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A prospective photographic study of the ocular fundus in obstructive sleep apnea

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Abstract

Background—The prevalence of optic nerve and retinal vascular changes within the obstructive sleep apnea (OSA) population are not well known, although it has been postulated that optic nerve ischemic changes and findings related to elevated intracranial pressure may be more common in OSA patients. We prospectively evaluated the ocular fundus in unselected patients undergoing overnight diagnostic polysomnography (PSG).

Methods—Demographic data, past medical/ocular history and non-mydratic fundus photographs were prospectively collected in patients undergoing polysomnography at our institution and reviewed for the presence of optic disc edema for which our study was appropriately powered *a priori*. Retinal vascular changes were also evaluated. OSA was defined using measures of both sleep disordered breathing and hypoxia.

Results—Of 250 patients evaluated in the sleep center, fundus photographs were performed on 215 patients, among whom 127 patients (59%) had an apnea/hypopnea index (AHI) 15 events per hour, including 36 with severe OSA. Those with AHI<15 served as the comparison group. None of the patients had optic disc edema (95%CI:0-3%). There was no difference in rates of glaucomatous appearance or pallor of the optic disc among the groups. Retinal arteriolar changes were more common in severe OSA patients (OR: 1.09 per 5 unit increase in AHI, 95%CI: 1.02-1.16; p=0.01), even after controlling for mean arterial blood pressure.

Conclusions—We did not find an increased prevalence of optic disc edema or other optic neuropathies in our OSA population. However, retinal vascular changes were more common in patients with severe OSA, independent of blood pressure.

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Keywords

sleep apnea; optic nerve; retina; neuro-ophthalmology

INTRODUCTION

Obstructive sleep apnea (OSA) is a condition consisting of intermittent upper airway obstruction during sleep, leading to periods of hypoxia, hypercapnia, and acute hypertension (1). It has been hypothesized that in OSA, physiological changes secondary to hypoxia can result in retinal ischemia and associated retinal vascular changes (2) and progression of glaucomatous damage to the optic nerve (3). In one large, recently-published evaluation of billing records (4), an increased risk of non-arteritic anterior ischemic optic neuropathy (NAION) and idiopathic intracranial hypertension (IIH) was reported in patients with untreated OSA, leading the authors to conclude that OSA patients should undergo ophthalmologic screening (4). Their findings mirror another study, which concluded that early screening for potentially blinding optic neuropathies in moderate to severe OSA patients is worthwhile from an economic standpoint (5). However, the risk for various ocular disorders among patients with OSA remains unclear, particularly because in prior studies, the retinal assessment was performed remote from the time of polysomnography (up to 3 years) and optic disc appearance was not assessed (2). Additionally, these studies did not adequately control for potential confounders of these associations, such as obesity and hypertension. Our primary aim was to prospectively examine for optic disc edema among OSA patients at the same time as routine diagnostic polysomnography (PSG). Our secondary aim was to evaluate other optic disc, retinal or vascular changes at the posterior pole of OSA patients recruited prospectively.

METHODS

Adult patients presenting to our Sleep Center for diagnostic polysomnography between July and December 2011 were eligible. Patients with known condition other than OSA that could cause raised intracranial pressure (ICP) were excluded. Informed consent was obtained. The study was approved by our Institutional Review Board and followed the tenants of the Declaration of Helsinki. An *a priori* sample size was calculated for the frequency of optic disc edema, our primary outcome, in order to set the precision of our estimate. Our sample size was based on exact 95% binomial confidence intervals to produce an upper bound of no more than 3%, if no optic disc edema was found among the OSA patients, and a margin of error of less than 6% even if up to 10% of OSA patients had optic disc edema. Enrollment of at least 122 patients with OSA was required to achieve this level of precision..

Demographics

Demographic details including age, sex, ethnicity, and body mass index (BMI) were recorded. A review of ocular and medical history, including previously diagnosed hypertension and measurement of blood pressure, was conducted.

Polysomnography

All patients underwent conventional, laboratory-based, overnight polysomnography with monitoring of electroencephalography, electrooculography, surface electromyography and electrocardiography. Breathing was measured with separate channels for oral/nasal airflow, nasal pressure, thoracic and abdominal respiratory effort, and pulse oximetry. All recordings were made using Embla N7000 digital polysomnography using Remlogic® software and were scored by Registered Polysomnographic Technologists (6) and reviewed by sleep

medicine certified specialists who were unaware of results of ocular fundus evaluation. Apneas were scored as >90% reduction in respiratory airflow for at least 10 seconds. Hypopneas were defined as a diminution of airflow of at least 50% from the preceding baseline accompanied by at least 4% fall in oxygen saturation. The total number of apneas and hypopneas were summed and divided by the total sleep time in hours and multiplied by 60 to yield an apnea/hypopnea index (AHI), as a rate per hour of sleep. We also defined hypoxic burden as the percentage of the sleep time in which the pulse oximetry fell below 90%.

Using these definitions for breathing events, we defined the presence of sleep apnea as an AHI of ≥ 15 events per hour. Individuals exceeding this threshold were compared to individuals with AHI < 15 as an initial comparison. We then performed subgroup analyses in which individuals with severe sleep apnea (AHI ≥ 20 and hypoxic burden $\geq 10\%$) were compared with a subgroup with minimal AHI (<5) and minimal burden (<2%). For individuals undergoing split-night studies, (studies in which the first part of the night was done at baseline and the second part to perform continuous positive airway pressure titration), we used polysomnography data from only the diagnostic portion of the recording to generate these values.

Fundus photography

Photographs centered at the optic disc and macula, from each eye, were obtained by an ophthalmologist, using a commercially available table-top nonmydriatic ocular fundus camera (Kowa nonmydriatic-D III, Kowa Optomed Inc., Torrance, CA)). All included patients had photographs taken of both eyes when they arrived at the sleep center around 8PM.

Two neuro-ophthalmology-trained investigators systematically reviewed the photographs of each eye for an *a priori* agreed-upon set of findings, without knowledge of the polysomnography results. The eye with the highest quality image (7) was used for measurements of continuous variables (fractal analysis, cup-disc ratio), if both were of the same quality, the image from the right eye as used. In cases of asymmetrical findings (i.e., disc edema or retinal findings), the most abnormal eye was chosen for analysis. In cases of asymmetrical disc cupping, a label of glaucoma suspect was given. The disc appearances for each patient were assessed for edema, pallor and glaucomatous changes (i.e., increased cup-to-disc ratio, focal neuro-retinal rim notching). Retinal vascular changes for each patient were classified according to the classification of hypertensive changes (8) with “mild retinopathy” consisting of arteriolar narrowing, arteriolar sclerosis, arteriovenous nicking, “moderate retinopathy” including retinal nerve fiber layer (RNFL) hemorrhages, exudate or cotton wool spots, and “malignant” including associated disc swelling. In the case of disagreement regarding any of these findings, a third neuro-ophthalmologist made the determination of whether an abnormality was present or absent. Any other ocular abnormalities were also recorded. Patients with poor quality fundus photographs were excluded.

Fractal analysis

The best fundus photograph from one eye was chosen for each patient and analyzed within ImageJ (National Institutes of Health, USA). An automated approach was used to extract the retinal vessels (Fig 1). Specifically, we measured the fractal dimension and lacunarity of the retinal vasculature using the box-counting method (FracLac, Charles Sturt University, Australia), an established method of measuring structures that are not perfectly self-similar (9).

Statistical analysis

The groups were compared using Wilcoxon rank-sum test for continuous data, Fisher exact test for categorical data, and Mantel-Haenszel chi-square for stratified categorical data. Linear regression was used to evaluate the relationship between continuous variables and AHI. Logistic regression was used to evaluate and control for potential confounding (using a 10% change in coefficient rule) by age, race, and BMI on the association between OSA and retinal vascular changes. Significance was set at the 0.05 level.

RESULTS

Two hundred fifty patients presented for overnight sleep studies when digital fundus photography was available. Of the 250 patients, 215 were enrolled (excluded: 15 refused, 5 unable to consent, 3 photographs of poor quality, and 2 cranio-synostosis with possible increased ICP). There were no other exclusions; in particular no patients had been referred for sleep studies during this period with a possible diagnosis of IIH or NAION. One hundred twenty-seven patients had OSA (59%), based on AHI ≥ 15 . Among those patients with an AHI < 15 , diagnoses were: subclinical sleep disordered breathing ($n=52$), primary snoring ($n=16$), periodic leg movement disorder ($n=12$), physiologic hypersomnolence ($n=4$), repetitive intrusions of sleep ($n=1$), and normal ($n=1$).

Relative to the comparison group, OSA patients were older, more likely to be men, had a higher BMI, and were more likely to have a previous diagnosis of hypertension (Table 1). There was no difference in the measured mean systolic (SBP) and mean arterial blood pressures (MAP) comparing OSA patients relative to the comparison group but severe OSA patients (AHI ≥ 20 , hypoxic burden $\geq 10\%$) had higher mean blood pressures when compared to the minimal AHI/minimal hypoxic burden group (AHI < 5 , burden $< 2\%$) patients. There were no differences comparing race or frequency of diagnosed diabetes mellitus.

No patient had an optic disc appearance suspicious for optic disc edema. There were no differences in glaucomatous optic disc appearances between OSA and the comparison group (5% vs. 2%, $p=0.84$; OR=1.46, 95% CI: 0.32-6.75 controlling for age, race, sex, hypertension, and diabetes; logistic regression) and the rates of clinical diagnosis of glaucoma or glaucoma suspect were equal between the two groups. The rates of sectoral disc pallor were low and equal between the groups.

There were more retinal vascular changes, similar to those seen in mild hypertensive retinopathy, (9), in severe OSA patients vs. minimal AHI/minimal hypoxic burden patients (Fig 2). These arteriolar changes remained more common in severe OSA patients even after controlling for history of diagnosed hypertension: (hypertensive severe OSA vs. hypertensive minimal AHI/minimal hypoxic burden: 33 vs. 8%; non-hypertensive severe OSA vs. non-hypertensive minimal AHI/minimal hypoxic burden: 28 vs. 9%; $p=0.04$). AHI remained an independent predictor of retinal arteriolar changes (OR: 1.09 per 5 unit increase in AHI, 95% CI: 1.02-1.16; $p=0.01$) even after controlling for measured MAP (OR: 1.99 per 10 mmHg increase, 95% CI: 1.38-2.88, $p=0.0003$). For example, for any given blood pressure, an AHI > 40 conferred a doubling of the odds of retinal vascular changes being seen, compared to a patient with AHI < 5 . These relationships were not confounded by age, race or BMI based upon multivariable logistic regression. None of the comparison group had RNFL hemorrhages compared to 4% of the OSA patients ($p=0.08$), which would be classified as moderate hypertensive changes. Of these 5 patients, one had known diabetes with hypertension, 2 had a diagnosis of hypertension and 2 had neither.

Fractal analysis of the retinal vascular tree found no differences in any measure of fractal dimension or lacunarity between the OSA patients and the comparison group ($p=0.16$, Table 1, Fig 1).

DISCUSSION

We evaluated 215 patients undergoing polysomnography, 127 with OSA, in what is, to our knowledge, the largest systematic investigation of the ocular fundus findings of OSA patients on the night of polysomnography.

Episodic ICP elevations occur during OSA patients' apneic episodes (10). In addition, hypercapnia can alter cerebral vascular reactivity, causing increased ICP with the potential for associated optic disc edema (11,12). Hypoxia can also occur during apneic episodes, and subjects with hypoxia at high altitude, have been shown on fundus photography to develop disc edema, markedly tortuous retinal vasculature, and pre-retinal hemorrhages (13). Of 41 OSA patients examined in one study (5), 2 were found to have "disc swelling", but no further comment was made about these patients because the study was designed to screen for glaucoma. Another study examined 35 OSA patients and found no optic disc edema (14). Similar to this latter study, we found no optic disc edema in our 127 OSA patients (0%, 95% CI 0-3%).

Other optic neuropathies have been associated with OSA. In the case of glaucoma, the findings have been contradictory, with one study showing no difference (15) and another reporting rates nearly 4 times higher than the expected population rate of 2% (3). Studies of NAION patients have found that 71-89% have OSA by diagnostic polysomnography compared to 18% of controls (16), but whether the association between OSA and NAION is only due to confounding by shared risk factors for both conditions (e.g., age) or truly represents a causal relationship between OSA and NAION remains unknown. In our study, we found no differences between the optic disc appearance of patients with OSA compared to those without OSA, and we found no differences in the frequency of disc pallor or diagnosed glaucoma between the two groups.

The only difference we demonstrated was that retinal vascular changes, similar to those seen in mild hypertensive retinopathy, were over three times more common in severe OSA than in the minimal AHI/minimal hypoxic burden patients, even after controlling for diagnosed hypertension. The odds of retinal vascular changes also increased with increasing AHI, even when controlling for the patients' measured blood pressure, age, race, and BMI. Previous fundus photographic studies have shown that retinal vascular changes are associated with hypertension (17), but not sleep disordered breathing (2). Therefore, one potential explanation for our observations is that the vascular changes are due to elevated blood pressure and are exacerbated by the presence of OSA. However, the changes seen could instead be due to the OSA and exacerbated by hypertension. As in any observational study, residual confounding from the use of a single blood pressure measurement or from unknown or unmeasured confounders could also explain our results. Selection bias is also a concern, since it is likely that hypertension and its co-morbidities play a role in which patients are referred for sleep studies.

Various human studies have shown that retinal, but not choroidal, blood flow is affected by hypercapnia (18,19), and oxygen saturation does not affect the flow in either ocular circulation (19). However, if OSA causes chronic physiological changes in blood flow, this may lead, over time, to the visible arteriolar changes we documented on fundus photography, independent of elevated blood pressure. Indeed, OSA has been shown to be an independent risk factor for other conditions associated with vascular changes, such as stroke,

heart disease (20) and impaired renal function (21). Vascular endothelial dysfunction has been documented in OSA patients, which is independent from hypertension (22). The arteriolar changes we found on fundus photography may be visible evidence of the end organ damage produced by OSA.

Fractal analysis is used in the spatial analysis of branching patterns in biological systems (23), including cardiovascular disease (24) and the retinal vasculature in patients with hypertension (6). However, our fractal analysis failed to show any of the sub-clinical changes in the overall branching patterns of the retinal vasculature that have been described in larger studies of hypertensive retinopathy (8,24). We acknowledge that our study may be relatively underpowered for this outcome, particularly for detecting subtle differences in retinal fractal analysis.

In conclusion, our study showed that arteriolar changes are more common in severe OSA patients than in those with no OSA. We did not find evidence of differences in the prevalence of glaucomatous changes or optic disc edema. Our results do not support the routine ophthalmoscopic screening of OSA patients for optic neuropathies. However, if our finding of retinal arteriolar changes as an independent association with OSA is confirmed, evaluation of the retinal vasculature may help inform future studies of the pathophysiology of end-organ damage in OSA.

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Figure 1. Fundus photograph of a patient with obstructive sleep apnea obtained during the study (**A**) and with extraction of the retinal vessels for fractal analysis (**B**).

Figure 2. Fundus photography of a patient with obstructive sleep apnea: **(A)** arterio-venous nicking (arrow) and focal arteriolar narrowing (arrowheads); **(B)** arteriolar sclerosis and narrowing (arrow); **(C)** arteriolar narrowing (arrow).

Comparison of the demographics, medical and ocular history, and ocular fundus photography findings among patients evaluated for obstructive sleep apnea.

TABLE

	Overall comparison			Subset analysis		
	OSA ^a (n=127)	Comparison ^b (n=88)	P-value ^c	Severe OSA ^d (n=36)	Minimal burden ^e (n=46)	P-value ^c
Apnea-hypoxia index	37 (+/- 29)	4.7 (+/- 4.4)	<0.001	57 (+/- 31)	1.2	<0.001
Hypoxic burden (%)	13 (+/- 20)	1.9 (+/- 9.6)	<0.001	32 (+/- 26)	0.2 (+/- 0.4)	<0.001
Age, years	60 (+/- 12)	52 (+/- 16)	0.01	60 (+/- 12)	50 (+/- 16)	0.18
Sex	62% men	40% men	0.001	58% men	24% men	0.002
Race	59% white	60% white	0.61	39% white	54% white	0.23
Body mass index, kg/m ²	32 (+/- 8)	28 (+/- 8)	<0.001	36 (+/- 9)	28 (+/- 6)	<0.001
Hypertension	49% (62)	28% (25)	<0.001	50% (18)	26% (12)	0.02
Systolic blood pressure, mmHg	134 (+/- 16)	131 (+/- 15)	0.24	138 (+/- 18)	128 (+/- 15)	0.01
Mean arterial blood pressure, mmHg	96.5 (+/- 11)	95.7 (+/- 11)	0.68	99.6 (+/- 12)	93.6 (+/- 10)	0.02
Diabetes mellitus	17% (21)	17% (15)	0.92	19% (7)	20% (9)	0.99
Optic disc edema	0% (0)	0% (0)	1.0	0% (0)	0% (0)	1.0
Glaucomatous discs	5% (6)	2% (2)	0.84	13% (5)	5% (2)	0.85
Diagnosis glaucoma	3% (4)	3% (3)	1.0	8% (3)	4% (2)	0.65
Glaucoma suspect	2% (2)	1% (1)	1.0	6% (2)	0% (0)	0.44
Sectoral pallor	2% (2)	1% (1)	1.0	6% (2)	0% (0)	0.19
Retinal vascular changes	17% (21)	10% (9)	0.19	31% (11)	9% (4)	0.01
RNFL hemorrhages	4% (5)	0% (0)	0.08	6% (2)	0% (0)	0.19
Fractal dimension	1.46	1.48	0.16	1.47	1.49	0.17
Lacunarity	0.0014	0.0012	0.42	0.0016	0.0012	0.17

Abbreviations used: (+/- standard deviation); retinal nerve fibre layer, RNFL.

^c t-test used for comparing continuous variables, two proportion test with continuity test used for comparing proportions.

^d Severe OSA: defined as AHI > 20 and hypoxic burden [cumulative time with SaO₂ < 90%] > 10% of recording

^e Minimal burden: defined as AHI < 5 and hypoxic burden [cumulative time with SaO₂ < 90%] < 2% of recording

^a OSA : defined as AHI > 15

^b Comparison: defined as AHI < 15