The Relationship Between Obstructive Sleep Apnea Syndrome and Glaucoma

Obstrüktif Uyku Apne Sendromu ve Glokom İlişkisi

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ABSTRACT Objective: In this study, we investigated the prevalence of glaucoma in patients with obstructive sleep apnea syndrome (OSAS). **Material and Methods:** Sixty-four patients with OSAS and 32 control subjects comprised the study group. Detailed ophthalmological examinations, computerized visual field analysis and imaging of the optic nerve head with Optical Coherence Tomography were performed. Diurnal intraocular pressure measurements were made on patients with OSAS. Patients with OSAS were divided into three groups (mild, moderate and severe) for severity of the disease based on their apnea-hypopnea indexes (AHI). **Results:** There was a statistically significant correlation among AHI, mean deviation and retinal nerve fiber layer thickness ($p<0.05$). Glaucoma was diagnosed in seven patients with OSAS (10.9%). One patient had primary open angle glaucoma and six patients had normal tension glaucoma. Five of the patients with glaucoma were in severe OSAS group. **Conclusion:** The results of this study show that OSAS is associated with glaucoma. Patients with OSAS should be followed regularly for glaucoma development and progression.

Key Words: Glaucoma; polysomnography; sleep apnea, obstructive

ÖZET Amaç: Bu çalışmada obstrüktif uyku apne sendromu (OUAS) tanısı almış hastalarda glokom sıklığı araştırıldı. **Gereç ve Yöntemler:** OUAS tanısı almış 64 hasta ve 32 kontrol olgusu çalışma grubunu oluşturdu. Çalışma grubuna detaylı oftalmolojik muayene, görme alanı ve optik koherens tomografi ile optik sinir başı analizi yapıldı. OUAS'lı hastaların yirmi dört saatlik göz içi basıncı (GİB) eğrisi çıkarıldı. OUAS'lı hastalar apne-hipopne indeksine (AHİ) göre üç gruba (hafif, orta ve ağır) ayrıldı. **Bulgular:** AHİ ile ortalama sapma ve sinir lifi kalınlığı arasında istatistiksel olarak anlamlı korelasyon saptandı ($p<0,05$). OUAS'lı hastalardan yedi hastada glokom saptandı (%10,9). Bir hastada primer açık açılı glokom (PAAG) ve 6 hastada normal basınçlı glokom (NBG) saptandı. Glokom tanısı konan yedi hastadan beş tanesi ağır OUAS'lı grupta yer aldı. **Sonuç:** Bu çalışmanın sonuları OUAS ile glokom arasında ilişki olduğunu göstermiştir. Obstüktif uyku apne sendromu tanılı hastalar glokom gelişimi ve ilerlemesi açısından düzenli takip edilmelidir.

Anahtar Kelimeler: Glokom; polisomnografi; uyku apnesi, tıkayıcı

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Glaucoma is an optic neuropathy characterized by progressive retinal ganglion cell damage, optic nerve cupping and visual field defect. The prevalence of primary open angle glaucoma (POAG) in the general white population is estimated to be between 1.7% to 3%.[1-5] The prevalence of normal tension glaucoma (NTG) increases with age, ranging from 0.2% in 43-54 age group, and up to 1.6% in those over 75 years of age.[4]

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The major optic nerve head changes in glaucoma are increased cup/disc ratio and thinning of the neuroretinal rim and the retinal nerve fiber layer thickness (RNFLT). Loss of RNFLT occurs earlier than optic nerve head changes and visual field defects. The pathophysiology of glaucomatous optic neuropathy is not well understood. Whether the site of primary damage is the ganglion cell body or their axons remains debatable. Irrespective of the initial site of neuronal injury and mechanisms involved, the terminal outcome is the death of retinal ganglion cells (RGC) and their axons leading to irreversible visual loss. Cellular responses to changes in intraocular pressure (IOP) leading to apoptosis of RGCs are not well understood. A possible mechanism of RGC apoptosis seems to be related to changes in extracellular matrix components in the retina of glaucomatous eyes in response to elevated IOP. The primary factors responsible for apoptotic cell death in glaucoma include not only elevated IOP but also vascular dysregulation, especially in people with NTG.[6] In recent years, vascular and other pathogenic mechanisms are considered in addition to elevated IOP.

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent airway obstructions and decreased oxygen saturation. Recurrent airway obstructions during sleep causes hypoxia, hypercapnia and intrathorasic pressure changes which affect autonomic, hemodynamic, humoral and neuroendocrine regulations. These changes may influence the optic nerve head perfusion and ganglion cell loss. As a result, optic nerve may become more sensitive to high intraocular pressure or optic nerve damage may develop without an increased IOP. Therefore, OSAS may be a possible risk factor for the development of open angle glaucoma and normal tension glaucoma.

The aim of this study was to examine and follow up patients with OSAS for prevalence of glaucoma and a tendency to glaucoma.

MATERIAL AND METHODS

This study was performed between January 2006 and May 2008 in Dokuz Eylul University, School of Medicine, Department of Ophthalmology. We recruited the patients consecutively referred from the Sleep Laboratory, Department of Neurology, Dokuz Eylul University, School of Medicine. After polysomnographic study, 64 patients with OSAS (diagnosed with polisomnography and apnea-hypopnea index) were compared with 32 age- and gender-matched control subjects. Patients with OSAS were evaluated in three groups according to apnea-hypopnea index (AHI) scores. According to AHI scores; 5-15 score was classifed as mild, 16-30 score was classifed as moderate and over 30 score was classified as severe OSAS. Patients with a history of ocular surgery, ocular trauma, anterior or posterior segment disease, cataract, those with secondary glaucoma, chronic steroid use, cerebrovascular disease and diabetes mellitus were excluded. The institutional ethical board approved the study, and Helsinki Declaration was followed. Informed consent was obtained from every subject participating in the study.

After polysomnography, all subjects underwent ophthalmic examination. Diurnal intraocular pressure measurements, corneal topography and perimetry were made. RNFLT measurements were made with Optical Coherence Tomography (OCT). Subjects who were diagnosed as glaucoma were referred to the glaucoma unit of Dokuz Eylul University, School of Medicine, Department of Ophthalmology. The investigators who made the ophthalmological examinations were blinded to the presence of OSAS.

The eye examination included the best corrected visual acuity with a recording of refractive correction, slit-lamp biomicroscopy of the anterior segment, and tonometry performed by the same ophthalmologist (M.O.Z) and with the same tonometer. We used the Perkins hand-held applanation tonometer (Clement Clarke International, Harlow, England), as this could be handled at these different times and in different body positions. Intraocular pressure was measured in a 24 hours diurnal period (8:00 am, 10:00 am, 12:00 am, 2:00 pm, 4:00 pm, 6:00 pm, 8:00 pm, 10:00 pm, 12:00 pm, 1: am, 3:00 am, 4:00 am and 7:00 am. Before pupillary dilation, automated perimetry was made with Humphrey Field Analyzer II (Model 750, Zeiss, USA). SITA-fast and in uncer-

tain patients blue on yellow perimetry was used. In results with low reliability, the test was repeated the day after. Mean deviation and patent standart deviation were evaluated. Central corneal thickness measurement was made with Orbscan II (Orbtek Inc., Salt Lake City, UT), and the iridocorneal angle was examined in four quadrants with Goldmann three mirror lens. After pupillary dilation, ophthalmoscopic examination was made. Optic disc and RNFLT analyses were performed with single-scan time-domain OCT (Stratus; Carl Zeiss Ophthalmic System Inc, Dublin, USA).

GLAUCOMA DIAGNOSIS

Glaucoma was diagnosed using the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) criteria.[7] According to this, the identification of glaucoma was made on three levels of evidence. The highest level (level 1) of certainty requires optic disc abnormalities [Vertical cup : disc ratio (VCRD) >97.5th percentile in the normal population] and visual field defect compatible with glaucoma. In level 2, if a visual field test could not be performed satisfactorily, a severely damaged optic disc (VCDR > 99.5th percentile of the normal population) would be sufficient to make the diagnosis. In level 3, if the optic disc could not be examined because of media opacity, an IOP exceeding the 99.5th percentile of the normal population, or evidence of previous glaucoma filtering surgery, may be sufficient for the diagnosis of glaucoma.

The following criteria were used to define primary open angle glaucoma in this study: Maximum IOP >21 mmHg, normal appearing anterior chamber angle on gonioscopy, glaucomatous optic disc damage with asymmetric cupping and thinning of the neuroretinal rim, compatible with defects in the visual field, and/or optic disc hemorrhage. Glaucomatous visual field loss was defined as a glaucoma hemifield test graded "outside normal limits" and a cluster of three contiguous points at the 5% level on the pattern deviation plot, using the threshold test strategy with the 24-2 test pattern of the Zeiss-Humphrey field analyser 2. Diagnosis of normotensive glaucoma was made with criteria similar to those stated for POAG except for the fact that IOP was <21 mmHg.

POLYSOMNOGRAPHY

Overnight polysomnography was performed in all subjects by a computerized system (Somnologica software) and included the following variables: Electrooculogram, electroencephalogram, electromyogram of submental muscles, electromyogram of the anterior tibialis muscles of both legs, electrocardiogram and nasal and oral airflow (with an oro-nasal thermistor). Chest and abdominal respiratory efforts were recorded using inductive plethysmography, arterial oxyhemoglobin saturation by pulse oximetry was recorded with a finger probe. Sleep recordings were scored in 30-s epochs and staged according to the standard criteria of Rechtschaffen and Kales.[8] Arousals were scored according to accepted definitions.[9] Apneas were defined as complete cessation of airflow ≥10 s. Hypopneas were defined as reduction of >50% in airflow signal with a fall of ≥3% in oxygen saturation or an arousal. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Patients with AHI<5 were included in control group.

STATISTICAL ANALYSIS

Statistical package SPSS 10.0 for Windows was used to perform the statistical analysis. Descriptive statistics were generated for all variables. Continuous variables are demonstrated as mean ± SD for normally distributed and as median (minimum-maximum) for non-normally distributed variables. Categorical variables are given as percentages. Categorical variables were compared with Chi-square test, normally distributed numeric variables were compared with independent samples student t test and analysis of variance (ANOVA). Non-normally distributed variables were compared with Mann Whitney U test. Correlations were tested with Pearson and Spearman correlation tests. A p value <0.05 was considered as statistically significant.

RESULTS

A total of 64 OSAS patients (mean age: 52.2±9.8 years) and 32 control subjects (mean age: 52.1±9.0 years) were included in the study. Baseline characteristics of the patients and the control group are

shown in Table 1. There were no significant differences with respect to sex and age. No patient and control subject had diabetes, chronic obstructive pulmonary disease. Fourteen percent of OSAS patients (9/64) and 12.5% of control subjects (4/32) were hypertensive, and were using antihypertensive medications. All hypertensive patients had well- controlled hypertension. There was no statistically significant difference between OSAS patients and control subjects with regard to hypertension or antihypertensive medications. The AHI was calculated as the number of apneas and hypopneas per hour of sleep. It was found to be significantly increased in OSAS patients compared to the control subjects (28.8±23.2 vs 0.9±0.2, p<0.001). Mean O_2 saturation was significantly decreased in OSAS patients compared to the control subjects (90.3±3.2 vs 94.6±2.1, p<0.001). In all subjects, central corneal thickness was measured and it was found in normal limits (522 μm-563 μm) in all subjects.

Seven (10.9%) patients had glaucoma among patients with OSAS. One of these patients had POAG and the rest (six patients) had NTG. No subjects had glaucoma in the control group. Ocular parameters in patients and control subjects are listed in Table 2 and ocular parameters in glaucoma patients are listed in Table 3. Average and quadrant RNFLT measurements were compared between the two study groups in Table 2. Inferior quadrant was significantly different between the two groups. MD was significantly lower in OSAS patients compared to control subjects. PSD was significantly higher in OSAS patients.

Twenty one patients were in the mild group, 21 patients were in the moderate group and 22 patients were in the severe group for OSAS. There was no statistically significant difference in these three groups according to age, gender or BMI distribution (p>0.05). The demographic characteristics of these three groups are shown in Table 4. One of seven patients diagnosed as glaucoma were classified as mild OSAS, one patient was classified as moderate OSAS and five patients were classified as severe OSAS. It is interesting to note that most of these glaucoma patients were in the severe OSAS group. There was a negative correlation between AHI and RNFLT (r=-0.329, p<0.001 and r=-0.266, p=0.002) or MD (r=-0.283, p<0.001).

DISCUSSION

Obstructive sleep apnea is a risk factor for cardiovascular and neurovascular diseases.[10] During sleep, repetitive episodes of airway occlusion with consequent hypoxemia, hypercapnia and changes in intrathoracic pressure elicit changes in the autonomic, hemodynamic, humoral, and neuroendocrine responses that can affect the circulation of the optic nerve with loss of ganglion cells.[11]

In this study, we measured diurnal intraocular pressure and evaluated other glaucoma parameters such as RNFLT and visual field including blue-on-yellow perimetry in OSAS patients, and compared those with OSAS (-) subjects. This study demonstrated that OSAS patients have a tendency to develop glaucoma. Glaucoma in relation with OSAS was first reported by Walsh and Montplaisir.[12] Recently, two reports studying the floppy eyelid syndrome in OSAS suggested an association between glaucoma and OSAS.[13,14]

TABLE 1: Baseline characteristics of the patients.

Characteristic	OSAS (n= 64)	Control (n=32)	p value
Age (mean ±SD) (years)	52.2±9.8 38/26(59/41%)	52.1±9.0 18/14(56/44%)	0.988
Male/female (%)	30.7±5.8	26.7±2.8	0.148
BMI (kg/m²)	28.8±23.2	0.9±0.2	0.002
AHI (mean± SD)	90.3±3.2	94.6±2.1	<0.001
Mean SaO_2	9(14 %)	4(12.5%)	<0.001
Hypertension			0.552

OSAS: Obstructive sleep apnea syndrome; BMI: Body mass index; AHI: Apnea-hypopnea index.

TABLE 2: Comparison of ocular parameters between OSAS patients and the control group.

	OSAS Group (n=64)	Control Group (n=32)	p value
MD (dB)	-1.66±2.24	-0.41±0.68	<0.001
PSD (dB)	2.52±1.81	1.74±0.67	<0.001
RNFLT (OCT average) µm	102.14±9.32	105.76±5.17	0.077
RNFLT (OCT superior) µm	118.28±11.04	120.15±9.12	0.102
RNFLT (OCT inferior) µm	112.65±10.78	122.68±10.76	0.001
RNFLT (OCT temporal) µm	86.45±11.09	87.87±8.76	0.366
RNFLT (OCT nasal) µm	91.18±9.63	92.34±7.22	0.453
IOP(median;range) (mmHg)	17.00 (14-27)	16.50(14-22)	0.233
Visual Acuity (LogMAR)	0.017±0.002	0.008±0.001	0.112
CCT (µm)	549.78±40.23	554.53±32.26	0.744

OSAS: Obstructive sleep apnea syndrome; MD: Mean deviation; PSD: Pattern standard deviation; RNFLT: Retinal nerve fiber layer thickness; OCT: Optical Coherence Tomography; IOP: Intraocular pressure; CCT: Central corneal thickness.

TABLE 3: Ocular parameters in glaucoma patients.

Case No	Glaucoma Type	MD (dB)	PSD (dB)	Average RNFLT (OCT) (µm)	IOP (mmHg)	Severity of OSAS
7	NTG	-3.49	3.53	82.25	16.83	Severe
33	NTG	-6.54	4.87	81.75	15.67	Severe
48	POAG	-5.34	4.34	79.50	23.67	Mild
55	NTG	-8.77	6.12	78.75	15.83	Severe
57	NTG	-5.97	5.46	81.25	17.00	Severe
60	NTG	-10.3	8.45	76.50	16.33	Moderate
63	NTG	-7.61	6.56	75.75	18.67	Severe

POAG: Primary open angle glaucoma; NTG: Normal tension glaucoma; MD: Mean deviation; PSD: Pattern standard deviation; RNFLT: Retinal nerve fiber layer thickness; OCT: Optical Coherence Tomography; IOP: Intraocular pressure; OSAS: Obstructive sleep apnea syndrome.

TABLE 4: Distribution of patients according to the severity of OSAS and demographic characteristics.

	Mild OSAS Group (n=21)	Moderate OSAS Group (n=21)	Severe OSAS Group (n=22)	p
Age years (mean.±SD)	51.8±12.0	54.2±7.9	54.4±7.6	0.055
Gender (male/female) %	11/10 (52.4-47.6%)	7/14 (33.3-66.7%)	8/14 (36.4-63.6%)	0.400
BMI (mean±SD)	30.8 ± 7.3	28.7 ± 4.5	32.5 ± 4.7	0.097

OSAS: Obstructive sleep apnea syndrome; BMI: Body mass index.

Current studies showed that OSAS was associated with glaucoma and it may be a risk factor for glaucoma.[15-17] The prevalence of glaucoma in the OSAS populations has been investigated in several studies and glaucoma prevalence was found between 3.3% and 27%.[11,18-21] In our study, seven of 64 patients with OSAS (10.9%) had glaucoma, while no patients in the control group had glaucoma. One of these patients had POAG and the rest (six patients) had NTG. The present study suggests that the prevalence of NTG in OSAS patients is higher than expected in a population at the same age, and that OSAS may be a more important risk factor for NTG rather than POAG. Diurnal IOP measurements were not performed in any of the previous studies investigating the relationship between OSAS and glaucoma, as it has been done in our study. Glaucoma can be assessed by measuring intraocular pressure, RNFLT, visual field and changes in the optic nerve head.

In glaucoma, RNFLT decreases progressively. This thinning can be present in the eyes of the patients with glaucoma before detectable changes occur in the visual field.[22,23] If a decrease in the RNFLT can be reliably detected, the clinician may be alerted for the risk of developing glaucoma. To the best of our knowledge, there is only one report evaluating RNFLT in patients with OSAS. Kargi et al. have demonstrated that sleep apnea syndrome is correlated with a proportional decrease in the RNFLT.[24] In our study, we detected a moderate correlation between AHI and RNFLT measurements. It may be suggested that diurnal IOP measurement, blue-on-yellow visual field test, RNLFT measurement, and regular follow up are important for OSAS patients suspected of glaucoma. In addition, most of patients with glaucoma were classified as severe OSAS and it can be suggested that AHI is an important factor for glaucomatous changes, as it leads to decreased oxygen saturation.

Batisse et al. found visual field alterations on blue-on-yellow computerized perimetry that were not apparent on standard perimetry. The visual field defects were more frequent when the respiratory disturbance index was high.[25] In our study, we also performed blue-on-yellow computerized perimetry in patients who had glaucomatous optic disc changes on normal standard automated perimetry. Blue-on-yellow computerized perimetry was performed in 22 patients. Five of 22 patients were detected to have glaucomatous visual field defects.

In addition to elevated IOP, vascular and other pathogenic mechanisms have been considered to result in glaucomatous optic nerve damage.[15,26] The ventilatory drive caused by hypoxia and hypercapnia reduces in sleeping state in a patient with OSAS. This causes a decrease in pO_2 and an increase in pCO_2.[27] Hypoxemia brings about increased vascular resistance via increased levels of the vasoconstrictor endothelin production and decreased levels of vasodilator nitric oxide production.[28,29] The endothelium-mediated vasoconstrictor and vasodilator balance is remarkably damaged in a patients with OSAS. Vasodilator response is remarkably decreased. The loss of ganglion cells caused by the hypoxia in some way secondary to this OSAS-induced imbalance between nitric oxide and endothelin results in optic disc damage.[28-30] Increased vascular resistance in patients with OSAS may impair perfusion and oxygenation of the optic nerve head.

Nocturnal vascular changes caused by OSAS may be the cause of RNFLT thinning and glaucomatous optic nerve damage. Increased intracranial pressure during sleep and decreased cerebral perfusion pressure indirectly caused by hypoxia may disturb the blood supply of the optic nerve in patients with OSAS.[31-34] Vascular disturbances may result in diffuse loss or localized defects of the RNFLT before initation of glaucoma.[35]

In conclusion, in this study we found that patients with OSAS have a tendency to develop glaucoma. These patients must be followed regularly for glaucoma development and progression.

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