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Original Research Article

A Case Control Comparison of Retinal Nerve Fiber Layer (RNFL), Ganglion Cell Layer (GCL), and Optic Nerve Head (ONH) Morphological Parameters Using Spectral Domain Optical Coherence Tomography (SD‑OCT) in OSA Patients

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Abstract

Aim: To compare the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and optic nerve head (ONH) morphological parameters between obstructive sleep apnea (OSA) patients and age-matched controls using spectral domain optical coherence tomography (SD‑OCT).

Material & Method: This case control study was conducted in the Department of Ophthalmology, Patna Medical College & Hospital, Patna, Bihar, India for 1 year. Epworth Sleepiness Scale (ESS) was employed to measure daytime sleepiness and rule out OSA while choosing control population. A scale of zero–four was chosen by the patient for eight different situations. **Results:** RNFL analysis in OSA patients showed statistically significant decrease of the mean Superior RNFL, Inferior RNFL, and Average RNFL. Ganglion cell analysis also showed a decrease in all six sectors of ganglion cell layer, average, and minimal ganglion cell layer‑inner plexiform layer thickness in OSA patients when compared to controls; the difference was statistically significant ($P < 0.05$).

Conclusion: OSA patients even with clinically normal optic disc showed significant decrease in the RNFL thickness, GCL thickness, and rim area when compared to age‑matched controls. Hence, these patients constitute a high‑risk population who need to be regularly screened and followed up for ocular co‑morbidities.

Keywords: Ganglion cell layer, glaucoma, obstructive sleep apnea, retinal nerve fiber layer

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Introduction

Obstructive sleep apnea syndrome (OSAS) is one of the most frequent sleep disorders in our population [1]. A recent estimation has shown that 13% of middle-aged men and 5% of middle-aged women are affected. An increase in prevalence by 30% between 1990 and 2010 was seen [2]. Continuous and maintained oxygen desaturation during sleep results in metabolic, cardiovascular, and neuropsychiatric consequences that impact quality of life and increase mortality [1, 3]. Cognitive alterations have, in particular, been associated with both the reduction in

the overall performance and the memory abilities of patients with OSAS [4].

The combination of OSAS with glaucoma was first drawn to our attention in 1982 by Walsh and Mont Plaisir's study which reported that 5 members of the same family had OSAS with glaucoma [5].While there are studies reporting high glaucoma prevalence or decrease in retinal nerve fiber layer (RNFL) thickness in patients with OSAS, there are also studies arguing that OSAS does not have any relationship with glaucoma [6, 7].

Obstruction Sleep Apnea (OSA) is characterized by repetitive episodes of complete or partial collapse of the upper airway during sleep resulting in complete cessation (apnea) or reduction (hypopnea) of airflow leading to arousal and hypoxia. [9] In Indian studies, the prevalence of obstructive sleep apnea varied from 4.4% to 13.7%. [10] The most prevalent ocular associations are primary open angle glaucoma and normal tension glaucoma. [11]

Hence, we aim to compare the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and optic nerve head (ONH) morphological parameters between obstructive sleep apnea (OSA) patients and age‑matched controls using spectral domain optical coherence tomography (SD ‑OCT).

Material & Method:

This case control study was conducted in the Department of Ophthalmology, Patna Medical College & Hospital, Patna, Bihar, India for 1 year.

Inclusion and exclusion criteria

Patients diagnosed to have OSA were categorized into mild, moderate, and severe OSA according to the apnea–hypopnea index (AHI)

- Mild Sleep Apnea: AHI 5–15 events per hour
- Moderate Sleep Apnea: AHI 15–30 events per hour
- Severe Sleep Apnea: AHI >30 events per hour

Patients with media opacity preventing acquisition of good OCT images, refractive error (>2.00 diopter spherical error, >1 diopter cylindrical error), history of uveitis, any retinal pathology such as diabetic retinopathy, hypertensive retinopathy, age‑related macular degeneration, family history of glaucoma, history of chronic steroid use, heavy smoking, alcohol abuse and co‑existing neurological diseases that might affect visual field were excluded from the study.

Methodology

Epworth Sleepiness Scale (ESS) was employed to measure daytime sleepiness and rule out OSA while choosing control population. A scale of zero–four was chosen by the patient for eight different situations.

Patients with no systemic co‑morbidities, no significant refractive error (>2.00 diopter spherical error, >1 diopter cylindrical error were excluded), no history of snoring, a score of < 10 on ESS, no evidence of glaucomatous optic nerve appearance and a cup disc ratio less than 0.5, open angles on gonioscopy, no previous history of chronic steroid use, ocular trauma, ocular surgery or laser treatment, and no history of heavy smoking or chronic alcohol intake were included as controls.

All subjects had a detailed ophthalmological examination, which included visual acuity by Snellen chart, intraocular pressure measurement by gold Mann's applanation tonometry corrected with central corneal thickness measured by ultrasound pachymetry, gonioscopy, slit lamp examination including biomicroscopy (90 D), and fundus examination using indirect ophthalmoscope.

After evaluation, the study population was classified into two groups. Cases included 100 eyes of 50 OSA patients with open

angles, normal optic disc and normal visual fields, and control group included 100 eyes of 50 age and sex‑matched controls.

Statistical analysis

Statistical analysis was done using IBM SPSS20. (SPSS Inc, Chicago, USA). For all the continuous variable, the results are either given in Mean ± SD and for categorical variable as percentage. To compare the mean difference of numerical variable between groups, independent two sample "t" test was applied. To obtain the relationship between two variables, Pearson correlation was applied. A *P* value <0.05 was considered statistically significant. Bonferroni test was used to get the corrected *P* value of $P < 0.002$.

Results:

The mean age was 50.21 ± 15.77 and 45.79 ± 9.21 years in cases and controls, respectively. The difference of mean age between cases and controls was not statistically significant with a *P* value of 0.122.

On comparison of parameters between OSA patients and controls, the central corneal thickness was not statistically different between the two groups ($P > 0.05$). Analysis of visual field parameters such as mean deviation and pattern standard deviation between cases and controls was not statistically significant as shown in Table 1.

RNFL analysis in OSA patients showed statistically significant decrease of the mean Superior RNFL, Inferior RNFL, and Average RNFL with a *P* value of 0.013, <0.001, and <0.001, respectively. The difference in mean temporal RNFL was not statistically significant between the two groups ($P = 0.291$) and the values are presented in Table 2.

On mean RNFL clock hour analysis, RNFL clock hour 1,4,5,6 was decreased in OSA patients and the difference was statistically significant with a *P* value of 0.003, 0.002, <0.001, and 0.004, respectively.

Ganglion cell analysis also showed a decrease in all six sectors of ganglion cell layer, average, and minimal ganglion cell layer‑inner plexiform layer thickness in OSA patients when compared to controls; the difference was statistically significant ($P < 0.05$) and the values presented in Table 3. Measurement of mean average and central subfield retinal pigment epithelium + inner plexiform layer thickness was not significant between the two groups.

Among the optic nerve head morphological parameters, the difference in average CD ratio, CD Volume and Disc area was not statistically significant between the two groups with a *P* value of 0.271, 0.088, and 0.512, respectively. However, the rim area was significantly decreased in OSA patients when compared to controls ($P < 0.001$), and the values are presented in Table 4.

Table 1: Comparison of visual field parameters between cases and controls (*n*=100)

Parameters	Group	Mean±standard deviation	*P*
Mean Deviation	Cases	-1.98±0.79	0.033
	Controls	-1.69±0.58	
Pattern Standard Deviation	Cases	1.77±0.51	0.184
	Controls	1.60±0.80	

Table 2: Comparison of Retinal nerve fiber layer (RNFL) parameters between cases and controls (*n*=100)

Parameters	Group	Mean	Standard deviation	P-value
Superior RNFL	Cases Controls	135.87 122.60	18.90 8.582	0.013
Inferior RNFL	Cases Controls	108.72 118.84	15.837 7.948	<0.001
Temporal RNFL	Cases Controls	73.79 61.53	10.841 5.093	0.291
Nasal RNFL	Cases Controls	54.82 66.09	9.274 7.173	0.046
Average RNFL	Cases Controls	76.60 86.29	8.280 3.284	<0.001

Table 3: Comparison of ganglion cell layer (GCL) between cases and controls (*n*=100)

Parameters	Group	Mean	Standard deviation	*P*
GCL Superior quadrant	Cases Controls	63.83 76.90	14.91 5.02	0.002
GCL Superonasal quadrant	Cases Controls	80.27 88.21	11.82 4.38	0.020
GCL Inferonasal quadrant	Cases Controls	73.11 79.01	11.99 4.09	0.002
GCL Inferior quadrant	Cases Controls	86.22 90.20	6.92 3.28	<0.001
GCL Inferotemporal quadrant	Cases Controls	83.91 91.20	8.72 3.71	0.002
GCL Superotemporal quadrant	Cases Controls	87.10 93.98	10.84 4.92	0.001
Average GCL + Inner plexiform layer thickness	Cases Controls	78.04 88.04	8.99 3.87	<0.001
Minimum GCL + Inner plexiform layer thickness	Cases Controls	79.36 86.39	15.61 2.81	<0.001

Table 4: Comparison of optic nerve head parameters between cases and controls (*n*=100)

Parameters	Group	Mean±Standard deviation	*P*
Avg Cup disc ratio	Cases	0.67±0.67	0.271
	Controls	0.68±0.21	
Cup disc volume	Cases	0.381±0.271	0.088
	Controls	0.371±0.281	
Rim area	Cases	2.339±0.280	<0.001
	Controls	2.791±0.391	
Disc area	Cases	3.812±0.361	0.512
	Controls	2.925±0.023	

Discussion:

Deterioration of autoregulation in blood flow to the optic nerve was due to recurrent apneas, and optic nerve blood flow dysregulation was due to OSAS [11].In this mechanism, mediators that cause dilatation or contraction of smooth muscle are secreted from normal endothelium tissue. It has been suggested that the balance of endothelial and nitric oxide is disturbed in patients with OSAS. Kato et al. have shown that, in the patients with OSAS, infusion of acetylcholine reduced vascular dilatation due to endothelium derivednitric oxide and therefore blood flow, compared with control group. However, there was no difference between the groups in endothelium-independent vasodilatation [12].

OCT is a technique that provides real measurements of the macula, peripapillary retinal layers, and the optic nerve, allowing a fast, non-invasive way to show possible retinal changes in OSAS patients. Accordingly, retinal changes demonstrated by OCT could function as a window into the brain and can be used as a biomarker [13].

As previously reported [14], during sleep, intermittent apneic episodes with oxygen desaturation activate proinflammatory and procoagulant mechanisms accompanied by the adrenergic system. These changes promote endothelial dysfunction and oxidative stress with an increase in vascular resistance that, in the end, compromises the optic nerve perfusion and leads to a reduction in retinal thicknesses. These findings can easily be shown with OCT.

A meta-analysis presented by Yu et al. reviewing 10 case-control studies, and another one by Wang et al. that includes 17 studies on OCT in OSAS, show that the average RNFL thickness in OSAS patients is significantly reduced compared to healthy controls [15, 16].

A study done by Zengin et al.[17]on OSA patients showed a significant thinning of superior, inferior, nasal, and average RNFL thickness. Another observational case control study by Casas et al. [18]also showed decrease only in peripapillary nasal RNFL thickness and no statistically significant thinning of other RNFL parameters on Stratus OCT. A study by Lin et al.[19]concluded that there was a reduction in average RNFL, superior RNFL, and temporal RNFL in patients with moderate and

Mwanza et al. reported that on SD‐OCT, the best discriminates between glaucomatous eye and normal eyes are RNFL thickness at the inferior temporal clock hour 7, superotemporal RNFL, inferior quadrant RNFL, average RNFL thickness, rim area, CD ratio, cup to disc

area ratio, and minimal GC‑IPL thickness.[20]

Our study has shown statistical difference in most of the above parameters among OSA patients when compared to controls, hence indicating that these OSA patients even with normal looking discs could be at risk of developing glaucoma. [20]

Geyer et al. found that the prevalence of glaucoma is similar in 228 patients with OSAS and normal subjects [21]. Moreover, they could not find any correlation between AHI and glaucoma. However they detected a positive correlation between VKI and AHI. Also, in our study, we could not find any difference between the OSAS group and the control group in terms of their RNFL thickness.[22]

Conclusion:

OSA patients even with clinically normal optic disc showed significant decrease in the RNFL thickness, GCL thickness, and rim area when compared to age‑matched controls. Hence, these patients constitute a high‑risk population who need to be regularly screened and followed up for ocular co‑morbidities.

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