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Sleep dysfunction in aspirin exacerbated respiratory disease: A prospective cohort study

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Abstract

Objective: Studies have described sleep dysfunction (SD) in patients with chronic rhinosinusitis (CRS). However, there is a paucity of literature describing sleep dysfunction in the context of aspirin-exacerbated respiratory disease (AERD). The purpose of this study was to evaluate the prevalence and severity of SD in patients with AERD relative to CRS.

Methods: This study is a prospective cohort study. Patients diagnosed with CRS without polyposis (CRSsNP, $n = 206$), CRS with nasal polyposis (CRSwNP, $n = 38$), and AERD ($n = 28$) were recruited prospectively in academic center rhinology clinic. SD was assessed using the Neuro-QOL Short Form v1.0-Sleep Disturbance (sleep-QOL), for which severe SD is defined as a score >2.0 standard deviations from the normalized mean. Demographic and patient-reported outcome measures (including SNOT-22 and PHQ-2) were collected to adjust for sleep confounders. Comparisons were made between groups using univariate and multivariate analyses.

Results: The prevalence of severe SD was significantly higher in AERD (57.1%) than in CRSsNP (32.5%) or CRSwNP (34.2%), $p = 0.038$. After adjusting for sleep confounders, the risk of sleep dysfunction remained higher among patients with AERD (odds ratio [OR] = 2.72 vs. CRSsNP, 95% confidence interval [CI] = 1.18–6.27, $p = 0.02$; OR = 3.06 vs. CRSwNP, 95% CI = 1.06–8.82, $p = 0.04$). SNOT-22 total score and the sleep subdomain showed no correlation with sleep-QOL score.

Conclusions: The frequency and severity of SD are greater in AERD patients than in patients with CRS with or without nasal polyposis, independent of confounders of sleep quality. While the putative link between AERD and SD remains elusive, this study suggests that SD in AERD may be greater than previously recognized.

KEYWORDS

aspirin exacerbated respiratory disease, chronic rhinosinusitis, sleep dysfunction

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Key points

- The frequency and severity of SD are greater in AERD patients than in patients with CRS with or without nasal polyposis.
- The observed differences in sleep disorder severity and frequency in AERD patients are significant even when controlling for other factors that might affect sleep quality.
- The effect of AERD on sleep may be greater than previously thought encouraging more research into this topic.

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is a distinct chronic inflammatory disorder involving both upper and lower airways, characterized by chronic rhinosinusitis with nasal polyposis, bronchial asthma, and reactions to cyclooxygenase-1 (COX-1) inhibitors like aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).[1,2] In contrast, chronic rhinosinusitis (CRS) is marked primarily by localized inflammation of the nasal and paranasal sinus mucosa.[3] CRS patients can be further categorized into those with nasal polyps (CRSwNP) and those without polyps (CRSsNP).[4] While AERD, CRSwNP, and CRSsNP have overlapping sinus-related symptoms, AERD represents a unique systemic inflammatory process that includes sensitivity to aspirin/NSAIDs and associated bronchospasm.[1,2]

Patients suffering from conditions characterized by a chronic inflammatory state demonstrate poor disease-specific quality of life, which can be attributed, in part, to the frequent occurrence of sleep dysfunction.[5] In the setting of sinonasal disease, 16% of patients report deficits in sleep dysfunction.[6] While the underlying mechanism remains elusive, sleep dysfunction in these patients is thought to be multifactorial in origin with contributions from nasal obstruction, efferent and/or afferent neural signaling, and neuroinflammation.[7,8] Indeed, the production of various pro-and anti-inflammatory cytokines is associated with direct impairment of sleep architecture.[5] Although there are reports of sleep dysfunction in the literature,[9] it remains unclear if the mechanistic differences in the pathophysiology of CRSwNP, CRSsNP, and AERD variably affect sleep quality.

In this study, we specifically sought to better understand the prevalence of sleep dysfunction in AERD compared to CRSwNP and CRSsNP. We further hypothesized that sleep dysfunction is significantly worse in AERD than in CRSwNP and CRSsNP. To accurately assess sleep dysfunction, we utilized the validated Neuro-Quality-of-Life (QOL) Short Form v1.0—Sleep Disturbance Questionnaire, which provides a comprehensive evaluation of self-reported sleep and allows categorization into normal, mild, moderate, or severe dysfunction based on standardized cutoffs.[10]

METHODS

Patient population

The study was approved by the University of Washington (UW) Institutional Review Board and registered under number (#STUDY00016523). Adult patients (≥18 years of age) presenting to the UW Sinus Center were prospectively enrolled at the time of initial evaluation into an ongoing observational cohort investigation between June 2021 and March 2023 intended to assess medical and surgical treatment outcomes. Study participants were ensured that participation would not alter their normal standard of care.

The diagnosis of CRS was confirmed by the enrolling physician using the criteria established in the 2015 Clinical Practice Guideline on Adult Sinusitis.[11] Diagnosis of AERD was determined on the basis of ≥2 respiratory reactions to aspirin or NSAIDs on clinical history per the Drug Allergy 2022 practice parameter update, presence of nasal polyposis on nasal endoscopy, and pre-existing EMR-documented diagnosis of asthma. In patients with ≥2 episodes of respiratory deterioration on ASA/NSAID ingestion, the likelihood of a positive aspirin challenge exceeds 90%, and aspirin challenge is no longer recommended per practice parameters issued by the American Academy of Allergy, Asthma, and Immunology.[12]

Clinical disease severity measures

During the initial clinic/enrollment visit, all study participants completed a medical history, head and neck clinical examination, and rigid nasal endoscopy. Endoscopic examinations were quantified using the modified Lund–Kennedy scoring system—which allows for scoring of polyposis, edema, and discharge—where higher scores represent more severe disease (score range, 0–12).[13] The Lund-Mackay score was used to grade the computed tomography scan of patient sinuses where higher scores represent more severe disease with score ranging from 0 to 24.[14]

Inclusion and exclusion criteria

Adult patients with ICD-10 diagnosed chronic sinusitis (J32.x), asthma (J45.x), and nasal polyposis (J33.9) were initially identified, and then a comprehensive chart review was conducted to identify patients with CRSwNP, CRSsNP, and AERD. Study patients were excluded from analysis if they failed to complete the validated questionnaires. Also excluded were those with concurrent autoimmune disease, including granulomatosis with polyangiitis, other granulomatous disorders, and systemic vasculitis due to the known influence of these disease processes and the associated use of systemic anti-inflammatory and/or immunosuppressive medications on underlying symptoms, including sleep dysfunction. Further exclusion criteria included the presence of ciliary dyskinesia, cystic fibrosis, and sinonasal malignancy.

Data collection

Study participants completed all baseline surveys in English. Demographic data, including age and gender, as well as medical, surgical and social history, were collected. Additionally, history of asthma, aspirin intolerance, allergy (by history and/or objective testing), tobacco use, and inhaled or oral corticosteroid use was obtained. Participants completed electronic versions of the Sinonasal Outcome Test (SNOT-22), Patient Health Questionnaire-2, and the Neuro-QOL Short Form v1.0-Sleep Disturbance (Sleep-QOL) validated surveys at baseline. The SNOT-22 is a validated treatment outcome measure of chronic sinonasal conditions in which each item is scored via Likert scale responses (0 = "no problem," 1 = "very mild problem," 2 = "mild or slight problem," 3 = "moderate problem," 4 = "severe problem," 5 = "problem as bad as it can be") where higher scores represent decreased patient functioning or worse symptom severity. Total SNOT-22 scores can be stratified where scores of 8–20, 21–50, and >50 equate to mild, moderate, and severe disease, respectively.[15,16] Neuro-QOL is a cluster of 13 validated short forms ranging from 8 to 9 items. The 8-item sleep disturbance short form (Sleep-QOL) focuses on participant's perception of overall sleep quality, sleep depth, perception of ease getting to and staying asleep, satisfaction with sleep, and sleep-related impairment in quality-of-life over the preceding 1 week. Each item was presented on a 5-point Likert scale and total scores were converted to a *T*-score using the Neuro-QOL conversion tables. The *T*-score metric allows interpretation of scores relative to a reference sample of the US general population. For example, a *T*-score of 60 indicates a level of outcome one that is one standard deviation above the mean in the reference population. Severe, moderate, and mild sleep dysfunction are defined as scores >2.0 (raw score>32), between 1.0 and 2.0 (raw score 20–32), and between 0.5 and 1.0 (raw score 20–24) standard deviations from the normalized mean, respectively.[10] Patient Health Questionnaire 2 item module (PHQ-2) inquiries about the frequency of depressed mood and anhedonia over the preceding 2 weeks, scoring each item as 0 ("not at all") to 3 ("nearly every day"). As previously reported, a PHQ-2 score of 3 was the optimal threshold to screen for depression.[17]

Statistical analysis

Data were stripped of all protected health information before statistical analysis. Descriptive statistics using mean and standard error of the mean (SEM) for continuous variables and count with percentage for categorical variables. Kruskal–Wallis rank sum test was used to compare between the three study groups for continuous variables while Fisher's exact test and Pearson's Chi-squared test were used for categorical variables. Multivariate regression analysis was used to determine whether the underlying rhinologic diagnosis was independently predictive of severe sleep dysfunction while adjusting for potential confounders of sleep quality. Univariate analysis was performed to determine potential associations between clinic factors and sleep dysfunction, and factors with $p < 0.200$ were also entered into the multivariate model. Each statistical test was two-sided with alpha level set at 5%. Analyses were conducted using GraphPad Prism v9.0 (GraphPad Software) and R studio (Posit) using the gtsummary package.[18]

RESULTS

Cohort characteristics

Following application of inclusion/exclusion criteria, a total of 272 patients, enrolled between June 2021 and March 2023, were analyzed in this study. These patients were stratified into three study groups consisting of CRSsNP ($n = 206$, 75.7%), CRSwNP ($n = 38$, 14.0%), and AERD ($n = 28$,10.3%). The mean age of patients was 45.04 ± 2.93 in the AERD group, 43.17 ± 1.09 in the CRSsNP group, and 46.79 ± 2.21in the CRSwNP group. Bivariate comparisons of baseline characteristics are described in Table 1. There were significantly more asthmatics in the AERD population—per definition—than in the other two groups. In AERD patients, 11 (39.3%) were mild, 12 (42.9%) were moderate, and 5 (17.9%) were severe. In CRSsNP 31 (15.0%) patients were mild, 18 (8.7%) were moderate, and 1 (0.5%) was severe. In CRSwNP, 8 (21.1%) patients were mild, 5 (13.2%) were moderate, 0 patients had severe asthma. AERD patients were also significantly more likely to have obstructive sleep apnea (OSA) than CRSsNP and CRSwNP (32% vs. 16% and 5.3%, respectively, $p = 0.014$).

Clinical characteristics

Facial pain was more prevalent in CRSsNP (59.0%) versus AERD (43.0%) or CRSwNP (34.0%), $p = 0.010$. No significant differences

TABLE 1 Demographics and clinical characteristics.

Variable	AERD ($n = 28$)	CRSsNP ($n = 206$)	CRSwNP ($n = 38$)	p Value
Demographics				
Age (years)	45.04 ± 2.93	43.17 ± 1.09	46.79 ± 2.21	0.300
Gender, male, n (%)	14 (50.0%)	100 (49.0%)	21 (55.0%)	0.700
BMI > 30 kg/m^2	9 (32.0%)	50 (24.0%)	7 (18.0%)	0.400
Comorbidities, n (%)				
Migraine	6 (21.0%)	34 (17.0%)	4 (11.0%)	0.500
Asthma	28 (100%)	50 (24.0%)	13 (34.0%)	<0.001*
Mild asthma	11 (39.3%)	31 (15.0%)	8 (21.1%)	-
Moderate asthma	12 (42.9%)	18 (8.7%)	5 (13.2%)	-
Severe asthma	5 (17.9%)	1 (0.5%)	0	-
OSA	9 (32.0%)	32 (16.0%)	2 (5.3%)	0.014*
GERD	10 (36.0%)	65 (32.0%)	8 (21.0%)	0.400
Depression	12 (43.0%)	67 (33.0%)	8 (21.0%)	0.200
Smoke	2 (7.1%)	17 (8.3%)	1 (2.6%)	0.500
CRS cardinal symptoms, n (%)				
Facial pain	12 (43.0%)	121 (59.0%)	13 (34.0%)	0.010*
Nasal discharge	13 (46.0%)	115 (56.0%)	21 (55.0%)	0.600
Nasal congestion	19 (68.0%)	142 (69.0%)	23 (61.0%)	0.600
Change in sense of smell	14 (50.0%)	53 (26.0%)	12 (32.0%)	0.028*
Objective endoscopic and computed tomography scores				
Modified LK endoscopy score	5.39 ± 0.58	1.82 ± 0.16	5.66 ± 0.59	<0.001*
LM CT score	15.67 ± 2.25	4.4 ± 0.4	10.3 ± 1.17	<0.001*
Treatment history, n (%)				
History of topical steroids	28 (100%)	192 (93.0%)	37 (97.0%)	0.400
History of oral antibiotic	19 (68.0%)	126 (61.0%)	19 (50.0%)	0.300
History of oral steroids	23 (82.0%)	67 (33.0%)	23 (61.0%)	<0.001*
History of ESS	22 (79.0%)	67 (33.0%)	18 (47.0%)	<0.001*

Abbreviations: AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; ESS, endoscopic sinus surgery; GERD, gastroesophageal reflux disease; LK, Lund–Kennedy endoscopic score; LM, Lund-Mackay computed tomography score; OSA, obstructive sleep apnea; -, no data.

*$p < 0.05$.

were seen between groups for nasal discharge, nasal congestion, or duration of sinus symptoms. Changes in sense of smell were more frequently reported in AERD (50.0%) versus CRSsNP (26.0%) versus CRSwNP (32.0%), $p = 0.028$ (Table 1). Nearly all patients reported prior use of topical intranasal corticosteroids, with no significant differences between groups (AERD 100%, CRSsNP 93.0%, CRSwNP 97.0%; $p = 0.400$). The history of oral antibiotic use was also similar between groups. However, the prevalence of prior oral corticosteroid use was significantly higher in the AERD group (82.0%) followed by CRSwNP (61.0%) and CRSsNP (33.0%) patients ($p < 0.001$). AERD cases were more likely to have a prior history of endoscopic sinus surgery than those with CRSwNP or CRSsNP (79.0%, 47.0%, 33.0%, respectively, Table 1). Patient endoscopic examination showed a mean value of modified Lund–Kennedy score higher in AERD and CRSwNP patients (5.39 ± 0.58 and 5.66 ± 0.59, respectively) and lower in CRSsNP cases (1.82 ± 0.16), $p < 0.001$. The CT score based on Lund-Mackay was higher in AERD patients (15.67 ± 2.25) followed by CRSwNP (10.30 ± 1.17) and CRSsNP (4.40 ± 0.40), $p < 0.001$.

Patient-reported outcome measures

The CRSsNP group reported higher total SNOT-22 scores (42.52 ± 1.42) compared to the AERD (36.32 ± 4.96) and CRSwNP groups (28.71 ± 3.14), $p < 0.001$. When evaluating SNOT-22 subdomains, patients with CRSsNP exhibited a higher preponderance of ear/facial symptoms, psychological symptoms, and sleep symptoms compared to other groups with no differences in the rhinologic or extranasal subdomains (Table 2). However, when evaluating sleep dysfunction using the Sleep-QOL instrument, there was a greater prevalence of sleep dysfunction among those with AERD (92.8%) than in CRSsNP(85.4%) or CRSwNP (68.4%), $p = 0.033$ (Table 3). When categorized by severity, a higher proportion of AERD patients (57.1%) had severe sleep dysfunction versus CRSsNP (32.5%) and CRSwNP (34.2%) patients ($p = 0.038$). Those with AERD reported significantly worse symptom scores (26.93 ± 1.80) compared to CRSsNP patients (22.58 ± 0.63) and CRSwNP patients (21.37 ± 1.87), $p = 0.037$. Similarly, AERD patients had higher normalized sleep *T*-scores (64.41 ± 2.48) than CRSsNP (58.06 ± 0.90) and CRSwNP (56.19 ± 2.71), $p = 0.037$. Only AERD patients had sleep dysfunction *T*-scores that were >1 standard deviation above the mean of the reference general population (Table 3). Importantly, severity of sleep disturbance as quantified by Sleep-QOL did not correlate with sleep dysfunction as quantified by total SNOT-22 score ($r = -0.041$, $p = 0.500$) or the sleep subdomain of the SNOT-22 ($r = -0.063$, $p = 0.300$) (Figure 1).

To further investigate which aspects of AERD may be contributing to severe sleep dysfunction, we performed a subgroup analysis comparing sleep dysfunction in AERD to that in patients with CRSsNP and CRSwNP who also had concurrent asthma. There was a trend toward higher rates of overall sleep disturbance, severe sleep disturbance, and higher Sleep-QOL scores in AERD versus CRSsNP with asthma or CRSwNP with asthma but this was not statistically significant (Table 4).

Multivariate analysis

After adjustment for age, gender, BMI, history of OSA, history of migraine, and SNOT score, patients with AERD had increased odds of severe sleep dysfunction compared to those with CRSsNP (odds ratio [OR] = 2.72, 95% confidence interval [CI] = 1.18–6.27, $p = 0.020$) and cases with CRSwNP (OR = 3.06, 95% CI = 1.06–8.82, $p = 0.040$). Indeed, age (OR = 1.00, 95% CI = 0.98–1.02, $p = 0.890$), gender (OR = 1.14, 95% CI = 0.67–1.94, $p = 0.640$), obesity (OR = 0.72, 95% CI = 0.38–1.37, $p = 0.320$), migraine (OR = 0.54, 95% CI = 0.25–1.15, $p = 0.110$), OSA (OR = 1.26, 95% CI = 0.60–2.65, $p = 0.530$), SNOT-22 score (OR = 0.99, 95% CI = 0.98–1.00, $p = 0.060$), modified LK endoscopy score (OR = 0.99, 95% CI = 0.92–1.08, $p = 0.980$), and LM CT score (OR = 0.95, 95% CI = 0.91–1.00, $p = 0.075$) were not independently associated with severe sleep dysfunction. These results suggest that AERD is an independent predictor of severe sleep dysfunction (Table 5).

DISCUSSION

Sleep dysfunction has been widely investigated in a variety of diseases and estimated to affect between 50 and 70 million patients annually in the United States.[19] Patients with chronic inflammatory conditions appear to be predisposed to higher rates of sleep dysfunction.[20–23] Poor sleep quality is present in 60%–75% of patients with CRS compared to 8%–18% in the general population.[24–26] However, there is limited knowledge about the prevalence and severity of sleep dysfunction in AERD.

In this study, we used the validated Neuro-QOL Sleep Disturbance Short Form instrument, termed Sleep-QOL in this study to evaluate sleep dysfunction. Sleep-QOL is 1 of 13 short forms developed as part of the National Institutes of Health Neurological Quality of Life Measurement Initiative intended to measure physical, social, and mental domains of health-related QOL.[10] A unique aspect

TABLE 2 Patient-reported outcomes.

Variable	AERD (*n* = 28)	CRSsNP (*n* = 206)	CRSwNP (*n* = 38)	*p* Value
SNOT-22 score (mean ± standard error of the mean)	36.32 ± 4.96	42.52 ± 1.42	28.71 ± 3.14	<0.001*
Rhinologic	9.79 ± 1.41	10.99 ± 0.42	8.55 ± 0.90	0.054
Extranasal	4.21 ± 0.64	5.42 ± 0.25	4.11 ± 0.53	0.058
Ear and face	7.07 ± 0.87	7.79 ± 0.29	5.74 ± 0.65	0.020*
Psych	13.18 ± 1.95	16.97 ± 0.64	10.61 ± 1.34	<0.001*
Sleep dysfunction	9.46 ± 1.25	10.41 ± 0.40	7.21 ± 0.92	0.008*
Depression (PHQ2), *n* (%)[a]	6 (21.0%)	32 (16.0%)	4 (11.0%)	0.500

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; PHQ2, Patient Health Questionnaire-2; SNOT-22, sinonasal outcome test.

[a]Depression is defined by PHQ2 score ≥3.

*$p < 0.05$.

TABLE 3 Neuro-QOL sleep disturbance in patients with AERD, CRSsNP, and CRSwNP.

Variable	AERD (*n* = 28)	CRSsNP (*n* = 206)	CRSwNP (*n* = 38)	*p* Value
Neuro-QOL sleep disturbance score (mean ± standard error of the mean)	26.93 ± 1.8	22.58 ± 0.63	21.37 ± 1.87	0.037*
Normalized sleep score (mean ± standard error of the mean)	64.41 ± 2.48	58.06 ± 0.90	56.19 ± 2.71	0.037*
Severity of sleep disturbance, *n* (%)				
Normal	2 (7.1%)	30 (14.6%)	12 (31.6%)	-
Mild	8 (28.6%)	77 (37.4%)	10 (26.3%)	-
Moderate	2 (7.1%)	32 (15.5%)	3 (7.9%)	-
Severe	16 (57.1%)	67 (32.5%)	13 (34.2%)	0.038*
Total mild/moderate/severe sleep disturbance, *n* (%)	26 (92.8%)	176 (85.4%)	26 (68.4%)	0.033*

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; QOL, quality of life; -, no data.

*$p < 0.05$.

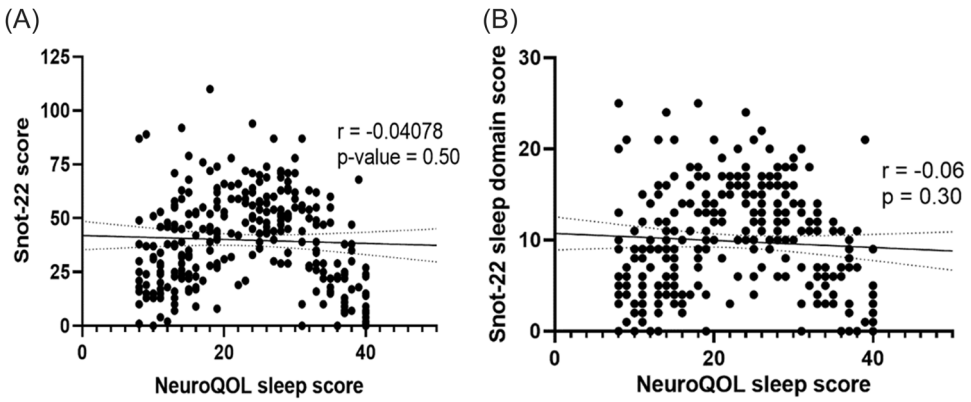

FIGURE 1 Correlation analysis between Neuro-QOL sleep disturbance short form score and total SNOT-22 score (A) or SNOT-22 sleep subdomain score (B). QOL, quality of life; SNOT-22, sinonasal outcome test.

TABLE 4 Neuro-QOL sleep disturbance in patients with AERD and with CRS with concurrent asthma.

Variable	AERD (*n* = 28)	CRSsNP (*n* = 43)	CRSwNP (*n* = 13)	*p* Value
Neuro-QOL sleep disturbance(mean ± standard error of the mean)	26.93 ± 1.8	23.84 ± 1.22	23.92 ± 3.27	0.300
Normalized sleep score(mean ± standard error of the mean)	64.41 ± 2.48	59.8 ± 1.73	59.39 ± 4.85	0.300
Severity of sleep disturbance, *n* (%)				
Normal	2 (7.1%)	5 (11.6%)	4 (30.8%)	-
Mild	8 (28.6%)	14 (26.4%)	1 (7.7%)	-
Moderate	2 (7.1%)	7 (16.3%)	2 (15.4%)	-
Severe	16 (57.1%)	17 (39.5%)	6 (46.2%)	0.300
Total mild/moderate/severe sleep disturbance, *n* (%)	26 (92.8%)	38 (82.2%)	9 (69.3%)	0.200

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; QOL, quality of life; -, no data.

of the Neuro-QOL tools is the option to normalize scores relative to a large sample of patients from the US general population. These data were reported in this study as normalized sleep scores.

Using Sleep-QOL, our study indicated that AERD was associated with a higher incidence of sleep dysfunction than CRSsNP and CRSwNP (92.8% vs. 85.4% vs. 68.4%, respectively, $p = 0.033$), a higher incidence of severe sleep dysfunction (57.1% vs. 32.5% vs. 34.2%, $p = 0.038$), and worse mean raw instrument scores (26.93 vs. 22.58 vs. 21.37, $p = 0.037$). Following normalization to the reference general population, AERD patients were the only study group with a mean sleep dysfunction score

TABLE 5 Univariate analysis and multivariate logistic regression for prediction of severe sleep dysfunction.

Analysis	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Characteristics						
Diagnosis	-	-	0.045*	-	-	0.050
AERD versus CRSsNP	2.76	1.24, 6.18	0.013*	2.72	1.18, 6.27	0.020*
AERD versus CRSwNP	2.56	0.94,7.00	0.066	3.06	1.06, 8.82	0.040*
Age	1.00	0.99, 1.02	0.740	1	0.98, 1.02	0.890
Male versus Female	1.16	0.71, 1.92	0.550	0.990	0.58, 1.68	0.970
BMI (obese vs. non obese)	0.74	0.40, 1.34	0.330	0.72	0.38, 1.37	0.320
History of topical steroids	1.53	0.51, 5.66	0.460	-	-	-
History of oral antibiotic	0.94	0.57, 1.57	0.820	-	-	-
History of oral steroids	1.08	0.65, 1.78	0.770	-	-	-
History of ESS	1.09	0.65, 1.80	0.750	-	-	-
Migraine	0.56	0.26, 1.14	0.110	0.54	0.25, 1.15	0.110
OSA	1.24	0.63, 2.41	0.530	1.26	0.6, 2.65	0.540
GERD	1.24	0.72, 2.12	0.440	-	-	-
Smoking history	1.72	0.66, 4.42	0.260	-	-	-
Mild asthma versus No asthma	1.95	1.00, 3.81	0.051	-	-	-
Moderate-severe asthma versus No asthma	2.23	1.12, 4.43	0.022*	-	-	-
SNOT22	0.99	0.97, 1.00	0.024*	0.99	0.98, 1.00	0.060
PHQ2	0.79	0.38, 1.58	0.520	-	-	-
LK endoscopy score	1.00	0.92, 1.08	0.982	-	-	-
LM CT score	0.95	0.90, 1.01	0.075	-	-	-

Note: Multivariate analysis is controlled for age, gender, BMI, migraine, OSA, and SNOT22 based on *p* values <0.2 derived on univariate analysis and inclusion of standard variables.

Abbreviations: AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; ESS, endoscopic sinus surgery; GERD, gastroesophageal reflux disease; LK, Lund–Kennedy endoscopic score; LM, Lund-Mackay computed tomography score; OSA, obstructive sleep apnea; PHQ2, Patient Health Questionnaire-2; SNOT-22, Sinonasal outcome test; -, no data.

*$p < 0.05$.

greater than one standard deviation worse than the population mean represented by a *T*-score >60 (normalized score 64.41). It is important to note that AERD patients also demonstrated a higher risk of OSA than those with CRSsNP or CRSwNP (32.0% vs. 16.0% vs. 5.3%, respectively, $p = 0.014$). We controlled for this factor and other confounders of sleep quality through a multivariate regression analysis, which showed that severe sleep dysfunction predicted by a diagnosis of AERD remained after controlling for demographic and clinical confounders, including age, gender, OSA, BMI, migraine, and sinonasal symptom severity as measured by SNOT-22 (OR = 2.72 vs. CRSsNP, $p = 0.020$; OR = 3.06 vs. CRSwNP, $p = 0.040$). This finding aligns with prior studies showing increased sleep dysfunction with AERD compared to normal populations, but adds to the literature by specifically identifying worse sleep dysfunction in AERD versus other CRS types.[27]

Asthma has itself been associated with sleep disturbance. As asthma is an integral component of AERD, collinearity between these variables prevented inputting both variables into the regression model. Consequently, we conducted a subgroup analysis of only patients with underlying asthma and this abrogated the association of AERD with sleep dysfunction when compared to other CRS types with concurrent asthma. However, there was a trend toward greater sleep dysfunction in AERD versus patients with CRS with or without polyposis and concurrent asthma, suggesting that in a larger study population of asthmatics, AERD patients could have worse sleep dysfunction than patients with CRSsNP and CRSwNP with concurrent asthma. This hints toward a potential pathophysiologic mechanism by which AERD disrupts sleep that is unique to this disease process.

We also investigated correlations between Sleep-QOL and the SNOT-22 sleep subdomain scores. Fried et al., in their systematic review, found that SNOT sleep domain scores were approximately doubled in patients with CRS versus "normal" scores.[28] Duffy et al. used SNOT sleep subdomain scores as a screening tool for OSA in CRS, noting that patients with OSA had significantly higher scores than those without.[29] There was no correlation between sleep dysfunction as measured by the Sleep-QOL and the sleep subdomain of the SNOT-22, suggesting that these tools may be measuring different aspects of sleep dysfunction. Our results expand upon the existing literature by both identifying and quantifying the severity of sleep dysfunction using Sleep-QOL, an instrument designed specifically for this purpose. Interestingly, the sleep disturbance identified by the Sleep-QOL instrument in patients with AERD, CRSsNP, and CRSwNP was independent of the presence of OSA, suggesting potential utility in identifying non-OSA-related sleep dysfunction. The role of each of these tools in identifying sleep dysfunction in CRS in clinical practice is a subject for future investigation.

While sleep dysfunction has been well characterized in other conditions such as asthma,[30,31] autoimmune disease,[22,32] and other disease states,[33,34] our current understanding of inflammation-mediated sleep dysfunction is limited. It has long been known that mammalian cerebrospinal fluid contains a plethora of cytokines involved in the regulation of sleep.[35] For example, central or systemic injection of interleukin (IL)-1 and/or tumor necrosis factor (TNF) enhance the duration and intensity of non-rapid eye movement (REM) sleep in every mammalian species tested. Non-REM slow-wave sleep is critically important for the rest and restoration of neocortical neurons. Interestingly, several cytokines that impair non-REM sleep have also been identified, including IL-4, IL-10, IL-13, and transforming growth factor beta (TGFβ). IL-4, for example, directly inhibits IL-1 and TNF production and enhances the production of IL-1 receptor antagonist (IL-1RA) and release of the soluble TNF receptor, which antagonizes the somnogenic actions of IL-1 and TNF, respectively.[36–39]

AERD is associated with the upregulation of key cytokines characteristic of a type 2 inflammatory signature, including IL-4, IL-5, and IL-13. Elevated levels of IL-4 have been documented in the sinonasal tissue of patients with AERD that significantly exceed levels measured in patients with aspirin-tolerant CRSwNP and controls.[37] Furthermore, AERD, in contrast to CRSwNP, exhibits a mixed Th1/Th2 inflammatory milieu in the airway epithelium which has been associated with a decreased induction of the IL-1 type 1 receptor, impairing the ability of sleep-promoting IL-1β to act on target cells. Lastly, a hallmark of AERD and a distinguishing feature relative to aspirin-tolerant CRSwNP is impairment of the COX pathway which disrupts the production of downstream prostaglandins. Earlier studies showed that inhibition of prostaglandin synthesis through COX-2 inhibition reduced spontaneous and TNF-induced increases in non-REM sleep in animal models.[40] In essence, the inflammatory milieu in CRS—particularly in AERD—may antagonize physiologic sleep function through the proliferation of anti-somnogenic mediators and the reduced production of somnogenic cytokines.

There are several limitations to this study. The study did not correlate subjective patient-reported outcome measures (Sleep-QOL) with objective measures of sleep quality such as polysomnography which would, potentially, provide more mechanistic insight into sleep disturbance in AERD versus aspirin-tolerant CRS. The study was underpowered to identify differences in sleep dysfunction among a subgroup of asthmatic patients, which would allow us to further delineate the role of sinonasal inflammation in AERD and CRS in sleep dysfunction beyond the known effects of asthma. Expansion of the overall cohort size and follow-up duration with collection of detailed pre- and post-medical and surgical treatment data would permit the evaluation of Sleep-QOL as a tool to measure treatment-associated improvements in sleep dysfunction, and to evaluate for differences in this improvement based on underlying CRS endotype. This will be the subject of a future study by our group.

CONCLUSION

Sleep dysfunction, as measured by the Neuro-QOL Sleep Disturbance Short Form, is present in patients with CRS. The frequency and severity of sleep dysfunction are greater in AERD patients than in patients with CRS with or without nasal polyposis, independent of other confounders of sleep quality. While the putative link between AERD and SD remains elusive, this study suggests that sleep severity may be a greater quality of life deficit in patients with AERD than previously recognized.

AUTHOR CONTRIBUTIONS

David J. Cvancara: Design; conduct and presentation of research. **Mohamed A. Aboueisha**: Analysis and presentation of research. **Ayush A. Sharma**: Conduct and presentation of research. **Dhruv Sharma**: Conduct. **Ian M. Humphreys**: Design and presentation of research. **Aria Jafari**: Design and presentation of research. **Waleed M. Abuzeid**: Design; conduct; analysis; and presentation of the research.

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CONFLICT OF INTEREST STATEMENT

Waleed M. Abuzeid is a member of *World Journal of Otorhinolaryngology—Head & Neck Surgery* (WJOHNS) editorial board and is not involved in the peer review process of this article.

DATA AVAILABILITY STATEMENT

Data are available upon request.

ETHICS STATEMENT

The study was approved by the University of Washington (UW) Institutional Review Board.

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