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Is Obstructive Sleep Apnea Associated With Progressive Glaucomatous Optic Neuropathy?

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Abstract

Purpose—To evaluate the relationship between obstructive sleep apnea syndrome (OSAS) and glaucoma progression, and to examine the correlation between OSAS severity and rate of visual field (VF) loss.

Methods—Patients with concurrent diagnoses of open-angle glaucoma and OSAS between 2010–2016 were identified. Enrollment criteria consisted of glaucomatous optic neuropathy and VF loss, 5 reliable VFs, 2 years of follow-up, and polysomnography (PSG) within 12 months of final VF. PSG parameters including apnea-hypopnea index (AHI) and oxygen saturation (SpO₂) were collected. Eyes were classified as “progressors” or “non-progressors” based upon event analysis using Glaucoma Progression Analysis™ criteria. Two-tailed t-test comparisons were performed, and correlations between rates of VF loss and PSG parameters were assessed.

Results—A total of 141 patients with OSAS and glaucoma were identified. Twenty-five patients (age 67.9±7.6 years) with OSAS (8 mild, 8 moderate, 9 severe) were enrolled. Eleven eyes (44%) were classified as progressors, and had more severe baseline VF loss (p=0.03). Progressors and non-progressors had non-significantly different (p>0.05) age (69.9±8.7 vs. 66.4±6.6 years), follow-up (4.4±0.7 vs. 4.3±1.0 years), intraocular pressure (13.1±2.8 vs. 14.9±2.5 mmHg), mean ocular perfusion pressure (49.7±5.5 vs. 48.8±9.0 mmHg), AHI (31.3±18.6 vs. 26.4±24.0), body-mass index (27.8±5.5 vs. 28.8±5.6), and SpO₂ (94.1±1.6% vs. 94.0±1.6%). AHI was not correlated with slopes of VF mean deviation (r=−0.271, p=0.190) or pattern standard deviation (r=0.211, p=0.312), and no substantial increase in risk of progression was found with increase in AHI.

Conclusions—This study does not support a relationship between OSAS and glaucomatous progression. No correlation was observed between OSAS severity and rate of VF loss.

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Keywords

obstructive sleep apnea syndrome; hypopnea; glaucoma; visual field progression

Introduction

Obstructive sleep apnea syndrome (OSAS) is a disorder of sleep and breathing that features recurrent episodes of apnea or hypopnea due to the collapse of upper airway tissues¹. Apneic or hypopneic episodes often induce significant hypoxemia that can have deleterious effects on the cardiovascular system, leading to hypertension, cardiomyopathy, arrhythmias, or heart failure^{1, 2}. OSAS is most often diagnosed with polysomnography (PSG), the simultaneous recording of sleep, airflow, respiratory effort and oxyhemoglobin saturation conducted while attended in a sleep testing facility. Patients are classified as mild, moderate, or severe OSAS based on an Apnea-Hypopnea Index (AHI)³, a frequency metric derived from the sum of apnea and hypopnea events divided by the total sleep time in hours. Treatment often consists of continuous positive airway pressure (CPAP) devices.

There has been considerable interest in the potential relationship between OSAS and various ophthalmic conditions, such as floppy eyelid syndrome^{4, 5}, keratoconus^{6, 7}, papilledema⁸, optic neuropathy⁹, and glaucoma¹⁰. Given its effects on vasculature^{11, 12}, OSAS is hypothesized to exacerbate glaucomatous optic neuropathy due to repeated episodes of nocturnal hypoxia adversely affecting retinal ganglion cells. However, a causal mechanism has not been clearly identified. A recent study conducted in non-glaucomatous Japanese patients has suggested that nocturnal intraocular pressure (IOP) decreases during apneic periods¹³. Prior studies suggest that low ocular perfusion pressure (OPP), particularly low diastolic perfusion pressure, is a major risk factor for glaucoma onset and progression^{14, 15}.

There is conflicting data regarding the relationship between OSAS and glaucoma. Some studies have suggested a strong link between the two, with a prevalence of glaucoma ranging from 3–27%,^{10, 16–20} while others have reported minimal or no correlation^{21–24}. Meta-analyses have supported an association between OSAS and the prevalence of glaucoma^{16, 25}, yet other large retrospective and prospective studies have demonstrated no difference in glaucoma prevalence amongst persons with OSAS compared to without OSAS^{22, 23}.

Glaucomatous eyes that continue to progress despite robust IOP lowering often prompts clinicians to pursue ancillary diagnostic testing to identify systemic disorders, such as OSAS, that could potentially influence the course of progressive glaucomatous vision loss. Although IOP remains the only modifiable risk factor in glaucoma, various IOP-independent factors have been proposed including nocturnal hypotension^{26, 27}, low cerebrospinal fluid (CSF) pressure^{28–31}, and OSAS.

To our knowledge, no prior studies have examined the association between glaucoma progression and OSAS. The purpose of this study was to evaluate the relationship between OSAS and glaucoma progression, and to examine the correlation between OSAS severity and the rate of visual field (VF) loss.

Patients and Methods

Study Population

A retrospective cross-sectional study was conducted to identify study patients from an electronic medical record database between January 1, 2010 and December 31, 2015. The study period was selected based upon the time period during which all Ophthalmology and Pulmonary records were available in the University of Miami electronic health record. Approval was obtained from the Institutional Review Board of the University of Miami Miller School of Medicine, and the study complied with the tenets of the Declaration of Helsinki. Patients with concurrent ICD-9 or ICD-10 diagnoses of OSAS and open-angle glaucoma were identified from an electronic database. All eyes had glaucomatous optic neuropathy defined as narrowing of the neuroretinal rim, notching, excavation, optic disc hemorrhage, or retinal nerve fiber layer defect, and reproducible VF loss defined as an abnormal pattern standard deviation ($p < 0.05$) and glaucoma hemifield test outside normal limits ($p < 1\%$). Enrollment criteria consisted of age ≥ 40 years, a minimum of 5 reliable (fixation loss $< 20\%$, false positive and negative responses $< 33\%$) VF exams (Swedish Interactive Threshold Algorithm (SITA) standard 24-2 strategy, Humphrey Field Analyzer 750 II-I, Carl Zeiss Meditec Inc., Dublin, CA), a minimum of at least 2 years of longitudinal follow-up, and a polysomnography (PSG) examination conducted within 12 months of the final VF that was used to determine the VF progression classification. One eye per-patient meeting enrollment criteria was included; if both eyes met inclusion criteria the study eye was randomly selected. Only patients with refractive error between $-7D$ and $+3D$ were included in this study. Exclusion criteria consisted of ocular disease other than cataract or glaucoma, anterior or posterior segment pathology that could affect visual field performance, or surgical intervention during the study period.

Polysomnography Examination

All patients had a PSG examination performed at the University of Miami Miller School of Medicine Sleep Disorders Center. The facility is accredited by the American Academy of Sleep Medicine (AASM) and PSG's were conducted, recorded and scored in accordance with AASM standards³². A 3% decline in SpO₂ and/or an arousal associated with a $\geq 30\%$ reduction in airflow lasting at least 10 seconds was required to identify hypopnea. Uncalibrated respiratory inductive plethysmography was used as the sensor for determining respiratory effort. All PSG studies were conducted within 12 months of final VF used to classify patients as progressors or non-progressors. OSAS outcome measures collected from the PSG examination consisted of AHI, body-mass index (BMI), average SpO₂, time of SpO₂ $< 88\%$, and SpO₂ nadir. OSA was categorized into mild (AHI ≥ 5 and < 15), moderate (AHI ≥ 15 and < 30), and severe (AHI ≥ 30)³. A subset of patients fitted with continuous positive airway pressure (CPAP) therapy was identified, and IOP measurements after CPAP initiation were collected. Compliance data stored on a CPAP smart card reflecting the usage during a consecutive 30-day interval was analysed to quantify adherence.

Data Collection Procedures

Systemic vascular risk factors (e.g., diabetes, blood pressure, history of heart disease) and ocular characteristics (visual acuity, intraocular pressure (IOP), prior optic disc hemorrhage)

were abstracted from the medical record. The use of systemic antihypertensive medication and systemic β -blocker medication was collected. The number and class of glaucoma medication were recorded, as well as any history of glaucoma surgery. Glaucoma severity was categorized using the Hodapp-Parrish-Anderson grading scale³³ based upon the severity of VF loss and proximity to central fixation (early stage as VF MD > -6 dB, moderate as MD -6 to -12 dB; severe as MD < -12 dB). IOP was measured using Goldmann applanation tonometry; IOP at the first visit was deemed as baseline, while the mean of all IOPs at subsequent visits during the study period was deemed mean follow-up IOP. Changes in medical treatment were allowed at the discretion of the treating physician; these were not considered exclusion criteria. No laser or incisional surgery were performed during the course of the study. Mean ocular perfusion pressure (MOPP) was calculated using the equation $MOPP = 2/3 * [DBP + 1/3 * (SBP - DBP)] - IOP$ ³⁴. Diastolic perfusion pressure (DPP) was calculated using the equation $DPP = DBP - IOP$.

Eyes were classified as “progressors” or “non-progressors” based upon Glaucoma Progression Analysis™ (GPA) criteria (Carl Zeiss Meditec Inc., Dublin, CA). GPA™ uses statistical criteria designed for the Early Manifest Glaucoma Trial and compares the locations on pattern deviation change probability map on follow-up visual fields to the average of 2 baseline exams³⁵. An automated analysis identifies points that show change greater than the expected variability in pattern deviation (at the 95% significance level). Progression was defined as a significant change detected in 3 points, and repeated in the same points in 3 consecutive follow-up tests, categorized by the GPA software as “Likely Progression”.

Statistical Analysis

Participants classified as progressors were compared to those not classified as progressors with exact permutation tests for proportions and with two-tailed two-sample t-tests for interval level variables. Pearson correlations were calculated to assess the strength of relationship between PSG parameters and the slopes of VF mean deviation (MD), pattern standard deviation (PSD) and visual field index (VFI). In our study, we had 80% power to observe $r = 0.53$, which can be interpreted as a sleep parameter explaining 28% of the variability in VF slope. Logistic regression analyses were performed to estimate the odds ratios associated with sleep parameters and risk of VF progression.

Results

A total of 141 patients with concurrent OSAS and glaucoma were identified from an electronic database during the study period. One hundred sixteen patients were excluded who did not have the requisite number of reliable VF exams to assess for glaucoma progression (103 of 116, 89%) or did not have a PSG examination performed at the University of Miami (13 of 116, 11%). Twenty-five patients (mean age 67.9 ± 7.6 years) with OSAS (8 mild, 8 moderate, 9 severe) were enrolled in this investigation. Eleven of 25 (44%) eyes were classified as progressors; 14 eyes (56%) were classified as non-progressors.

The characteristics of the study population are summarized in Table 1. Progressors had significantly ($p=0.03$) more severe baseline VF loss compared to non-progressors as judged

by the Hodapp-Parrish-Anderson classification. All other clinical characteristics including age, mean length of follow-up, IOP (baseline, mean, and peak), and central corneal thickness were similar between the groups ($p>0.05$). Notably, IOP measurements (baseline, mean, and peak IOP) and IOP reducing therapy (medical and surgical) were similar between the two groups.

Table 2 describes baseline vascular characteristics of the study population. Progressors and non-progressors had similar ($p>0.05$) arterial blood pressure, OPP, and vascular risk factors including treatment for diabetes and hypertension. Table 3 summarizes the PSG characteristics of the study groups. Progressors and non-progressors had similar ($p>0.05$) BMI (27.8 ± 5.5 vs. 28.8 ± 5.6), AHI (31.3 ± 18.6 vs. 26.4 ± 24.0), and SpO_2 ($94.1\pm1.6\%$ vs. $94.0\pm1.6\%$).

We examined the correlation (Table 4) between PSG parameters and the rate of change in VF mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) to evaluate any potential relationship between the OSAS severity and the rapidity of glaucomatous VF change. No statistically significant correlations were identified between AHI and mean MD, PSD, or VFI (Figure 1). The strongest correlation was between MD slope and AHI, $r=-0.271$ and a 95% confidence interval around it ranges from -0.60 to $+0.14$. Thus, if AHI is related to MD slope, it likely explains less than 36% of the variability in VF loss. We also calculated odds ratios to assess the risk of classification as a progressor based on clinically meaningful differences in each of the interval level variables. Compared to non-progressors, the odds ratio of being a progressor: with a 5-point increase in BMI was 0.82 (95% CI: 0.4–1.8); with a 5-point increase in AHI was 1.06 (95% CI: 0.09–1.3); with a 2% decrease in SpO_2 was 0.93 (95% CI: 0.3–2.7); with a 1-minute increase in time $\text{SpO}_2<88\%$ was 1.27 (95% CI: 0.7–2.2); with a 5% decrease in SpO_2 nadir was 1.15 (95% CI: 0.6–2.1). Thus, even with our small sample size, we could rule out a doubling of the odds of being a progressor with BMI and AHI increases, but not with changes in SpO_2 variables.

A subset of eyes consisting of 6 of 11 (54%) progressors and 7 of 14 (50%) non-progressors were fitted for CPAP therapy after the baseline PSG examination. The mean IOP after initiation of CPAP therapy in progressors (14.2 ± 3.3 mmHg) and non-progressors (13.9 ± 2.7 mmHg) was similar ($p=0.85$) during the course of follow-up (mean 1.3 years after CPAP initiation). Among those with CPAP compliance data, the device was used $89.4\pm15.3\%$ of the time during a 30-day period with a mean residual AHI of 4.12.

Discussion

Glaucoma is a progressive disorder characterized by structural and functional abnormalities of the optic nerve^{1, 36, 37}. Even though IOP is the most important modifiable risk factor for disease onset and progression^{38–42}, glaucoma can exist even among individuals for whom IOP measurements are within the statistically defined “normal range”^{43–46}, suggesting non-IOP dependent mechanisms of optic nerve injury. These may include impaired optic nerve perfusion due to nocturnal hypotension⁴⁷ producing low OPP^{14, 15, 27, 48, 49} and low CSF pressure^{28, 31, 50}

OSAS has been proposed as a potential risk factor for open-angle glaucoma (OAG), and in particular OAG at normal IOP^{19, 51, 52}. It has been suggested that repeated intermittent periods of hypoxia might influence the development of ganglion cell loss. Lin et al suggested that normal-tension glaucoma (NTG) was correlated with moderate to severe OSAS¹⁸, while a prospective study by Bilgin found a higher rate of NTG among patients with moderate-severe OSAS⁵³. In contrast, Stein et al demonstrated no increased risk of NTG or primary open-angle glaucoma among a cohort of over 150,000 OSAS patients²². To our knowledge, the present study is the first that seeks to examine the relationship between OSAS and glaucoma progression.

The results of the present study do not support a strong relationship between OSAS and glaucoma progression. We found that progressors and non-progressors had similar PSG characteristics including BMI, AHI and SpO₂ metrics. We also found that OSAS severity, as determined by AHI, was not correlated with the rates of VF loss based upon the slope of MD, PSD, or VFI. Progressors and non-progressors were similar with respect to other potential confounding factors that could otherwise influence the risk of glaucoma progression including age, IOP control during follow-up, CCT, vascular risk factors including OPP, and the severity of glaucomatous VF loss judged by MD and PSD. It is noteworthy, however, that based upon the HAP classification, which also considers the location of the glaucomatous scotoma relative to central fixation, progressors had more severe VF loss at baseline. Finally, topical medications such as brimonidine and timolol have been found to influence the rate of VF progression in NTG eyes¹⁵. In the present study, progressors and non-progressors were similar with respect to the proportion of eyes receiving these medication classes.

There are reports that suggest a potential deleterious effect of CPAP therapy on IOP. Some reports speculate that CPAP equipment, which is placed along the nasal bridge in order to treat both the nasopharynx and oropharynx, may actually induce mechanical pressure on the eyes, causing IOP elevation. One prospective study showed that CPAP use was associated with greater nocturnal IOP fluctuation and absolute IOP, with a significant decrease in IOP with cessation of CPAP therapy⁵⁴. However, more recent studies have confirmed nocturnal IOP elevation in OSAS, but have found no difference between CPAP and non-CPAP treatment groups^{22, 55}. Chen et al found that in their study, there was a higher rate of glaucoma among OSAS patients, but this increased risk was not mitigated by medical or surgical therapy for OSAS⁵⁶. Nasal CPAP has been shown to restore normal nyctohemeral IOP patterns, which may be lost in OSAS⁵⁷. In our study, the mean IOP after initiation of CPAP therapy in progressors and non-progressors was similar during the course of follow-up. Among those with measurements, CPAP compliance was high. In a subset of patients (6 progressors, 7 non-progressors), CPAP therapy was initiated within 9 months prior to the final visual field. Given the short duration of CPAP therapy and the use of approximately 4.5 years of visual field data to assess progression, we do not believe this short use of CPAP would have confounded the determination of progression.

Our analysis of this dataset has potential weaknesses that include a retrospective study design and small sample size. However, stringent inclusion criteria, especially the use of GPA analyses to objectively detect progression, were utilized in hopes of rigorously

studying any potential relationship, naturally leading to a smaller sample size. Almost 90% of subjects with both OSAS and glaucoma were excluded from the study due to an insufficient number of reliable visual fields required for progression analysis using the GPA algorithm. Even with our small sample size we were able to rule out a moderate to strong (r^2 40%) association of polysomnography measurements with VF losses. In addition, our study was designed such that the PSG examination was performed within 12 months of the final VF used to classify patients based upon their VF progression status. A prospective study including PSGs would be financially intensive and potentially cost prohibitive. OSAS is a chronic condition similar to glaucoma, thus it was presumed to have been present in all subjects during the 4 years of follow-up from the initial VF. However, it is theoretically plausible that a variable dose-response relationship existed and that not all patients had manifest OSAS at the initiation of the study. This could potentially confound our assessment of the influence of OSAS on glaucomatous progression. The possibility of an underpowered study remains plausible; however, that does not preclude our ability to draw useful conclusions from the data. This is the reason we supplied 95% confidence limits around the effects we studied. These 95% confidence limits account for the sample size and are not compromised by power considerations. Our 95% confidence interval allows us to likely rule out a large effect of sleep apnea on visual field MD slope ($r^2 > 36\%$), ruling out a strong effect, as opposed to a clinically significant one.

In summary, this study does not support a substantial increase in the risk of VF progression with OSAS. No correlation was observed between OSAS severity and rates of VF loss in glaucomatous eyes. Larger prospective studies could be considered to determine the value of diagnosing and controlling OSAS in eyes with progressive glaucomatous vision loss.

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Figure 1. Scatter plots demonstrating the relationship between Apnea-Hypopnea Index (AHI) and the rates of change of visual field (A) mean deviation (MD), (B) pattern standard deviation (PSD), and (C) visual field index (VFI).

Table 1

demonstrates clinical characteristics of the study population (n = 25).

	Progressors (n = 11)	Non-progressors (n = 14)	p-value
Mean age (years)	69.9 ± 8.7	66.4 ± 6.6	0.26 [*]
Gender (male/female)	5 (46%)	8 (57%)	0.70 [‡]
Mean follow-up (years)	4.4 ± 0.7	4.3 ± 1.0	0.79 [*]
Glaucoma diagnosis			0.99 [‡]
NTG	3 (27%)	4 (29%)	
POAG	7 (64%)	8 (57%)	
XFG	0 (0%)	1 (7%)	
Other	1 (9%)	1 (7%)	
Glaucoma Severity (HAP criteria)			0.024 [‡]
Mild	1 (9%)	3 (21%)	
Moderate	0 (0%)	5 (36%)	
Severe	10 (91%)	6 (43%)	
Prior laser trabeculoplasty	0 (0%)	3 (21%)	0.23 [‡]
Prior incisional glaucoma surgery	2 (18%)	6 (43%)	0.23 [‡]
Baseline IOP (mmHg)	15.8 ± 4.7	15.3 ± 3.3	0.74 [*]
Mean follow-up IOP (mmHg)	13.1 ± 2.8	14.9 ± 2.5	0.10 [*]
Mean peak IOP (mmHg)	16.2 ± 4.1	18.1 ± 3.3	0.21 [*]
Mean central corneal thickness (μm)	557 ± 71	556 ± 42	0.96 [*]
Baseline no. of glaucoma medications	2.7 ± 0.5	2.6 ± 1.2	0.81 [*]
Topical beta-blocker use	10 (91%)	11 (79%)	0.60 [‡]
Brimonidine use	3 (27%)	6 (43%)	0.68 [‡]
Visual Field			
MD (dB)	-9.2 ± 5.7	-6.2 ± 5.6	0.20 [*]
PSD (dB)	7.1 ± 3.5	5.5 ± 3.5	0.27 [*]
VFI (%)	75.8 ± 18.1	84.3 ± 17.3	0.25 [*]
RNFL thickness (um)			
Average	72.3 ± 9.0	71.3 ± 15.7	0.92 [*]
Superior	72.0 ± 13.7	83.7 ± 18.9	0.37 [*]

	Progressors (n = 11)	Non-progressors (n = 14)	p-value
Inferior	81.3 ± 9.3	83.4 ± 25.8	0.90 [*]
Optic disc hemorrhage during follow-up	2 (18%)	1 (7%)	0.56 [‡]

NTG = normal-tension glaucoma; POAG = primary open-angle glaucoma; XFG = exfoliation glaucoma; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation; VFI = visual field index; RNFL = retinal nerve fiber layer

^{*} Student's t-test;

[†] Exact permutation chi-square test;

[‡] Fisher exact test

Table 2

demonstrates baseline vascular characteristics of the study population (n = 25).

	Progressors (n = 11)	Non-progressors (n = 14)	p-value
Treatment for diabetes mellitus	2 (18%)	2 (14%)	0.99 [‡]
Treatment for coronary artery disease	2 (18%)	7 (50%)	0.21 [‡]
Treatment for arterial hypertension	6 (55%)	9 (64%)	0.70 [‡]
Systemic beta-blocker use	2 (18%)	4 (29%)	0.66 [‡]
Baseline blood pressure (mmHg)			
Mean systolic	121 ± 18	128 ± 21	0.50 [*]
Mean diastolic	69.5 ± 6.8	68.9 ± 11.5	0.66 [*]
Mean arterial pressure	88.5 ± 12.7	86.5 ± 9.6	0.66 [*]
Baseline ocular perfusion pressure (mmHg)			
MOPP	45.7 ± 5.5	43.7 ± 9.4	0.66 [*]
DPP	53.6 ± 12.5	57.5 ± 4.3	0.29 [*]

MOPP = mean ocular perfusion pressure; DPP = diastolic perfusion pressure

* Student's t-test;

[‡]Fisher exact test

Table 3

demonstrates polysomnography characteristics of the study population (n = 25).

	Progressors (n = 11)	Non-progressors (n = 14)	p-value
Body mass index	27.8 ± 5.5	28.8 ± 5.6	0.63 [*]
Apnea-hypopnea index (range 0–78)	31.3 ± 18.6	26.4 ± 24.0	0.58 [*]
OSA severity			0.41 [†]
Mild	6 (43%)	2 (18%)	
Moderate	4 (29%)	4 (36%)	
Severe	4 (29%)	5 (46%)	
SpO ₂	94.1 ± 1.6	94.0 ± 1.6	0.90 [*]
Time SpO ₂ <88% (minutes)	1.2 ± 2.2	0.59 ± 1.2	0.38 [*]
SpO ₂ nadir %	83.4 ± 5.9	84.6 ± 7.8	0.66 [*]

OSA = obstructive sleep apnea; SpO₂ = oxygen saturation

^{*} Student's t-test;

[†] Fisher exact test

demonstrates the Pearson correlation between polysomnography characteristics and rates of visual field change for the study population (n = 25).

Table 4

	MD Slope		PSD Slope		VFI Slope	
	R	P-value	R	P-value	R	P-value
Body mass index	-0.221	0.289	0.092	0.663	-0.122	0.562
Apnea-hypopnea index	-0.271	0.190	0.211	0.312	-0.250	0.228
SpO ₂	-0.029	0.891	-0.127	0.547	-0.070	0.740
Time SpO ₂ <88% (minutes)	-0.151	0.472	0.166	0.429	-0.069	0.742
SpO ₂ nadir (%)	0.181	0.387	-0.099	0.637	0.010	0.964

SpO₂ = O₂ saturation