>191*</td>
<td>No</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Myelitis</td>
<td>CSF</td>
<td>IVMTP x3 PO Prednisolone</td>
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<tr>
<td>Baba et al 2009</td>
<td>35/F</td>
<td>NA</td>
<td>+</td>
<td>91</td>
<td>No</td>
<td>NT1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Myelitis</td>
<td>CSF, HLA, PSG, MSLT</td>
<td>High dose MTP PO Prednisolone</td>
</tr>
<tr>
<td>Samart et al 2010</td>
<td>34/F</td>
<td>NA</td>
<td>+</td>
<td>NT</td>
<td>No</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bilateral Optic Neuritis, Myelitis</td>
<td>CSF</td>
<td>High dose corticosteroids</td>
</tr>
<tr>
<td>Nakano et al 2011</td>
<td>31/F</td>
<td>NA</td>
<td>+</td>
<td>187*</td>
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<td>CSF, MSLT</td>
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<td>+</td>
<td>-</td>
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<td>Hyperthermia, seizures, weight gain, irregular menses</td>
<td>CSF, EEG Brain Biopsy</td>
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<td>+</td>
<td>Y</td>
<td>SOOS</td>
<td>CSF</td>
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<th>85.8</th>
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<th>-→</th>
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<th>CSF, HLA</th>
<th>MTPx12</th>
<th>PO Prednisolone</th>
<th>SOOS &amp; RTA post steroid taper. IVMTP &amp; PO prednisolone Resolved EDS. CSF Orexin increased</th>
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<tr>
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<td>Diplopia, seizures, ataxia hemiparesis dysphagia</td>
<td>CSF</td>
<td>Steroids Azathioprine</td>
<td>Improved but persistent EDS (sleep duration 22→16 hours).</td>
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<td>Y</td>
<td>Nil</td>
<td>EEG, CSF</td>
<td>IVMTP x3 PO Prednisolone Mycophenolate</td>
<td>Resolved EDS at 1 week. Asymptomatic at 3 years</td>
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<td>Consciousness disorder 1 year prior</td>
<td>EEG, CSF</td>
<td>IVMTP x5, CYCL, IA, OMTP Tacrolimus Methylphenidate Modafinil</td>
<td>Improved but persistent EDS</td>
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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 hypersonsomnolence 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{64} HLA DQB1*0602 was only assessed in 3 patients and was negative in all cases.\textsuperscript{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.\textsuperscript{53, 67} Narcolepsy was also associated with autonomic and endocrine dysfunction 8/17 (47%) of cases.\textsuperscript{55-57, 60, 61, 63, 64, 66}

Most cases of hypersonsomnolence (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.\textsuperscript{63, 64, 69}

At last review 1 patient had died, 4 had severe disability (ventilator dependence and disabling hypersonsomnolence), 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.\textsuperscript{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
hypersonmolence often with impaired social function. Examples of CRSWDSs include advanced, delayed, irregular and non-24-hour sleep-wake phase disorder, jet lag disorder, and shift work disorder. CR SWDSs are associated with mental and physical health disorders such as depression and cancer. 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. In keeping with these findings, visual impairment correlated significantly with sleep impairment (p=0.025) in the study by Chanson et al. 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. To our knowledge there are no other reports analysing for chronotype or the presence of CRSWDSs 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. 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.

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. IRLSSG criteria includes a “specifier for clinical significance” 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).

Primary RLS is a disorder of unknown aetiology; several factors may be involved including genetic, cortical-spinal excitability, iron and dopamine dependent neurotransmission. 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. 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. 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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), postero lateral 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 chiasmatisis 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.

Acknowledgements
Image in figure 1 created by Biorender.com
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