Sleep Quality in Neuromyelitis Optica Spectrum Disorder: A Systematic Review

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ABSTRACT

BACKGROUND: This review summarizes the literature on sleep quality in neuromyelitis optica spectrum disorder (NMOSD) and discusses these findings in the context of current knowledge of sleep physiology.

METHODS: A literature search was performed using Ovid MEDLINE, Embase, and Scopus from inception to September 3, 2020. All included studies reported at least 1 measure of sleep quality in individuals with NMOSD. Pittsburgh Sleep Quality Index (PSQI) scores of individuals from 4 studies were compared with those from a data set of controls.

RESULTS: Thirteen studies (1041 individuals with NMOSD) were included in the review. Disturbed sleep was demonstrated across subjective metrics based on patient surveys and objective metrics such as polysomnography. An estimated 70% of individuals with NMOSD can be classified as poor sleepers. Standardized mean difference between PSQI scores of 183 individuals with NMOSD and those of 9284 controls was 0.72 (95% CI, 0.57-0.86; $P < .001$). Decreased sleep quality was significantly associated with decreased quality of life and increased anxiety, depression, and disability status. Sleep disturbances in NMOSD were similar in severity to those in multiple sclerosis.

CONCLUSIONS: Sleep disturbances are a major contributor to NMOSD disease burden and may arise from the disruption of sleep circuitry, in addition to physical and psychological complications. Multiple processes involved in sleep regulation may be affected, such as, but not limited to, neural circadian circuit disruption, direct effects of inflammation, aminergic projecting system abnormalities, glymphatic system impairment, and development of sleep disorders such as restless legs syndrome/sleep apnea. A better understanding of these mechanisms is necessary for developing effective therapies for NMOSD-associated sleep disturbances.

Int J MS Care. 2022;24(3):124-131. doi:10.7224/1537-2073.2021-019

Neuromyelitis optica spectrum disorder (NMOSD) is a rare and devastating disease that causes autoimmune inflammation of the central nervous system. Discovery of autoantibodies against the water channel AQP4 as a cause of NMOSD has expanded the repertoire of recognized clinical manifestations beyond those of the traditionally reported optic neuritis and longitudinally extensive transverse myelitis.[1] Patients with AQP4 seropositivity can present with brainstem syndromes, intractable hiccups, and nausea due to area postrema lesions, cerebritis, and symptomatic narcolepsy.

Although narcolepsy in NMOSD is rare,[2] sleep disturbances are increasingly recognized as common concerns. Nearly half of all patients experience restless legs syndrome (RLS),[3] and more than 70% report fatigue.[4] These changes may be precipitated by disruption of sleep-wake circuitry because NMOSD can damage periventricular regions of the brain,[5] notable both for high density of AQP4 receptor expression and for their role in the regulation of sleep and circadian rhythms.[6] Other sources of sleep disturbances in NMOSD may be secondary to the physical manifestations of the disease. Individuals with NMOSD frequently experience bladder dysfunction that may result in nocturia alongside bouts of muscle spasticity during nighttime sleep.[7,8] Individuals with NMOSD experience high rates of depression, which is undertreated in as many as 50% of severe cases[9] and may be caused by, or contribute to, poor sleep.[10]

This systematic review aimed to synthesize current evidence regarding sleep-related quality of life (QOL) in individuals with NMOSD. We discuss our findings in light of current understanding of sleep-wake circuitry and its disruption in inflammatory central nervous system conditions such as multiple sclerosis (MS).

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Note: Supplementary material for this article is available at ijmsc.org.

TABLE 1. Baseline Demographic Characteristics in the 13 Included Studies

Study	Country of origin	Participants, No.		Age of NMOSD participants, mean ± SD, y	Female sex, %	Disease duration, mean ± SD, y	AQP4 antibody positive, %
		NMOSD group	Comparison group				
Hyun et al,[23] 2020	South Korea	99	58 (MS)	46.4 ± 10.3	87.8	9.7 ± 6.1	92
Barzegar et al,[16] 2019	Iran	41	46 (controls)	37.2 ± 9.53	73.2	6.93 ± 5.21	29
Shin et al,[17] 2019	South Korea	35	24 (MS)	48.97 ± 13.36	85.7	6.80 ± 9.28	NR
Shaygannejad et al,[3] 2019	Iran	24	359 (MS)	35.98 ± 9.12	91.6	NR	NR
Miao et al,[10] 2017	China	42	NR	41 ± 13	92.9	5.7 ± 4.4	62
Seok et al,[24] 2017	South Korea	35	NR	46.5 ± 14.1	82.9	3.0	100
Eaneff et al,[22] 2017	United States	522	39,732 (MS)	43	79.3	NR	NR
Shi et al,[20] 2016	China	73	NR	40.05 ± 11.18	91.8	4.28 ± 4.27	73
Song et al,[21] 2015	China	33	20 (controls)	46.9 ± 14.9	78.8	4.7 ± 3.4	70
Mutch et al,[7] 2015	United Kingdom	60	NR	49	83.3	6.5	100
Kanamori et al,[18] 2011	Japan	37	51 (MS)	50.8 ± 14.5	97.2	13.0 ± 10.8	95
Pan et al,[19] 2015	China	33	20 (controls)	46.9 ± 14.9	78.8	4.7 ± 3.4	70
Chanson et al,[15] 2011	France	40	NR	45.2 ± 13.7	65.0	9.5 ± 9	39

MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; NR, not reported.
Note: All 13 studies had cross-sectional design.

METHODS

Search Strategy and Data Extraction

A literature search was conducted across Ovid MEDLINE, Embase, and Scopus from the inception of the databases to September 3, 2020. An example of the search strategy for one of the databases can be found in **TABLE S1** (published in the online version of this article at ijmsc.org). Two reviewers (A.E., D.E.-J.) independently conducted a 2-stage screening process. Articles were first screened using only their titles and abstracts, then the full texts of articles were evaluated for selection based on the inclusion criteria. If there were any discrepancies between the reviewers in the selection process, they were resolved by consensus with input from a third reviewer (K.Z.). The reference lists of included papers were also searched to ensure no relevant studies were missed. Studies were included if they had any quantitative measure of sleep quality in individuals who have received a diagnosis of NMOSD, such as Pittsburgh Sleep Quality Index (PSQI) or Epworth Sleepiness Scale (ESS) scores. Eligible study designs were randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, and case series. The exclusion criteria were: (1) non–English language studies; (2) abstracts and unpublished studies; (3) review papers, case reports, and editorials; (4) studies with a pediatric population; and (5) studies reporting on general QOL measures without describing specific sleep outcomes. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID:CRD42020171918).

The following data were extracted from included studies: study identifiers (authors, design, year of publication, etc), baseline demographic characteristics, types of measuring tools used, and outcomes related to sleep, fatigue, and QOL. The quality of cross-sectional studies was evaluated using a modified version of the Newcastle-Ottawa Scale.[11]

Data Synthesis and Statistical Analysis

Because most of the included studies used dissimilar comparison groups and measures of sleep, most outcomes were not combined to provide a final estimate. Instead, they were described and contrasted between studies, as appropriate.

For the comparison between individuals with NMOSD and controls, mean PSQI scores with SDs were extracted from primary studies. The PSQI was chosen for this comparison because it was the most commonly reported outcome, and a large normative database of PSQI scores for 9284 individuals has been recently published that reported an overall mean ± SD score of 5 ± 3.37 (women, 5.54 ± 3.58; men, 4.38 ± 3.00).[12] The PSQI is a validated instrument and self-reported patient questionnaire in which higher scores indicate worse sleep quality, and a score greater than 5 suggests a poor sleeper.[13] From community samples, PSQI scores have been found to follow a near-normal distribution, with slight right skewness.[14]

Standardized mean differences (SMDs, also known as Cohen *d*) between PSQI scores of individuals with NMOSD in each study, and those in the normative database, were computed. A random-effects model for SMD was then fitted for the entire pool of studies to derive an

TABLE 2. Sleep Outcomes in the 13 Included Studies

Study	Sleep-related measures	Main sleep outcomes	Newcastle-Ottawa Scale score[a]
Hyun et al,[23] 2020	BPI	Pain-related interference with mean ± SD sleep score of 4.3 ± 3.3 (vs 3.6 ± 3.2 in MS).	8
Barzegar et al,[16] 2019	PSQI, OSA, RLS questionnaire, ESS	Higher ESS scores vs controls.b Trend toward higher scores of PSQI, sleep apnea, and RLS.	7
Shin et al,[17] 2019	Borderline Symptom List-95	Sleep problem subscale mean ± SD score of 57.34 ± 12.76 (vs 56.29 ± 11.47 in MS).	7
Shaygannejad et al,[3] 2019	OSA, ESS, RLS	No significant difference in daytime sleepiness between NMOSD and MS. RLS rate of 45.8% (vs 28.7% in MS). 8.3% prevalence of self-assessed OSA. Age and EDSS scores associated with higher RLS, OSA scores.[b]	5
Miao et al,[10] 2017	PSQI	Mean ± SD PSQI score of 7.5 ± 4.9. Individuals with NMOSD score lower on physical function dimension of Multiple Sclerosis Quality of Life-54 if they also have poor sleep.[b] Correlation between anxiety, depression, EDSS scores, and PSQI scores.[b] No association between poor sleep and AQP4 antibody. Annual NMOSD relapse rate not influenced by poor sleep.	7
Seok et al,[24] 2017	PSQI	Mean ± SD PSQI score of 6.7 ± 3.5.	7
Eaneff et al,[22] 2017	PatientsLikeMe symptom severity report	28% of patients reporting moderate or severe level of excessive daytime sleepiness (vs 41% of patients with MS).[b]	4
Shi et al,[20] 2016	PSQI	Mean ± SD PSQI score of 7.7 ± 4.4.	7
Song et al,[21] 2015	PSQI, ESS, nocturnal polysomnography	Mean ± SD PSQI score of 7.5 ± 4.9. Decrease in sleep efficiency, total sleep time, N3 sleep, oxygen saturation compared with controls.[b] Increase in wake time after sleep onset, N1 sleep, REM sleep, periodic leg movement rate, apnea-hypopnea index.[b]	8
Mutch et al,[7] 2015	Lower Urinary Tract Quality of Life Survey	62% claim urinary symptoms affect their sleep.	5
Kanamori et al,[18] 2011	BPI	Pain-related interference with mean ± SD sleep score of 3.5 ± 3.6 (vs 2.2 ± 3.1 in MS).	5
Pan et al,[19] 2015	PSQI, ESS	Mean ± SD PSQI score of individuals with fatigue was 9.2 ± 1.2 (vs 5.8 ± 1.0 in individuals without fatigue).b Mean ± SD ESS score in individuals with fatigue was 7.3 ± 1.3 (vs 3.8 ± 0.7 in patients without fatigue).[b] Fatigue scores were higher among individuals with NMOSD compared with controls.[b]	8
Chanson et al,[15] 2011	Multiple Sclerosis Quality of Life-54	No association between sleep and sex, age, duration of disease, EDSS score, and presence of antibodies. Significant association between sleep and visual acuity.[b]	7

BPI, Brief Pain Inventory; EDSS, Expanded Disability Status Scale; ESS, Epworth Sleepiness Scale; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; RLS, restless legs syndrome.

[a]Total possible score is 10.

[b]$P < .05$.

estimate of the aggregate SMD. Because most individuals in reported studies were women, and women score approximately 1 point higher than men on the PSQI, the analysis was repeated by computing SMDs relative to the 4864 women from the previously mentioned database to derive a conservative estimate of the difference between individuals with NMOSD and controls.

The frequency of sleep disturbances in individuals with NMOSD was determined by compiling the weighted mean ± SD of patient scores on the PSQI. The PSQI scores from individual studies are summarized as weighted mean ± SD. To estimate the proportion of poor sleepers (PSQI score > 5), a z score was calculated by subtracting 5 from the weighted mean and dividing the result by weighted SD. The corresponding area under the curve of a standard normal distribution was then calculated. All analyses were performed in R software, version 4.0.3 (r-project.org), using the metafor and Hmisc packages.

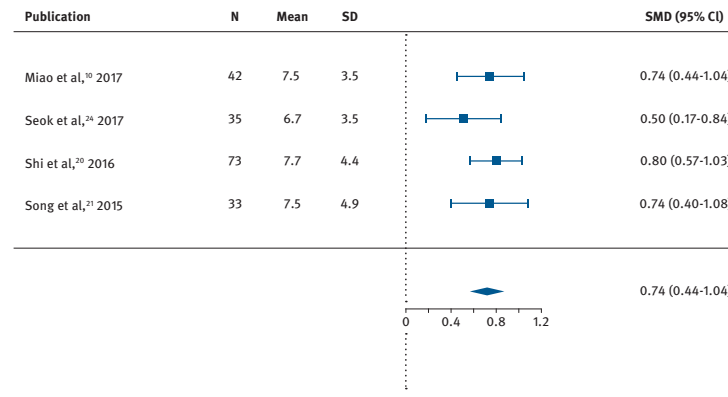
RESULTS

Study Characteristics

The literature search yielded 625 results across the 3 databases. After screening, 13 studies remained and

were included for analysis (**FIGURE S1**).[3,7,10,15-24] All the included studies had cross-sectional designs. Most of the studies were conducted in Asia (10 of 13), with 4 from China, 3 from South Korea, 2 from Iran, and 1 from Japan. The other 3 of 13 studies were conducted in the United Kingdom, the United States, and France. The total number of individuals with NMOSD in the included studies was 1041, 82.2% of whom were women. The mean age of the participants was 43.8 years. The mean duration of disease in individuals with NMOSD was 7.2 years. Most individuals with NMOSD (76.3%) tested positive for serum AQP4 IgG antibodies in the studies that specifically measured this marker. The most common sleep evaluation tool, which was used in 6 studies, was the PSQI, or a minor variation of it. **TABLE 1** summarizes the baseline characteristics of the included studies.

FIGURE 1. Forest Plot of PSQI Scores From Individual Studies Compared With Normative PSQI Scores for 9284 Individuals from Study by Hinz et al[12] and Estimation of Overall Effect Size



PSQI, Pittsburgh Sleep Quality Index; SMD, standardized mean difference.

Risk-of-Bias Analysis

Overall, there was a medium risk of bias among included studies. The Newcastle-Ottawa Scale domains, in order from highest to lowest risk of bias, were selection, assessment, and comparability. Most studies (12 of 13) enrolled fewer than 100 participants with NMOSD, and none of the studies justified their choice of sample size. Moreover, most studies did not differentiate between the characteristics of questionnaire responders and nonresponders, introducing a potential for selection bias. The mean score achieved by studies was 6.5 of 10, where a higher score is indicative of higher quality (**TABLE 2**).

Main Analysis

Table 2 summarizes the sleep outcomes.

Sleep Quality Disturbance in NMOSD

A variety of survey-based instruments have been used to assess sleep quality in patients with NMOSD. Among 4 studies that reported global PSQI scores[10,20,21,24] (1 additional study used a repeated study population and was excluded from this calculation), individuals with NMOSD had a weighted mean ± SD score of 7.42 ± 4.54 (range, 6.7-7.7). Relative to the PSQI's "poor sleep" cutoff score of 5, it can be estimated that 70% of individuals with NMOSD are poor sleepers. The SMD between PSQI scores of 183 individuals with NMOSD and those of 9284 controls was 0.72 (95% CI, 0.57-0.86; $P < .001$) (**FIGURE 1**). Because most individuals with NMOSD are women, and women controls score approximately 1 point higher than men on the PSQI, we next restricted the analysis to comparisons with only women controls to derive a conservative estimate of the difference. The aggregate SMD between individuals with NMOSD and those of 4864 women controls was 0.53 (95% CI, 0.38-0.67, $P < .001$). Taken together, these data suggest NMOSD has a moderate to large effect size on sleep quality.

Other self-reporting tools were used to demonstrate higher levels of daytime sleepiness and prevalence of RLS in NMOSD. Eaneff et al[22] found that 28% of individuals with NMOSD reported experiencing moderate or severe levels of excessive daytime sleepiness. Although the study by Eaneff et al did not have a control group, Barzegar et al[16] identified a significant increase in daytime sleepiness on the ESS score in individuals with NMOSD relative to controls ($P < .01$). Individuals with NMOSD were also found to have a high prevalence of RLS. Using the International Restless Legs Study Group Rating Scale, Barzegar et al[16] showed that individuals with NMOSD report higher scores of RLS, and Shaygannejad et al[3] found that 45.8% of individuals with NMOSD experienced RLS.

Only 1 study compared the sleep structure of individuals with NMOSD with that of controls using polysomnography.[21] Song et al[21] showed that individuals with NMOSD had decreased levels of sleep efficiency (79% vs 86%; $P = .0341$), a 13-minute decrease in total sleep time ($P = .0471$), and a 44-minute increase in wake time after sleep onset ($P < .0001$). Individuals with NMOSD had a 7% increase in stage N1 sleep ($P = .013$), similar durations of N2 sleep, a 12% decrease in N3 sleep ($P < .0001$), and a 4% increase in rapid eye movement (REM) sleep ($P = .0423$). The frequency of periodic leg movements was increased in individuals with NMOSD, who experienced a mean of 20 per hour, as opposed to 2 per hour in controls. An

apnea-hypopnea index greater than 5, suggestive of at least mild obstructive sleep apnea, was found in 18% of individuals with NMOSD compared with only 5% of controls (P = .0067). Accordingly, oxygen saturation was lower in individuals with NMOSD (94% vs 96%; P = .0111; with a nadir of 89% vs 92%; P = .0391). Taken together, the subjective and objective measures of sleep quality suggest that individuals with NMOSD have significant disturbances in sleep.

Sleep Disruption and QOL in NMOSD

Most studies demonstrated a relationship between poor sleep and diminished QOL in individuals with NMOSD. The only study that did not find this was that of Chanson et al,[15] who did not find a correlation between Expanded Disability Status Scale scores and sleep scores in NMOSD. Higher Expanded Disability Status Scale scores were correlated with worse PSQI scores (r = 0.65; P < .001),[10] obstructive sleep apnea, and RLS.[3] Individuals with NMOSD with poor sleep also scored significantly lower than controls in the physical function dimension of the Multiple Sclerosis Quality of Life-54 (mean ± SD: 57 ± 34 vs 80 ± 24; P = .041).[10] Similarly, fatigue was more severe and prevalent in individuals with NMOSD than in controls (mean ± SD: 6.4 ± 0.6 vs 3.8 ± 0.4; P = .002) and was associated with higher PSQI and ESS scores.[19]

Clear associations have also been found between diminished sleep quality and mood disorders in NMOSD. The PSQI scores were correlated with both anxiety and depression scores (r = 0.67, P < .001; r = 0.67, P < .001, respectively).[10] This effect is likely moderated by fatigue, as Pan et al[19] showed that individuals with NMOSD who reported more fatigue had a higher burden of depression. Supporting this idea, illness duration and higher fatigue scores were associated with poor sleep quality.[16] Taken together, these data suggest that disruption of sleep is significantly correlated with the burden of mood disorders in NMOSD, although the direction of causality cannot be inferred.

NMOSD can also disrupt sleep-related QOL by other mechanisms. Based on the Lower Urinary Tract Quality of Life Survey, 62% of individuals who were AQP4 positive felt their urinary symptoms were affecting their sleep, with 30% of individuals reporting a bothersome score greater than 7 of 10.[7] Interestingly, lower visual acuity was associated with poorer sleep subscores on the Multiple Sclerosis Quality of Life-54 (P = .025), which suggests that the disruption of visual pathways might reflect interference with sleep in NMOSD.[15]

Overall, these findings demonstrate a strong relationship between sleep quality and various QOL measures in NMOSD. Nonetheless, the cross-sectional nature of these studies makes the direction of causality between poor sleep and psychological symptoms or disability ambiguous.

Comparison With MS

Apart from an increased prevalence of RLS in individuals with NMOSD (45.8% vs 28.7%),[3] no clear sleep differences were found between individuals with NMOSD and individuals with MS. Eaneff et al[22] did report a higher prevalence of moderate or excessive daytime sleepiness in individuals with MS through a nonvalidated questionnaire (41% vs 28% in NMOSD; P < .005), but this result contradicted that of Shaygannejad et al,[3] who found no significant differences in daytime sleepiness between 24 individuals with NMOSD and 359 individuals with MS. Similarly, Shin et al[17] found no difference between the scores of individuals with NMOSD and individuals with MS on the "sleep problem" subscale of the Borderline Symptom List-95.

The impact of pain on sleep was also found to be similar in both patient populations. There were no differences between individuals with NMOSD and individuals with MS using the Brief Pain Inventory across 2 studies,[23] although Kanamori et al[18] found that pain was much more common (83.8% vs 47.1%) and severe (Pain Severity Index of 3.6 vs 1.5; P < .0001) in NMOSD.

DISCUSSION

In this review, the most consistent and significant finding in individuals with NMOSD was poor sleep quality compared with controls, and decreased QOL associated with anxiety, depression, and disability. In the following subsections, we review sleep-related outcomes in NMOSD and use them to explore the pathophysiology of disturbed sleep.

Measures of Sleep Quality in NMOSD

The quality of sleep in individuals with NMOSD was quantified by 4 studies, with a mean ± SD PSQI score of 7.42 ± 4.54 (range, 6.7-7.7). Although these scores were pooled from a limited number of studies, they demonstrate a trend for poor sleep quality in NMOSD. In comparison, a recent German study attempted to provide reference values for PSQI scores in the general population, reporting a mean ± SD PSQI score of 5.00 ± 3.37.[12] Other previous normative population studies have found mean ± SD PSQI scores of 4.55 ± 3.71 and 5.30 ± 3.25 in Austria and Hong Kong, respectively.[25,26] The present comparison compared PSQI scores among individuals with NMOSD with the German normative sample and found a significant mean difference of 0.72 (95% CI, 0.57-0.86; P < .001), demonstrating poorer sleep quality in individuals with NMOSD than in the general population. Previous studies have demonstrated high rates of psychiatric comorbidities in individuals with NMOSD.[9,27] This review further highlights a link between many of these psychological factors and poor sleep. Miao et al[10] found significant correlations between anxiety or depression and PSQI scores, whereas Barzegar et al[16] and Pan et al[19] found correlations

between fatigue and poor sleep. Sleep disturbances in NMOSD seem to be similar to those seen in MS, both in pathophysiology and severity. In comparing NMOSD and MS, similar scores were found between patients for pain-related interference with sleep.

Mechanisms of Disturbed Sleep in NMOSD

A brief review of the literature suggests the disturbed sleep observed in NMOSD may be attributable to primary disruption of neural sleep circuits, a secondary effect of other neurologic complications, and psychiatric etiologies. Understanding these mechanisms and their complex interplay in NMOSD is necessary for safe and effective symptom management.

NMOSD preferentially affects periventricular regions of the brain, which are notable for their high densities of AQP4 channels and their neuronal subpopulations responsible for circadian rhythm regulation. Serotonergic signaling from the dorsal and medial raphe nuclei, noradrenergic signaling from the locus coeruleus, and histaminergic signaling from the tuberomammillary nucleus (TMN) form the basis of dense arousal circuits that extend throughout the forebrain.[28] Inhibitory modulation of these circuits by the ventrolateral and median preoptic areas is responsible for the induction of restful non-REM sleep.[28] AQP4 autoantibody-mediated inflammatory damage to the ventrolateral and median preoptic areas may prevent effective inhibition of arousal signaling at night, leading to disrupted non-REM sleep. This effect was observed by Song et al,[21] who saw a significant reduction in N3 non-REM sleep, sleep efficiency, and arousal index in individuals with NMOSD compared with controls. Direct inflammatory damage to the dorsal and medial raphe nuclei, locus coeruleus, and TMN could prevent effective arousal signaling during the day, which, combined with the loss of restorative sleep, could lead to the increased daytime sleepiness that is often associated with NMOSD.

NMOSD may also cause aberrant histaminergic signaling in the brain. Histaminergic signaling from the TMN is completely shut off during sleep, unlike other neurotransmitter arousal systems, which simply reduce their activity.[29] Histamine cannot pass through an intact blood-brain barrier, so TMN neurons are the only neural source.[29] Neuroinflammation associated with NMOSD flares may cause blood-brain barrier disruption[30] and possibly increase permeability of systemic histamine. This may cause aberrant histaminergic signaling, resulting in increased wakefulness and disruption of sleep at the beginning of a flare.

Impairment of the glymphatic system by NMOSD may also contribute to daytime sleepiness, as reflected by high ESS scores. The concentration of metabolic waste, such as adenosine, regulates the sleep-wake cycle. The clearance of adenosine and other neurotoxic waste products by the glymphatic system is thought to significantly contribute to the restorative effects of sleep.[31-33] This clearance is achieved by the convective exchange of cerebrospinal fluid and interstitial fluid through AQP4 channels on perivascular astrocytic endfeet.[34,35] The NMOSD autoantibodies cause the destruction of AQP4 channels at astrocytic endfeet, which can prevent effective glymphatic clearance of adenosine.[34,35] The glymphatic system is also responsible for the clearance of proteins such as β-amyloid and tau, which are implicated in Alzheimer disease.[36] Given this alternate function of AQP4 channels, one may predict progressive cognitive decline to be seen in individuals with NMOSD. However, cognitive decline is not a clinical feature of NMOSD. As such, clinical symptoms cannot completely be predicted using current knowledge of pathophysiology.

Apart from neural sleep circuits, the disruption of sleep in NMOSD may be secondary to other neurologic complications. NMOSD has a high rate of co-occurrence with RLS, which produces uncomfortable sensations that can impair sleep.[3] Through spinal cord damage, NMOSD can contribute to an overactive bladder, resulting in nocturia, thereby further disrupting sleep.[7] Sleep apnea may be increased by a sedentary tendency with disability.[37]

One of the most debilitating symptoms of NMOSD is severe neuropathic and nociceptive pain. The chronic pain experienced by individuals with NMOSD was consistently rated as being more severe than that associated with MS and could also contribute to poor sleep. In NMOSD, pain is prevalent in more than 80% of individuals[38] and is often persistent despite treatment with medications. This pain often peaks in the evening and can prevent patients from falling asleep.[39] In the present literature review, only 2 studies evaluated the impact of pain on sleep.[18,23] On average, individuals with NMOSD in these studies reported mild to moderate pain-related interference with sleep, with considerable variability between individuals.

Pain in NMOSD is typically treated with antiepileptic medications, muscle relaxants, antidepressants, and

PRACTICE POINTS

- Many individuals with neuromyelitis optica spectrum disorder experience sleep disturbances, as determined through subjective questionnaires and polysomnography.
- The reason for disturbed sleep likely involves a combination of factors, including neural circadian circuit disruption, direct effects of inflammation, aminergic projecting system abnormalities, glymphatic system impairment, chronic pain, mood disorders, medication adverse effects, and other neurologic symptoms.
- Future studies should explore the relative contribution of each of these factors to poor sleep.

analgesics. The adverse effects of these medications can affect sleep in both harmful and beneficial ways, although this was not specifically measured in any of the included studies. The use of sedating medications, such as opioid analgesics, during the day may contribute to a disrupted sleep-wake cycle and sleep disturbances.[40,41] Alternatively, medications for neuropathic pain, such as gabapentin, has been shown to reduce insomnia by increasing slow-wave sleep and sleep efficiency.[42] In patients with chronic pain, various agents may also cause sedation and improve sleep by reducing the perception of pain.

Finally, individuals with NMOSD are at increased risk for mood disorders.[9] This may reflect involvement of the midline projecting systems that are important for sleep/alertness and mood regulation. Mood disorders and disturbed sleep can reciprocally cause and exacerbate each other,[43] compounding the suffering of patients with NMOSD.

Ultimately, although there are many theorized causes of poor sleep in NMOSD, the most likely explanation involves a combination of many of these factors. To address sleep-related complaints, clinicians managing NMOSD should closely investigate all these factors because they present uniquely in each patient.

Limitations and Conclusions

The main limitations of this review are the limited number of studies and variability among measuring tools used. This makes it difficult to precisely assess the magnitude of sleep deficits in patients with NMOSD. As more data are collected on patients with NMOSD, future literature reviews should also explore the generalizability of these findings to patients from different ethnic backgrounds and across various age groups. The pathophysiology of NMOSD and its relationship to sleep is multifaceted and complex. Certain pathologic processes may uniquely occur in each patient, causing a large spectrum of sleep disorders, ranging from normal sleep to chronic insomnia to symptomatic narcolepsy. It is still unclear what factors are driving poor sleep in NMOSD. None of the studies compared the relative contribution of each of the aforementioned factors with poor sleep. Despite the high prevalence of pain in NMOSD, only 2 studies evaluated its effect on sleep. Furthermore, studies did not assess the impact of disease localization or lesion burden on sleep quality; a patient with NMOSD with isolated optic neuritis may experience different sleep-wake cycle disturbances than a patient with systemic manifestations of the disease. Therefore, future studies should clarify the impact of pain and disease localization on sleep outcomes. Studies also did not compare differences in sleep quality in patients with and without AQP4 antibodies. Future comparisons of sleep outcomes in patients with varying antibody levels may help clarify whether poor sleep is more attributable to the disruption of AQP4-involving sleep circuits vs other causes. Given the high prevalence of other psychological comorbidities in NMOSD (eg, anxiety, depression, fatigue), it is also difficult to determine where poor sleep lies in a sequence of cause and effect. It remains unclear whether the poor sleep is causing fatigue and decreased QOL or whether the poor sleep is simply a manifestation of ongoing psychological issues such as anxiety and depression.

Overall, this review demonstrates that sleep disturbances are very common in individuals with NMOSD and are a significant source of suffering. Such disturbances are associated with decreased QOL and increased anxiety, depression, and disability. It is possible that damage to circadian circuity, direct effects of inflammation, aminergic projecting system abnormalities, glymphatic system impairment caused by NMOSD autoantibodies, and development of sleep disorders underlie the observed sleep pathologies. Targeted treatments must address specific sleep abnormalities in this population to avoid broad therapies that may not specifically address the specific sleep problem in an individual patient.[44] □

FINANCIAL DISCLOSURES: The authors declare no conflicts of interest.

FUNDING/SUPPORT: None.

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