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Research Article

Patients with Dry Age-Related Macular Degeneration are at Higher Risk for Sleep Apnea

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Abstract

Objective: To explore the association between disordered sleep and age-related macular degeneration (AMD).

Design: A prospective nonrandomized observational study.

Subjects: Patients from 3 retina specialists at a tertiary academic hospital.

Methods: One hundred patient volunteers with AMD were recruited, 50 nonexudative and 50 exudative. Nonexudative AMD patients were further divided into subgroups based on the presence or absence of geographic atrophy. Exudative AMD patients were further divided into treatment responsive versus resistant based on resolution of intraretinal and subretinal fluid at 3 months. Demographic information was obtained from the electronic medical record. Patients completed 3 surveys on disordered sleep that screened for symptoms of insomnia, general sleep quality, and sleep apnea to assess the relationship between type of AMD and scores on metrics of sleep quality and disordered sleep.

Main Outcome Measures: Symptoms of sleep apnea, symptoms of insomnia, symptoms of general sleep disturbance.

Results: Patients with dry AMD displayed significantly more symptoms of sleep apnea compared to wet AMD (36% vs 16%, p=0.023). Dry AMD patients without geographic atrophy displayed more symptoms of sleep apnea compared to those with geographic atrophy (41.9% vs 0%, p=0.016). Rates of sleep apnea across all AMD subtypes in the study group were higher than estimated population norms. Patients did not differ significantly on assessments of insomnia or general sleep quality.

Conclusions: AMD and sleep apnea appear to be associated, most strongly between patients with dry AMD. There is perhaps a further delineation among those with and without geographic atrophy, with the association favoring the latter.

Keywords: Age-related macular degeneration; Macular degeneration; AMD; Sleep apnea; Sleep quality; Ophthalmology; Retina; Low-vision

Introduction

Age-related Macular Degeneration (AMD) is a chronic, progressive eye disorder that affects the elderly. It is the leading cause of blindness in industrialized nations and the third most common cause of blindness worldwide [1]. Advanced AMD is divided into two subcategories: "dry" (nonexudative) and "wet" (exudative). The dry type is more common, accounting for 85-90% of cases, while the wet type is responsible for greater than 80% of severe visual loss or blindness in patients with AMD [2]. In addition, AMD is known to be associated with decreased quality of life, with patients reporting increased rates of depression and decreased ability to perform activities of daily living such as reading and driving [3]. Furthermore, a recent article reported an association between decreased duration of sleep and exudative AMD as well as higher sleep medication use in these subjects [4].

Sleep dysfunction has been the subject of significant study in recent years. Poor sleep quality has been associated with increases in several organic deleterious health outcomes such as hypertension, diabetes, obesity, heart attack, and stroke [5]. Visual pathology is not exempt from this relationship. One study found higher rates of sleep disturbance in the visually impaired elderly as defined by frequent awakenings, difficulty falling back asleep, and subjective poor sleep quality [6]. Among blind patients, those with no light perception suffered from worse sleep disturbance [7]. Blindness is associated with disruption of circadian rhythms, presumably by interruption of visual signals required for sleep cycle regulation in the suprachiasmatic nucleus [8]. It has also been shown that obstructive sleep apnea (OSA), a sleep disorder characterized by periods of nighttime respiratory disturbances and hypoxia, may hinder the response to anti-VEGF therapy in patients with exudative AMD; this occurs presumably by interrupting the microcirculation of the retina and optic nerve [9]. The reader should note that two directions of the relationship between sleep and vision are mentioned here. On the

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Table 1:

	Dry, No Geographic Atrophy (N=43)			Dry, Geographic Atrophy (N=7)			Wet, Responder (N=36)			Wet, Incomplete-Responder (N=14)			P
	Mean	N	%	Mean	N	%	Mean	N	%	Mean	N	%	
Age	76_a			87_b			82_b			$80_{a,b}$			
logMAR of Best Eye Visual Acuity (Snellen)	$.088_a$ (20/24.5)			$.491_b$ (20/61.9)			$.149_a$ (20/136.2)			$.105_a$ (20/25.5)			
logMAR of Worst Eye Visual Acuity (Snellen)	0.201_a (20/31.8)			0.833_b (20/136.2)			0.655_b (20/90.4)			$0.356_{a,b}$ (20/45.4)			
Gender													
Female		31	72.1%		6	85.7%		21	58.3%		8	57.1%	0.355
Male		12	27.9%		1	14.3%		15	41.7%		6	42.9%	
Tobacco Use		2	4.7%		0	0.0%		0	0.0%		2	14.3%	0.124
Depression		11	25.6%		1	16.7%		4	11.1%		1	7.1%	0.286
Working		10	23.3%		0	0.0%		6	16.7%		5	35.7%	0.268
Previous OSA Diagnosis		6	14.0%		1	14.3%		4	11.1%		4	28.6%	0.418
Cataract Surgery		19	44.2%		6	85.7%		28	77.8%		9	64.3%	0.010

This table shows the demographic information of the study population stratified by subtype of AMD.
Note: Values of scale variables not sharing the same subscript are significantly different at p< .05 by two-sided t-test, assuming equal variances with Bonferroni correction.

one hand, visual impairment seems to have an effect on sleep quality. In most studies sleep quality is a subjective measure, determined by how well a person sleeps through the night and how tired they feel the next day. On the other hand, we find a specific disorder of sleep, OSA, mediating visual damage via repeated hypoxia. With respect to the latter relationship, the literature is unclear on whether sleep quality is associated with severity of disease in AMD. One study of sleep quality found no association with severity, visual acuity, or disease staging of AMD and sleep disturbance [10], while another suggested a link between obstructive sleep apnea and exudative AMD [11]. To our knowledge, there has not been a study that characterizes the overall sleep quality in patients with AMD compared with the general population nor one that compares wet and dry macular degeneration. Given known data that patients with impaired vision suffer from sleep disorders [6,7], we hypothesized that patients with AMD would differ from the general population when assessed with assays for overall sleep quality, insomnia, and obstructive sleep apnea as endpoints. Furthermore, we also hypothesized that we may observe a variance in sleep quality between subjects with the two different subtypes of AMD, wet and dry. As a secondary outcome, we analyzed any differences among patients with and without geographic atrophy in the dry AMD group and good responders to treatment versus incomplete responders in the wet AMD group.

Methods

Data collection

This prospective nonrandomized observational study was approved and monitored by the Institutional Review Board of Northwestern University, Feinberg School of Medicine. A total of 100 patients were included, 50 with nonexudative macular degeneration and 50 with exudative macular degeneration. These patients were further divided into subgroups based on the presence or absence of geographic atrophy for dry AMD. The wet AMD group was divided into good responders to anti-VEGF (resolution of intraretinal and subretinal fluid at 3 months) versus incomplete responders. Incomplete responders were defined as having persistent fluid of any type on optical coherence tomography (OCT) after 3 injections of an anti-VEGF agent.

All patients were from the Northwestern Ophthalmology Department. Patient inclusion criteria were the diagnosis of AMD and age 55-100; patients with a diagnosis of other retinal disease or findings were excluded from the study. The best-corrected visual acuity of each patient was recorded in both eyes at the time of their study visit. Patients were given a survey that included demographic information (age, gender, previous diagnosis of depression or sleep apnea, working status, smoking status and previous cataract surgery) as well as 3 assessments of sleep quality. These were the Patient-Reported Outcomes Measurement Information System (PROMIS™) Short Form Sleep Disturbance questionnaire, the Insomnia Severity Index (ISI), and the Berlin Questionnaire for obstructive sleep apnea (OSA). Each have been validated for their use as measures of sleep disturbance [12,13], insomnia [14], and risk of sleep apnea [15], respectively. The PROMIS questionnaire is an 8-item Likert-scale form derived from surveys of the general population (mean age 52) and study data (mean age 44) [13] that assesses the "[p]erceptions of sleep quality, sleep depth, and restoration associated with sleep [16]." Scores are converted to T-scores with a mean of 50 and standard deviation (SD) of 10, where higher scores represent more severe sleep impairment. The ISI is a 5-item Likert-scale form with scores ranging from 0-28, with scores greater than 8 representing subhthreshold or greater degrees of insomnia [14]. Lastly, the Berlin sleep questionnaire is a 10-item questionnaire that identifies patients as having a high or low risk of OSA based on assessments of sleep behaviors (e.g. snoring) as well as the presence of hypertension and obesity [15]. Three assessments were used in order to distinguish general sleep disturbances from sleep apnea.

Statistical analysis

All analyses were performed using SPSS version 21 (IBM Corporation, Copyright 2012). Age and visual acuity of the better and worse eye were compared between wet and dry, as well as the 4 subcategories (dry without geographic atrophy, dry with geographic

Table 2:

	Dry, No Geographic Atrophy (N=43)			Dry, Geographic Atrophy (N=7)			Wet, Responder (N=36)			Wet, Incomplete Responder (N=14)			P
	N	%	Mean	N	%	Mean	N	%	Mean	N	%	Mean	
Positive Berlin OSA score	18_{i}	41.90%		0_{ii}	0%		6_{ii}	16.7%		$2_{i,ii}$	14.3%		0.016
PROMIS T-score			44.1_{a}			45.8_{a}			41.4_{a}			43.6_{a}	--
Insomnia Severity Index (ISI)			6_{a}			5_{a}			4_{a}			6_{a}	--

This table shows the distribution of positive scores on 3 metrics of sleep quality stratified by subtype of AMD

Notes:

Values of Berlin OSA not sharing the same subscript are significantly different at p<0.05 by Chi-squared test

Values for PROMIS and ISI not sharing the same subscript are significantly different at p<0.05 by two-sided t-test, assuming equal variances, with Bonferroni correction.

Table 3:

	Dry			Wet			p
	N	%	Mean	N	%	Mean	
PROMIS T- score			44.4			42.0	0.153
ISS Score			6			5	0.184
Positive Berlin OSA Score	18	36%		8	16%		0.023

This table shows the distribution of positive scores on 3 metrics of sleep quality in patients with wet and dry AMD.

atrophy, wet treatment responsive, and wet treatment resistant) using two-sided t-tests for equality of means. Gender, working status, presence and treatment status of depression, presence and treatment status of obstructive sleep apnea (OSA), smoking status, and prior cataract surgery were compared across these categories using chi-squared tests and Fisher's exact test where appropriate.

Results

100 patients were enrolled in the study. 50 had the diagnosis of exudative AMD, and 50 had nonexudative AMD. Patients were further divided into subgroups of 1) dry AMD with no geographic atrophy (n=43), 2) dry AMD with geographic atrophy (n=7), 3) wet AMD treatment responsive (n=36) and 4) wet AMD treatment resistant (n=14). Table 1 shows the demographic information of the population. Among the dry AMD group, non-geographic atrophy patients were significantly younger than geographic atrophy. Among the wet AMD group, the mean ages were equivalent. Geographic atrophy patients had significantly worse best corrected visual acuity on average than all other subgroups (mean logMAR 0.491). Gender, tobacco use, depression, working status, previous OSA diagnosis, and cataract surgery did not differ significantly between subgroups. Not shown in the tables were treatment status of OSA patients. Of the eight patients with wet AMD and OSA, 1 used CPAP treatment.

Patients did not differ significantly between subgroups in their sleep quality scores on the PROMIS or ISI questionnaires (Table 2). However, one sample t-test showed a significant difference (p<0.001) between the mean scores of our sample population and the mean of the PROMIS sample population (mean=50, standard deviation=10); in other words, our population reported worse overall sleep quality than a normative population. Subjects did differ significantly on their scores on the Berlin assessment of OSA risk. 41.9% of dry AMD non-geographic atrophy 0% with dry AMD geographic atrophy, 16.7% of wet AMD treatment-responsive patients, and 14.3% of wet AMD treatment-resistant patients scored high risk on the Berlin assessment of OSA risk (p=0.016). Rates of high risk for sleep apnea were significantly higher among dry AMD patients with no geographic atrophy and wet AMD patients that responded to treatment. **Table 3** compares overall scores on assessments for patients with wet and dry AMD. 36% of all dry patients compared to 16% of wet were at high risk for sleep apnea (p=0.023). There were no significant differences in scores on the other two sleep assessments, PROMIS or ISI.

Conclusions

Our results demonstrated that patients with dry and wet AMD did not differ significantly in their scores on assessments of insomnia or sleep disturbance, but did vary in terms of their risks of sleep apnea. Patients with dry AMD, specifically those with no geographic atrophy, were at higher risk of sleep apnea than those with wet AMD. While the overall rates of diagnosed sleep apnea in our study population did not differ significantly between subgroups, they were much higher overall than estimates of the prevalence of sleep apnea in the general population (11-28% vs. 3-7%) [17]. Even more unexpected was that our population contained a female majority; this is interesting because the prevalence of sleep apnea is actually higher in males, with estimates of the male: female ratio ranging from 2-3: 1 [18]. This lends further credence to the notion that AMD and sleep apnea are associated; indeed, Keenan et al [11], (2016) found evidence in a large cohort that sleep apnea predisposed patients to a higher risk of AMD, as well as AMD increased the risk of sleep apnea. While a causative direction cannot be implied by our analysis, our results support a link between these two conditions.

Our study showed another interesting aspect to this trend. While rates of previously diagnosed OSA were higher than population norms in all subpopulations, dry AMD patients without geographic atrophy had the highest risk for OSA by the Berlin questionnaire. This indicates that rates of OSA may have been even higher in that subpopulation. In some ways, this is not surprising, as OSA is thought to be underdiagnosed [19]. However, it is important to note that these patients were younger than their counterparts with geographic atrophy, perhaps indicating they were, on average, less far along in their disease progression. Furthermore, a low sample size (n=7) potentially makes any observed differences less meaningful. When looking at dry patients as a whole, they were at much higher risk than wet patients for sleep apnea by the Berlin questionnaire. The aforementioned study by Keenan et al. [11] did not discriminate by type of AMD; our results indicate that dry AMD may be more strongly associated with an increased risk for sleep apnea.

In 2014, Nesmith et al. demonstrated that poor responders to anti-VEGF therapy had a higher risk of sleep apnea [20]. The authors

hypothesized that increased levels of VEGF caused by chronic hypoxia in OSA may hinder the response to VEGF inhibitors. A subsequent study by Nesmith et al. found that patients with wet AMD whose OSA was treated with continuous positive airway pressure required less injections [19]. In contrast to what might be expected based on the findings of the 2014 study, we found no significant difference in rates or risk of OSA by the Berlin questionnaire between exudative AMD patients who responded to treatment and those who did not respond to treatment. There was only one patient with OSA and exudative AMD who endorsed CPAP treatment, which precluded substantive statistical analysis of the relationship between treated and untreated OSA and AMD.

Limitations

Our study is limited by sample size and distribution of sample size, which led to low uneven absolute numbers of patients with OSA and makes comparison to other, larger studies difficult. Additionally, our patient population is not necessarily representative of the population with AMD as a whole, consisting of patients who may be more likely than average to adhere to treatment and may be more aware of their concomitant conditions, such as OSA. While this study may be internally consistent, it is not necessarily generalizable to the entire population with AMD. Recall bias is also inherent in any study that implements surveys that require patients use their memory to estimate their answers. Ours is not immune to this bias. Lastly, a positive score on the Berlin questionnaire is not equivalent to a diagnosis of sleep apnea, which can only be confirmed by a sleep study. Since screening measures are typically designed to be more sensitive than specific, our analysis runs the risk of over-estimating the true prevalence of OSA in the study population.

Conclusion

The current study demonstrated higher scores on an assessment for sleep apnea among patients with dry AMD over those with wet AMD. Furthermore, overall rates were higher than those of the general population. When taken together with the results of other studies in the literature, ours lends further credence to the idea that there is a physiologic link between these two illnesses, and the degree of involvement may be more extensive in patients with dry AMD.

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References

1. Prevention of Blindness and Visual Impairment: Priority Eye Diseases: Age-related macular degeneration World Health Organization, 2016.
2. Jager RD, Mieler WF, Miller JW. Age-Related Macular Degeneration. New England Journal of Medicine. 2008; 358: 2606-2617.
3. Mitchell J, Bradley C. Quality of life in age-related macular degeneration: a review of the literature. Health and quality of life outcomes. 2006; 4: 97.
4. Perez-Canales JL, Rico-Sergado L, Perez-Santonja JJ. Self-Reported Sleep Duration in Patients with Neovascular Age-Related Macular Degeneration. Ophthalmic epidemiology. 2016; 23: 20-26.
5. Colten HR, Altevogt BM. Sleep disorders and sleep deprivation: an unmet public health problem: National Academies Press; 2006.
6. Asplund R. Sleep, health and visual impairment in the elderly. Archives of gerontology and geriatrics. 2000; 30: 7-15.
7. Tabandeh H, Lockley SW, Buttery R, et al. Disturbance of sleep in blindness. American journal of ophthalmology. 1998; 126: 707-712.
8. Hilaire MAS, Lockley SW. Caffeine does not entrain the circadian clock but improves daytime alertness in blind patients with non-24-hour rhythms. Sleep medicine. 2015; 16: 800-804.
9. Schaal S, Sherman MP, Nesmith B, Barak Y. Untreated Obstructive Sleep Apnea Hinders Response to Bevacizumab in Age-Related Macular Degeneration. Retina. 2016; 36: 791-797.
10. Purbrick RMJ, Wong JC, Safa R, et al. Sleep Quality in Age-Related Macular Degeneration (AMD). Investigative Ophthalmology & Visual Science. 2014; 55: 3494.
11. Keenan, Tiarnan DL, Raph Goldacre, and Michael J. Goldacre. "Associations between obstructive sleep apnoea, primary open angle glaucoma and age-related macular degeneration: record linkage study." British Journal of Ophthalmology. 2017; 101: 155-159.
12. Buysse DJ, Yu L, Moul DE, et al. Development and Validation of Patient-Reported Outcome Measures for Sleep Disturbance and Sleep-Related Impairments. Sleep. 2010; 33: 781-792.
13. Yu L, Buysse DJ, Germain A, et al. Development of Short Forms from the PROMIS Sleep Disturbance and Sleep-Related Impairment Item Banks. Behavioral Sleep Medicine. 2011; 10: 6-24.
14. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Medicine. 2001; 2: 297-307.
15. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Annals of internal medicine. 1999; 131: 485-491.
16. List of Adult Measures: Available PROMIS® Measures for Adults. 2016.
17. Punjabi NM. The Epidemiology of Adult Obstructive Sleep Apnea. Proceedings of the American Thoracic Society. 2008; 5: 136-143.
18. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of Age on Sleep Apnea in Men. American Journal of Respiratory and Critical Care Medicine. 1998; 157: 144-148.
19. Lecomte, P., et al. "Underdiagnosis of obstructive sleep apnoea syndrome in patients with type 2 diabetes in France: ENTRED 2007." Diabetes & metabolism. 2013; 39: 139-147.
20. Nesmith BL, Ihnen M, Schaal S. Poor responders to bevacizumab pharmacotherapy in age-related macular degeneration and in diabetic macular edema demonstrate increased risk for obstructive sleep apnea. Retina. 2014; 34: 2423-2430.

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