·Clinical Research·

Diurnal changes in retinal nerve fiber layer thickness with obstructive sleep apnea/hypopnea syndrome

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Abstract

• AIM: To compare the retinal nerve fiber layer (RNFL) thickness in the morning and evening in Thai patients with varying degrees of obstructive sleep apnea/hypopnea syndrome (OSAHS).

• METHODS: In this cross-sectional study, potential OSAHS patients at Siriraj Hospital underwent polysomnography to determine the severity of OSAHS and an eye examination (including best corrected visual acuity, slit-lamp examination, and Goldmann applanation tonometry). RNFL thickness was recorded once in the morning and once in the evening, using spectral domain optical coherence tomography. Thickness was expressed as an average and given for each quadrant. Patients with ocular or systemic diseases that might affect RNFL thickness were excluded.

• RESULTS: Forty-one eyes of 41 patients were classified into 4 OSAHS groups. The average and mean RNFL thickness in most of the four quadrants of the severe OSAHS group trended toward being less than those in the comparable quadrants of the other groups in both the morning and evening. In the moderate OSAHS group, the average RNFL thickness and temporal and superior quadrant thickness in the morning were significantly higher than in the evening (P=0.01, P=0.01, and P=0.03, respectively). In the severe OSAHS group, the inferior quadrant thickness in the morning was significantly higher than in the evening (P=0.03).

• CONCLUSION: The RNFL thickness in the morning was higher than in the evening in moderate OSAHS.

• KEYWORDS: retinal nerve fiber layer thickness; sleep apnea/hypopnea syndrome; optical coherence tomography

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INTRODUCTION

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is characterized by repetitive episodes of upper airway occlusion during sleep, associated with or without hypoxic changes in various tissues. Severity of OSAHS is determined by total episodes of apnea (a pause in breathing) and hypopnea (decrease in airflow during breathing with oxygen desaturation). Average numbers of apnea episodes plus hypopnea episodes per hour of sleep time, the apnea-hypopnea index (AHI), is used widely to classify OSAHS severity [1]. Studies [2-4] have shown OSAHS to be an independent risk factor for the development of hypertension, cardiovascular morbidities, cerebrovascular diseases, and poor quality of life from excessive daytime somnolence. Additionally, several studies [2,5-11] have demonstrated an association between OSAHS and ophthalmic conditions such as floppy eyelid syndrome, papilledema, optic neuropathies in the form of nonarteritic anterior ischemic optic neuropathy (NAION), and glaucoma. Correlations have been found between OSAHS and clinical features of glaucoma such as retinal nerve fiber layer (RNFL) thinning, glaucomatous optic disc changes, visual field defects, and increased intraocular pressure (IOP)[11-16]. Glaucoma causes RNFL thinning as early as 6y before visual field loss[17], thus determinations of RNFL thickness may help in the early diagnosis and monitoring of this disease [18-19]. Furthermore, the relationship between OSAHS and RNFL thickness may be dependent on OSAHS severity [11-13,16,20]. Optical coherence tomography (OCT) is noninvasive, noncontact, rapid, reliable and sensitive to measuring small changes in RFNL thickness. Therefore, for clinicians, this could provide a method to monitor OSAHS episodes and the OSAHS-associated progression of eye damage. For patients, this could translate into better control of apnea episodes, and methods to monitor treatment efficacy.

Although several mechanisms have been proposed to explain optic neuropathies in OSAHS, the exact mechanism remains unknown. Proposed theories include direct hypoxic injury to the optic nerve, disrupted autoregulation of blood flow to the optic nerve from multiple periods of hypoxia and hypercapnia, or disruption of blood flow during periods of hypotension during sleep [11-12,15,21]. It is well known that ischemia results in tissue swelling in the acute phase. Increased RNFL thickness was also found during the acute stage of NAION, compared with the normal fellow eye [22]. Huseyinoglu *et al* [16] suggested optic nerve head changes start with subtle optic disc edema in mild and moderate OSAHS patients, followed by RNFL loss in cases of severe OSAHS. Whether the RNFL in OSAHS patients becomes swollen after repetitive hypoxia during sleep is unknown. To our knowledge, there is currently no existing report of diurnal RNFL changes in OSAHS patients of more or less severity. In this study, we measured RNFL thicknesses of OSAHS patients in the morning and in the evening. If hypoxic changes induced RNFL swelling, the thickness in the morning would be higher than at other times of the day and, possibly, this could contribute to further damage in more severe OSAHS patients.

SUBJECTS AND METHODS

Study Design and Subjects A cross-sectional study was conducted after approval from the Siriraj Institutional Review Board. All subjects participated voluntarily and gave their written informed consent.

We recruited 41 new subjects without any prior OSAHS therapies, clinically suspected to have OSAHS as diagnosed by snoring, observed pauses in breathing, and daytime sleepiness. To confirm OSAHS, candidates were given a polysomnography test (PSG) at the Sleep Clinic, Department of Otorhinolaryngology, Faculty of Medicine, Siriraj Hospital, Mahidol University. Demographic data, including sex, age, height, body weight, body mass index (BMI), and underlying systemic diseases were collected.

Ophthalmic Examinations Each subject underwent a complete ophthalmic examination (8:00 a.m.) without knowing the results of the PSG. Eye examination included best-corrected visual acuity (BCVA), automated refractometry, Goldmann applanation tonometry, stereoscopic slit-lamp biomicroscopy, and fundus examination. A 90-D lens was used to assess optic disc morphology and retina background. The criteria used for subject inclusion were, 1) ≥18 years of age, 2) BCVA ≥20/40, and 3) spherical equivalent within ±5.0 D. Exclusion criteria were any ocular or systemic diseases which might affect RNFL thickness, including diabetes mellitus, glaucoma, age-related macular degeneration, and optic neuropathy.

RNFL thickness in each eye was measured by OCT. This was performed by one trained ophthalmic technician using the spectral-domain OCT instrument (Heidelberg Engineering, Heidelberg, Germany), which uses a tracking system to compensate for eye movements. The details of the principles of spectral-domain OCT were previously described [23-24]. RNFL thickness was automatically segmented using Spectralis v4.0. Minimum image quality was 15 dB. RNFL thickness was measured twice for each patient. Evening (7:30 p.m.) measurements were made on the same day prior to admission for overnight PSG. Morning (8:00 a.m.) measurements were made the next morning after discharge from the sleep laboratory. The measurements were obtained with nondilated pupils. RNFL thicknesses were automatically generated for each of four quadrants (superior, nasal, inferior, and temporal) and as an average value. Both eyes of each subject were measured and recorded separately.

Sleep Studies The standard overnight technician-attended PSG (Somte, Profusion III software; Compumedics, Victoria, Australia) was performed on each patient. Recordings included electroencephalograms, bilateral electrooculograms, electromyograms, electrocardiograms, airflow measurements, respiratory measurements, body position sensor recordings, and pulse oximetry measurements. All PSG parameters were scored manually by well-trained sleep technologists, and were reviewed by certified sleep specialists. Patients were then divided into four groups according to their AHI: those without OSAHS (AHI<5), mild OSAHS (5≤AHI<15), moderate OSAHS (15≤AHI<30), or severe OSAHS (AHI≥30).

Statistical Analysis All data were analyzed using SPSS v11.5.0 (SPSS Inc., Chicago, IL, USA). Demographic data are described as mean, range, and standard deviation for continuous data and as numbers for categorical data. The left eye was selected for analysis. Continuous data were compared among the groups using an independent t-test and one-way analysis of variance (ANOVA) when appropriate. Post-hoc analysis and Tukey's multiple-comparisons test were used for pairwise comparisons. Data within the same eye were compared using a dependent t-test. Results were considered statistically significant at $P \leq 0.05$.

RESULTS

Forty-one eyes of 41 patients were included in this study. Nine subjects (22%) did not have OSAHS (non OSAHS), 12 (29%) had mild OSAHS, 11 (27%) had moderate OSAHS, and 9 (22%) had severe OSAHS. Demographic data are summarized in Table 1. The BCVA of each eye was 6/9 or better (data not shown). No significant differences in age, BMI, and cup:disc ratio were found among the four groups (P=0.92, 0.07, and 0.13, respectively, when compared with control subjects). IOP was elevated but within the normal range in the severe group only (P=0.04, one-way ANOVA); this was not significant when compared with Tukey's multiple comparison.

Table 1 Demographic information for each OSAHS group

Parameters	Non-OSAHS	Mild OSAHS	Moderate OSAHS	Severe OSAHS	[1]*P*
No. of eyes	9	12	11	9	
Male: Female	2:7	7:5	7:4	7:2	
Age (a)	49.4±9.1	53.1±8.2	50.5±18.2	51.3±11.9	0.92
BMI (kg/m²)	24.5±6.3	26.5±3.7	29.8±4.9	28.5±3.3	0.07
AHI (h)	2.2±1.5	12.0±7.9	20.2±3.6	64.4±25.5	
IOP (mm Hg)	14.2±1.6	14.3±2.7	14.3±2.3	16.5±4.2	0.04
C:D ratio	0.28±0.03	0.34±0.06	0.33±0.06	0.34±0.05	0.13

OSAHS: Obstructive sleep apnea/hypopnea syndrome; BMI: Body mass index; AHI: Apnea-hypopnea index; IOP: Intraocular pressure; C:D ratio: Cup:disc ratio; Non-OSAHS, AHI<5; Mild OSAHS, 5≤AHI<15; Moderate OSAHS, 15≤AHI<30; Severe OSAHS, AHI≥30. All data are presented as mean±standard deviation. [1]One-way ANOVA.

Table 2 Mean RNFL thickness in the morning and evening from each OSAHS group

RNFL sector	Mean RNFL thickness (μm)				
	Non-OSAHS	Mild OSAHS	Moderate OSAHS	Severe OSAHS	[1]*P*
Morning					
Average	105.11±9.55	102.08±12.35	108.27±13.37	99.66±5.54	0.33
Temporal	85.00±14.32	89.00±19.03	87.09±17.76	74.44±13.15	0.23
Superior	139.66±12.52	133.33±19.46	142.04±16.73	134.77±15.01	0.57
Nasal	64.11±11.21	54.00±18.65	63.00±13.48	60.11±7.42	0.32
Inferior	133.27±14.90	135.58±16.10	140.45±18.70	129.22±9.71	0.44
Evening					
Average	104.44±8.03	102.00±12.44	107.00±13.28	99.66±5.40	0.46
Temporal	84.77±13.55	89.16±18.20	86.18±17.26	75.33±14.38	0.28
Superior	139.27±10.68	132.95±19.67	139.81±17.24	135.27±15.01	0.72
Nasal	61.66±7.41	53.83±18.32	62.54±12.93	59.33±7.51	0.39
Inferior	131.88±12.62	136.12±17.93	139.09±17.66	127.88±10.16	0.40

RNFL: Retinal nerve fiber layer; OSAHS: Obstructive sleep apnea/hypopnea syndrome; Morning: 8:00 a.m.; Evening: 7:30 p.m. Results are presented as mean±standard deviation. Groupings are based on the apnea-hypopnea indices as described in Table 1. [1]One-way ANOVA with significance at <0.05.

The average RNFL and mean RNFL thickness in most of the four quadrants of the severe OSAHS group trended toward being less than those in the comparable quadrants of the other groups in both the morning and evening. However, there were no statistically significant differences. The mean RNFL thicknesses in each sector of all groups are shown in Table 2.

Differences in RNFL thickness measured in the morning and evening are shown in Table 3. In the moderate OSAHS group, the RNFL was significantly thicker in the morning than in the evening as an average value and in the temporal and superior quadrants (P=0.01, 95%CI 0.36-2.17; P=0.01, 95% CI 0.20-1.61; and P =0.03 95% CI 0.26-4.19, respectively), but not in the other quadrants. In the severe OSAHS group, diurnal differences in RNFL thicknesses were found only in the inferior quadrant (P=0.03, 95% CI 0.08-2.57).

Thirty-three (80.4%) subjects slept in the supine position most of the time and the episodes of apnea and hypopnea. Four (9.8%) and 4 (9.8%) subjects slept on their right or left side. No subjects slept in the prone position. There was no relationship between sleep position and RNFL thickness.

DISCUSSION

We found RNFL thicknesses to be lower in the severe OSAHS group. This was consistent with results from previous studies [11-13,20]. As proposed in previous studies, thinning of RNFL in severe OSAHS individuals may result from partial axonal death, which is a consequence of chronic hypoxia [11-14]. However, in the present study the lower RNFL thickness was not statistically significant. This may have been because of our small sample size as well as differences in disease onset.

In the present study, we determined if spectral domain OCT was useful to assess diurnal variations in RNFL thicknesses of patients with varying severity of OSAHS. RNFL thickness in patients with no and mild OSAHS did not differ between morning and evening, but those with moderate and severe OSAHS showed some significant differences (Table 3). During sleep, repetitive upper airway obstructions in OSAHS could cause insufficient optic nerve head blood flow and hypoxia [11-14]. This may induce optic nerve ischemia and subsequent RNFL swelling, eventually leading to cell death. Consequently, measurements of RNFL thickness in the early

Table 3 Diurnal differences and 95%CI of the mean RNFL thickness in each of four sectors between morning and evening and the average for the four categories of patients with OSAHS

Groups	RNFL sector	Mean RNFL thickness (μm)		^1P
		Difference	95%CI	
Non-OSAHS	Average	0.66	-1.4, 2.73	0.47
	Temporal	0.22	-1.39, 1.84	0.76
	Superior	0.38	-2.29, 3.07	0.74
	Nasal	2.44	-1.67, 6.56	0.20
	Inferior	1.38	-1.95, 4.72	0.36
Mild OSAHS	Average	0.08	-0.34, 0.5	0.67
	Temporal	-0.16	-0.87, 0.54	0.61
	Superior	0.37	-0.21, 0.96	0.19
	Nasal	0.16	-0.36, 0.69	0.5
	Inferior	-0.54	-2.04, 0.95	0.44
Moderate OSAHS	Average	1.27	0.36, 2.17	0.01
	Temporal	0.90	0.20, 1.61	0.01
	Superior	2.22	0.26, 4.19	0.03
	Nasal	0.45	-0.36, 1.27	0.24
	Inferior	1.36	-0.6, 3.33	0.15
Severe OSAHS	Average	0	-0.54, 0.54	1
	Temporal	-0.88	-2.75, 0.97	0.3
	Superior	-0.50	-2.14, 1.14	0.5
	Nasal	0.77	-0.29, 1.85	0.13
	Inferior	1.33	0.08, 2.57	0.03

RNFL: Retinal nerve fiber layer; OSAHS: Obstructive sleep apnea/hypopnea syndrome; CI: Confidence interval. Groupings are based on the apnea-hypopnea indices as described in Table 1. Statistical significance was set at <0.05. Difference: the difference in thickness between morning (8:00 a.m.) and evening (7:30 p.m.) as measured by optical coherence tomography and expressed in microns. [1]By independent *t*-test.

morning may be higher than at other times of the day, depending on the severity of the OSAHS. However, the RNFL thickness changes in the morning were small, and not clinically significant. The OCT could be a method to monitor visual disease in OSAHS and clinicians would not need to consider the time of day when measuring RNFL.

Swelling of RNFL might also occur in papilledema, from increasing cerebral spinal fluid (CSF) pressure during sleep, due to chronic hypercapnia, induced vasodilatation, and increased cerebral blood volume [8-9,25]. A previous study reported OSAHS patients with symptoms of idiopathic intracranial hypertension but no sign of a disc edema [25], which could have been from subclinical papilledema. This would not be detected by a fundus examination but could be apparent as a swelling of RNFL in OCT images. During the day, with no upper airway obstruction, optic nerve perfusion would be improved, CSF pressure would not be elevated, and RNFL may not become swollen.

RNFL thickness in the severe OSAHS group was thinner than that in moderate OSAHS. Detection of RNFL swelling in thinner RNFL thickness may be more difficult because of the thinness of the layer and the lower level of hypoxia required to induce substantial swelling. This may indicate induced partial axonal death due to chronic hypoxia and RNFL loss in the severe OSAHS group. A thin RNFL with partial axonal death in patients with severe OSAHS may not show significant RNFL swelling; thus, a change in RNFL thickness secondary to acute hypoxia may not be observed in some quadrants of the eyes in such patients. These findings support our hypothesis that significant hypoxic changes during OSAHS may result in RNFL swelling, and ultimately as the disease progresses, in RNFL loss from chronic intermittent hypoxia or ischemia.

During sleep, chronic intermittent upper airway obstructions in OSAHS resulted in insufficient optic nerve head blood flow, direct hypoxic damage to the optic nerve and progressive thinning of RNFL and choroidal thickness[11-13,20-21]. Subclinical RNFL thinning caused from OSAHS can be detected by OCT, but may be misdiagnosed as glaucoma. In this case, the appropriate treatment to prevent RNFL loss should be OSAHS management, not drugs which lower IOP.

IOP and fluctuation of IOP play a role in glaucomatous optic nerve head damage [26]. The trans-lamina cribrosa pressure (TLCP) difference is the most important factor in the physiology and pathophysiology of the optic nerve [27-29]. The TLCP difference depends on the retrobulbar CSF pressure and IOP [30]. Thus, TLCP fluctuations depend on either the CSF pressure or IOP fluctuation. In patients with OSAHS, fluctuations in the CSF pressure during the day and night cause fluctuations in the TLCP and might be a factor in optic nerve head damage.

In the severe OSAHS group, RNFL thickness was less than in the other groups; however, the BCVA in all eyes was 6/9 or better. This suggests that decreases in RNFL thickness do not immediately result in decreased visual acuity. However, a previous study reported that multifocal visual evoked potentials detected early subclinical optic nerve abnormalities in patients with OSAHS[31].

There are limitations to the present study. Unfortunately, we did not collect data on other visual functions, and the sample size was relatively small. The time varied from onset of symptoms to disease diagnosis and examination, and longer durations of OSAHS may have affected RNFL thinning from chronic hypoxia. Finally, although OCT is less invasive and provides a quantitative measurement of RNFL thickness, spectral domain OCT may not be sensitive enough to detect diurnal acute changes in RNFL and does not provide any functional visual information. Cohort studies of RNFL thickness and visual function analyses, such as visual field or contrast sensitivity measurements, may provide more information on how OSAHS induces abnormalities of RNFL.

In conclusion, impaired optic nerve head perfusion and hypoxia from repetitive upper airway obstructions in OSAHS may initially induce optic nerve ischemia and RNFL swelling. In general, RNFL thickness measurements taken in the morning can be expected to be above the diurnal average in OSAHS patients, and these measurements could vary with

the severity of the OSAHS. Chronic intermittent hypoxia could induce partial RNFL death and loss in patients with severe OSAHS, and this could be determined using OCT.

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