Neurology Asia 2017; 22(3) : 235 – 241

The impact of pain, anxiety and depression on sleep quality in Chinese patients with neuromyelitis optica spectrum disorders

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Abstract

Background & Objective: Sleep quality in neuromyelitis optica spectrum disorders (NMOSD) were investigated in two recent studies. However, factors affecting sleep quality have not been studied in NMOSD. This study aimed to investigate the prevalence of sleep disorders in Chinese outpatient clinics with NMOSD and its clinical correlates. *Methods:* We administered Chinese validated self-questionnaires on HRQOL (MSQOL-54), sleep (PSQI), pain (SF-MPQ-2), anxiety (HARS) and depression (HDRS) to 42 patients followed up in our outpatient department. We assessed the relationships between sleep quality with pain, anxiety, depression, gender, age, disability, disease duration, NMO-antibody status and explored the determinants of poor sleep quality. *Results:* Sixty four percent of NMOSD patients were poor sleepers. Significant correlations were found between duration, disability, pain, anxiety, depression and sleep quality. Disability, depression and the domain of affective descriptors of pain were the three main predictors of poor sleep in NMOSD.
Conclusion: This study reveals that poor sleep in NMOSD is common and it decreases physical function of quality of life. It is worthwhile considering exploring adjuvant strategies aimed at controlling pain associated affect, and treatment of depression may help to improve sleep quality in NMOSD.

Keywords: Neuromyelitis optica spectrum disorders, pain, anxiety, depression, disability, sleep quality

INTRODUCTION

Neuromyelitis optica (NMO), a severe autoimmune disease of the central nervous system (CNS), is characterized by longitudinally extensive transverse myelitis (LETM) and optic neuritis.[1] NMO spectrum disorders (NMOSD)[2] is a recent unifying term for NMO. Although considered as a subtype of multiple sclerosis (MS) previously, growing evidence supports that these are two different diseases. Among NMOSD patients, pain[3], fatigue[4], bladder and bowel dysfunction[5] and sleep disorders[6] are common and burdensome symptoms which significantly decrease quality of life. Pan *et al.*[4] reported that 54% NMOSD patients were poor sleepers. Song *et al.*[6] found sleep architecture markedly disrupted in NMOSD patients who also had low sleep efficiency, with non-REM sleep N3, arousal index and REM sleep to be higher in patients as compared to healthy controls. However, few published studies have examined the factors affecting poor sleep quality in NMOSD. Our study aimed to investigate the prevalence of sleep disorders in Chinese outpatient clinics with NMOSD and its clinical correlates.

METHODS

A total of 44 NMOSD patients were continuously enrolled from the Outpatient Department of Neurology, West China Hospital, Sichuan University from March 2016 to August 2016. Patient enrollment satisfied the following inclusion criteria: (1) the diagnosis as defined by Wingerchuk *et al*. in 2007[7]; (2)⩾16 years of age; (3) in a stable state; and (4) able to complete the surveys. The exclusion criteria were: (1) the presence of comorbidities (e.g., endocrine, respiratory or psychiatric disease); and (2) dependence on psychoactive substances, such as alcohol. Informed consent was obtained from each participant, and our study was approved by West China Hospital Institutional Review Boards and Ethics Committee.

Demographic characteristics, such as age, sex, educational level and other information were obtained in this study. Expanded Disability Status Scale (EDSS), disease duration and AQP4 antibody positive were also collected as clinical features of patients.

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Sleep quality.

We applied the Chinese version of Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality and disturbances over the last month. It has an overall reliability coefficient of 0.82-0.83 and an acceptable test-retest reliability coefficient of 0.77-0.85.[8] It contains 19 individual items and 5 questions rated by a bed partner or roommate (the last 5 questions are used for clinical information only and are not reported in this article). The 18 items comprised seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication and daytime dysfunction. Every component has a possible score of 0-3 and a higher score indicating greater sleep disturbance. According to the previously suggested cutoff point 6 of PSQI[9], we divided NMOSD patients into two groups (PSQI $\geqslant$6 and PSQI <6). Patients with PSQI $\geqslant$6 are poor sleepers.

Pain.

Short Form-McGill Pain Questionnaire-2 (SF-MPQ-2)[10] was used to assess the severity of pain. This measure was revised by Robert *et al.*[10] and provides a comprehensive assessment and characterization of the symptoms of both neuropathic and non-neuropathic pain. It consists of 22 individual items, divided into 4 divisions: continuous pain, intermittent pain, neuropathic pain and affective descriptors. Chinese version of SF-MPQ-2 had a good reliability (Cronbach's alpha coefficients and Guttman split-half coefficients were greater than 0.7) and can be used in patients whose language is Chinese.[11]

Anxiety and depression

The 21-item Hamilton Depression Rating Scale (HDRS)[12] and the 14-item Hamilton Anxiety Rating Scale (HARS)[13] were used to measure the depression and anxiety symptoms, separately. HDRS score ranges from 0 to 64 and HARS score from 0 to 56. These two scales were used widely among Chinese population.[14,15] HDRS and HARS were scored by a psychologist.

Quality of life.

MS Quality of Life (MSQOL-54) was used to estimate the patients' life quality, and contains 54 items: 52 items measuring 12 dimensions, one item change in health status and one satisfaction with sexual function. The twelve dimensions are physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life and sexual function. Analysis showed that internal consistency was excellent (Cronbach's alpha was 0.96) as was construct validity (correlation coefficient of criteria validity was 0.96) in Chinese version of MSQOL-54.[16]

Statistical analysis.

SPSS for Windows version 17.0 software (SPSS Inc, Chicago, IL) was used for data analysis. Two-sample t test for normal continuous data and Mann-Whitney *U* test for nonparametric data were used to compare most of the characteristics between the two groups. Chi-square test was used for the presence of AQP4 antibody and Fisher's exact test was for gender between two groups. Correlations between characteristics and dimension scores of sleep quality were calculated using Spearman's r (for nonparametric data) or Pearson's r (for normal continuous data). Next, the relationships between EDSS, anxiety, depression, duration and pain were analyzed with multiple regression analysis (stepwise method), using sleep quality as the dependent variable. Statistical significance was defined as $P< 0.05$.

RESULTS

We enrolled 44 NMOSD patients. Two patients refused to undergo examination of anxiety and depression. Finally, information on 42 patients were collected. Sample characteristics and scale scores were shown in Table 1.

In our NMOSD sample, the prevalence of poor sleep was 64%. In NMOSD patients with poor sleep, the domain of physical function score of life quality was significantly lower comparing with those without (Table 2, 57 ± 34 vs 80 ± 24, P=0.041).

Correlations between characteristics, scores and sleep quality in NMOSD patients

Table 3 illustrates correlations between characteristics, scores and sleep quality in NMOSD. Moderate significant correlation was found between anxiety, depression, EDSS, affective descriptors and PSQI scores (r = 0.67, $P< 0.001$; r = 0.67, $P < 0.001$; r = 0.54, $P < 0.001$ and r = 0.65, $P < 0.001$, respectively). Significant correlation was also discovered between disease duration and PSQI score (r = 0.37, $P = 0.017$, data

Table 1: Sample characteristics and scale scores of NMOSD patients

Characteristics and scores	Patients (n=42)
Female, n (%)	39 (93%)
Mean age (years)	41± 13
Education, years	11± 3.9
EDSS, median (range)	2.0 (2.1)
AQP4 antibody positive, n (%)	26 (62%)
Disease duration, years	5.7± 4.4
Annual relapse rate, median (range)	0.92 (0.22 – 5.1)
HDRS score (0-64)	11± 7.3
HARS score (0-56)	11± 7.3
SF-MPQ-2 score (0-10)	1.4± 1.1
PSQI score(0-21)	7.5± 4.9

Values are mean ± SD (Standard Deviation) unless otherwise noted.
EDSS: Expanded Disability Status Scale; AQP4: Aquaporin-4; HDRS: Hamilton Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale; SF-MPQ-2: Short Form-McGill Pain Questionnaire-2; PSQI: Pittsburgh Sleep Quality Index.

not shown) but not found in age and education (data not shown).

We did not find association between poor sleep quality and the presence of serum AQP4 antibody (59% vs 67%, P =0.64, data not shown). There was no significant difference in the annual relapse rate between NMOSD patients with poor sleep (median 1.07, range 0.22-5.10) and those without (median 0.78, range 0.45-3.00) (P =0.439, Mann-Whitney U test, data not shown).

Poor sleep among patients with NMOSD

The model consisted of EDSS, depression and one dimension of pain explained 61% of the variance in PSQI. Our model showed that depression (β = 0.42, P = 0.001), one pain domain – affective descriptors (β = 0.34, P = 0.006) and EDSS (β = 0.26, P = 0.024) were three main factors of poor sleep quality in NMOSD patients.

Table 2: Quality of life in two patients groups (PSQI⩾6 and PSQI<6)

	PSQI < 6 (n = 15)	PSQI ⩾ 6 (n =27)	P-value
Physical function	80.33 ± 23.56	56.85 ± 33.55	**0.041***
Role limitations-physical, median (range)	35 (0 – 100)	15.28 (0 – 100)	0.250
Role limitations-emotional, median (range)	60 (0 – 100)	30.77 (0 – 100)	0.101
Social function	67.78 ± 22.68	63.58 ± 26.16	0.445
Pain	43.78 ± 22.36	35.06 ± 17.74	0.125
Emotional well-being	65.07 ± 18.79	59.11 ± 15.18	0.291
Energy	62.93 ± 18.85	45.78 ± 15.35	0.285
Health perceptions	46.67 ± 22.81	29.44 ± 18.20	0.362
Health distress	68.00 ± 18.59	53.33 ± 24.06	0.405
Cognitive function	76.67 ± 17.69	63.52 ± 19.06	0.980
Sexual function	68.33 ± 35.52	53.09 ± 32.86	0.927
Overall quality of life	66.85 ± 17.49	54.22 ± 20.86	0.540

Values are mean ± SD (Standard Deviation) unless otherwise noted.
* Significance at P< 0.05(2-tailed).
PSQI: Pittsburgh Sleep Quality Index.

Table 3: Correlations between clinical features and each subscore of sleep quality in NMOSD patients

	Pain				Anxiety	Depression	EDSS
	Continuous pain pain	Intermittent pain	Neuropathic pain	Affective descriptors			
PSQI scores	**0.447****	**0.398****	**0.363***	**0.646****	**0.677****	**0.677****	**0.542****
Subjective sleep quality	**0.313***	0.208	0.292	**0.409****	**0.481****	**0.377***	0.249
Sleep latency	**0.481****	**0.307***	0.188	**0.454****	**0.530****	**0.516****	0.284
Sleep duration	0.254	0.274	0.278	**0.402****	**0.461****	**0.493****	**0.455****
Habitual sleep efficiency	0.225	0.185	0.238	**0.528****	**0.386****	**0.445****	**0.404****
Sleep disturbance	**0.374***	**0.487****	**0.526****	**0.584****	**0.525****	**0.621****	**0.505****
Use of sleep medications	0.210	0.052	0.111	**0.345***	0.245	0.293	0.193
Daytime dysfunction	**0.516****	**0.473****	**0.414****	**0.521****	**0.650****	**0.547****	**0.383***

Numbers represent the value of correlationcoefficient (r) calculated for each correlation between characteristic and a subscale.
PSQI: Pittsburgh Sleep Quality Index; EDSS: Expanded Disability Status Scale.
*Significance at $P < 0.05$(2-tailed); **Significance at $P < 0.01$(2-tailed).

DISCUSSION

Our current study revealed these following results: (1) Poor sleep was common in NMOSD patients. (2) Anxiety, depression, pain, disability and disease duration were correlated with the sleep quality in NMOSD patients. (3) Disability, affective score of pain and depression were the three main factors related to poor sleep quality in NMOSD.

Our research found more than half (64%) of the NMOSD patients were poor sleepers, which was similar with the results from a previous study[4], which found that 54% NMOSD patients were subjected to poor sleep. This can be explained by the negative impact of physical or mental limitations from NMOSD[4,5] on the patients' ability to maintain normal sleep. We found a significant difference in the domain physical function of life quality between patients with poor sleep and those without, demonstrating that poor sleep was associated with a reduced physical function and lowered life quality in NMOSD.

In our current study, NMOSD patients with higher EDSS score had significant poorer sleep quality. Moreover, EDSS affects sleep quality in regression analysis. EDSS reflects the severity of disability in MS[17-19] and previous study in MS[20] found that EDSS was significantly associated with PSQI scores, which is in line with our result.

Significant association was discovered between disease duration and sleep quality. A recent investigation[21] also identified that disease duration exhibited significant correlations with depression and fatigue in NMO which was not found in MS. We speculated that NMOSD, with more frequent and earlier relapses, has worse clinical outcomes than MS.[7]

Our regression result underlines the significant roles of EDSS, affective descriptors and depression in NMOSD patients' sleep quality (Table 4). Pain[22,23] and depression[24-26] were also common symptoms in MS and affect their life quality.[27-31] Similarly, pain intensity and depression were confirmed to be the contributors to poor sleep among MS with duration > 5 years in an earlier study.[32]

Several previous studies has showed that pain in NMOSD was more frequent and severe than in MS[29,30] with over 80% of NMOSD patients experiencing pain.[3] However, there were only few studies in the mechanism of pain in NMOSD and contemporary therapy for pain is largely ineffective.[29] Chronic neuropathic pain was common in NMOSD patients.[3] Interestingly, the contributor to poor sleep was not neuropathic

Table 4: Linear regression model: determinants associated with poor sleep in NMOSD patients

	PSQI
EDSS	**0.256* (0.024)**
Continuous pain	0.008 (0.951)
Intermittent pain	0.060 (0.614)
Neuropathic pain	-0.014 (0.907)
Affective descriptors	**0.338* (0.006)**
Anxiety (HARS)	0.265 (0.077)
Depression (HDRS)	**0.416* (0.001)**
Duration	0.152 (0.148)
R^2/adjusted R^2	**0.638/0.610**

PSQI: Pittsburgh Sleep Quality Index; EDSS: Expanded Disability Status Scale; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale. Adjusted R^2: explained variance; * Significance at $P< 0.05$.

pain or other domains but affective descriptors in our present study. The score on this domain is significantly correlated with all dimensions of PSQI. Affective descriptors include four items (sickening, fearful, punishing-cruel and tiring-exhausting) describing the severity of pain related emotional symptoms. We speculate that the reason for this finding was that pain in NMOSD patients was severe but not well controlled and it severely affects activities of daily life[27] thus eliciting such feelings in patients. As the pain was chronic and patients unable to perform regular activities, the pain was felt to be tiring-exhausting. Harrison *et al*.[33] suggested that pain related emotion should be considered as potentially important treatment targets in MS. Our findings highlight the importance of affects induced by pain in NMOSD patients. Controlling pain may relieve these related affective symptoms thus improve the patients' sleep quality.

Depression has been confirmed to be significantly associated with poor sleep among MS patients.[34-38] Our previous study[39] in 2011 found that the scores for depression in NMOSD patients were significantly higher than health controls. Another study[32] revealed that depression was a major determinant of poor sleep in MS with duration > 5 years but not in those with duration < 5 years. In our study, the mean duration of 5.6 years was in line with the result in MS patients. Correlations showed that anxiety and depression were both significantly associated with PSQI. However, the final determinant of poor sleep quality in NMOSD was not anxiety but depression. The possible explanation was that soon after diagnosis patients suffered more from anxiety caused by the uncertainty of the disease progression, but patients with longer disease duration (> 5 years) had adapted to the state of disease and depression played a more significant role given the progression of disability. Clinicians need to pay more attention to depressive state in NMOSD patients especially those with longer disease duration. Taken together, treatment of depression is a reasonable strategy in managing sleep disorder in NMOSD.

In summary, our results demonstrate that poor sleep in NMOSD is common. Association between PSQI and EDSS suggests that sleep quality may decrease alongside neurological disability and association with disease duration supports a gradual deterioration of sleep quality over time. Affective descriptors and depression are two major determinants of poor sleep in NMOSD. It is worthwhile considering exploring adjuvant strategies aimed at controlling pain associated affect and treatment of significant depression may help to improve sleep quality.

DISCLOSURE

Financial support: This work was supported by the National Natural Science Foundation of China (Grant No. 81271321) and the Department of Science and Technology Research Projects of the Sichuan Province of China (Grant No. 2013FZ0015).

Conflict of interest: None.

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