Retinal evaluation by optical coherence tomography in adults with obstructive sleep apnea syndrome

Subtitle: OCT in OSAHS

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Abstract

Objective: to assess the peripapillary retinal nerve fiber layer (RNFL) thickness, optic nerve head (ONH) morphologic parameters, and macular thickness and volume in patients affected by obstructive sleep apnea-hypopnea syndrome (OSAHS).

Methods: the prospective, observational, case-control study consisted of ninety-six eyes of OSAHS patients (mean age 50.9±12.4 years, best corrected visual acuity ≥20/20, refractive error less than three spherocylindrical diopters, and intraocular pressure <21mmHg) who were enrolled and compared with sixty-four eyes of age-matched controls. ONH parameters, RNFL thickness, macular thickness and volume were measured by optical coherence tomography (OCT).

Results: OSAHS patients showed a significant reduction of the nasal quadrant RNFL thickness (74.7±15.8 µm) compared with those values observed in control patients (81.1±16.6µm, p=0.047, t-student test). No differences in peripapillary RNFL thickness were observed when dividing the OSAHS group in accordance with the severity. Vertical integrated rim area (VIRA) (p=0.043), horizontal integrated rim width (HIRW) (p=0.039) and disc area (p=0.002) showed significant differences, being all of them higher in OSAHS group. Severe OSAHS had significant higher VIRA value comparing to controls (p=0.016). Temporal inner macular thickness was significantly higher in mild-moderate OSAHS patients compared severe OSAHS patients (p=0.021).

Conclusions: OSAHS patients showed decreased peripapillary nasal RNFL thickness and increase in ONH area and volume parameters when they were evaluated by OCT. These findings suggest that neuronal degeneration might be present in the retina of OSAHS patients as previously observed in some neurodegenerative disorders.

Key words: Macular volume; optical coherence tomography; OCT; retinal nerve fiber layer thickness; obstructive sleep apnea syndrome; OSAHS.

Introduction

Obstructive sleep apnea syndrome (OSAHS) is part of a broad group of disorders known as “sleep related breathing disorders”. OSAHS is characterized by brief episodes of complete or partial upper airway collapse during sleep, causing an increased thoraco-abdominal effort and a decreased arterial oxygen saturation, leading to an arousal response[1] which take the form of apneas and periodic hypopneas during sleep. This produces an excessive daytime sleepiness. There are many evidences that local and systemic inflammation play an important role in the pathogenesis of OSAHS, contributing to anatomic narrowing of the upper airway, increased collapsibility of the airway tissues, abnormalities in reflexes that affect upper respiratory tract caliber and pharyngeal inspiratory muscle function[2].

OSAHS has recently been associated with numerous ophthalmological disorders, such as floppy eyelid syndrome, visual field defects, retinal vein occlusion, central serous chorioretinopathy, and certain optic nerve dysfunctions[3]. Thus, papilledema and increased intracranial pressure, have been reported in OSAHS patients[4, 5], improving after continuous positive airway pressure (CPAP) treatment [6,7]. Non-arteritic anterior ischemic optic neuropathy has also been described to be associated with OSAHS[8]. Likewise, an increased incidence of glaucoma in OSAHS patients is assumed[9-11]. Nevertheless, the pathogenesis of optic disc damage in OSAHS is complex and remains unknown. Frequent episodes of nocturnal hypoxemia would compromise optic nerve perfusion and oxygenation, leading to optic neuropathy[12]. Clinical features of OSAHS have inspired studies about brain structural abnormalities in this disease. Magnetic resonance imaging studies have reported a loss of gray and white matter in certain brain areas, suggesting a premature degeneration of the Central Nervous System in patients suffering from OSAHS[13,14].

Optical coherence tomography (OCT), a relatively new noninvasive imaging technique, provides reproducible, high-resolution cross-sectional imaging of the retinal nerve fiber layer (RNFL) and optic nerve head (ONH) topography, providing an objective tool to diagnose axonal damage. OCT is used in various ophthalmological disorders including glaucoma[15] and macular diseases[16]. Likewise, a significant reduction in the peripapillary RNFL thickness has been reported in patients with various neurologic disorders[17], such as multiple sclerosis[18,19], Alzheimer´s disease[20,21], Parkinson´s disease[22,23] and schizophrenia[24], suggesting that this technology might also prove useful in other neurodegenerative diseases. Recently, a decreased RNFL thickness measured with OCT has been found in patients with moderate/severe OSAHS[25].

The goals of our study were to determine, by using OCT, the differences in the ONH parameters, peripapillary RNFL thickness, macular thickness and volume between OSAHS patients and control subjects, as well as to assess whether a correlation exists between the OCT measurements and the clinical severity of the disease. The research followed the tenets of the Declaration of Helsinki, and the protocol was approved by the local ethics committee.

Material and methods

Ninety-six eyes from 50 patients (41 males and 9 females) with OSAHS were consecutively recruited in the department of Otolaryngology at the Miguel Servet University Hospital in Zaragoza, Spain. The selected patients have a newly discovered and previously untreated mild to severe OSAHS diagnosed according to clinical features and an apnea-hypopnea index (AHI), greater than 4. Before OSAHS was confirmed, the patients completed a questionnaire concerning epidemiological data (age, height, weight, co-morbidities, smoking, previous treatment and past surgeries) and information about symptoms such as loud snoring, observed apnea, or excessive

daytime sleepiness. The most common vascular risk factors, hypertension, diabetes and hyperlipidaemia were studied and treated if necessary. All smoker OSAHS patients were encouraged to stop the habit. After appropriate information, written informed consent of all subjects was obtained.

Every OSAHS patient was diagnosed with a full sleep study during an entire attended night. This investigation consisted of continuous polygraphic recording of two electroencephalographic leads; right and left electro-oculographic leads; and chin electromyography for sleep staging. Ribcage and abdominal motion were monitored by inductive plethysmography (Alice 4, Philips, Eindhoven, Holland), airflow by thermistor (Ambulatory monitoring, Ardsley, NY, USA), and arterial oxyhaemoglobin saturation by finger pulse oximetry (Ohmeda Biox 3700, Ohmeda, Boulder, CO, USA). Sleepstage scoring was done for 30-s intervals by trained technicians according to standard criteria[26]. Apnea was defined as the complete cessation of airflow, and hypopnea as a discernible reduction in airflow or thoracoabdominal excursion lasting for 10 s or more, accompanied by a decrease in oxygen saturation of at least 4%. AHI was defined as the total number of apneas and hypopneas per hour during sleep. In patients with a confirmed diagnosis, an individualized multidisciplinary treatment was initiated according to the sleep study, the severity of clinical symptoms and signs, the exploration of the superior airway and the wishes of the patient[27].

The control group was formed by sixty-four eyes of 33 age-matched healthy control subjects (19 males and 14 females) who were recruited from the Department of Ophthalmology at the Lozano Blesa University Clinic Hospital in Zaragoza, Spain. The same epidemiological data as in cases group were collected. Tabaquism and vascular risk factors were treated in the same way.

Patients and controls were subsequently referred for a comprehensive ophthalmological examination at the ophthalmologic department at “Lozano Blesa”

University Clinic Hospital from December 2010 to December 2011. Patients who had a history of stroke with central apnea, chronic uveitis, glaucoma, optic neuropathy, and previous ocular trauma or surgeries were excluded from this study.

All OSAHS patients and control subjects underwent a complete ophthalmologic examination, including assessment of best-corrected visual acuity (BCVA), ocular motility, pupillary reflexes, slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, automated visual field examination and dilated fundus examination. The examiners were masked to the diagnosis. All participants had a BCVA of 20/20 or better with a refractive error lower than 3 spherical diopters and 2 diopters of astigmatism. Eyes with visual field defects compatible with glaucoma, posterior pole pathology such as macular degeneration or diabetic retinopathy, or patients with media opacification such as cataract or vitreous hemorrhage, that prevented ocular and OCT examination, were excluded.

OCT was performed with the Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) following 1% tropicamide instillation for dilation of the pupils. Only high-quality images (signal strength ≥ 7) were included. Each patient underwent scans to measure peripapillary RNFL thickness, ONH parameters, and macular thickness and volume at the same visit. Peripapillary RNFL thickness was automatically calculated by the fast RNFL algorithm. Three 360º circular scans with a diameter of 3.4 mm centered on the optic disc were performed. The software allows the mapping of the thickness data according to both quadrant-by-quadrant and a clock hour analyses. We considered the average values of three different measurements per quadrant (superior, inferior, nasal and temporal): the overall data obtained in all quadrants were identified as overall RNFL thickness. ONH measurements were obtained by the fast optical disc scanning protocol, which consists of six radial scans centered on the ONH. ONH parameters were automatically calculated, including vertical integrated rim area (VIRA, measurement of neurorretinal rim volume, in mm^3), horizontal integrated rim width

(HIRW, measurement of neurorretinal rim area, in mm^2), disc area, cup/disc area ratio, horizontal cup/ disc ratio, and vertical cup/disc ratio. Macular thickness measurements were obtained by the fast macular thickness protocol, which consists of six radial scans (each 6 mm) in a spoke-like pattern centered on the fovea, with each radial scan spaced 30º apart. To fill the gaps between scans, the OCT uses interpolation. Stratus OCT software calculates retinal thickness as the distance between the first signal from the vitreoretinal interface and the signal from the anterior boundary of the retinal pigment epithelium. The map is composed of nine sectorial thickness measurements in three concentric circles with diameters of 1 mm, 3 mm, and 6 mm. The area bounded by the outer (6-mm) and middle (3-mm) circles forms the outer ring, and the area bounded by the middle (3-mm) and inner circles (1-mm) forms the inner ring. The central 1-mm circular region represents the foveal area. Total average macular thickness, average macular thicknesses in the inner (1-3 mm) and outer (3-6mm) rings, and the central 1-mm fovea thickness were analyzed in the study. Total macular volume was calculated automatically by the OCT software (figure 1).

Statistical analysis

Data analysis was conducted using SPSS software version 19.0 (SPSS, Inc, Chicago, IL, USA). Values were presented as mean ± standard deviation (SD) and expressed in microns (µm) for the peripapillary RNFL thickness and macular retinal thickness, and in mm^3 for macular volume. Qualitative differences between the study variables were assessed using Pearson's chi-squared test. The relationship between AHI and ophthalmologic significant variables was evaluated using Pearson's correlation coefficient. A p value < 0.05 was considered statistically significant.

We conducted two separate analyses. In the first one, mean values of the studied variables obtained in all OSAHS patients were compared with those obtained in the

control group (only taking into account the presence of OSAHS, regardless of severity), the two-sample t-Student test was used for determining whether the values of a particular quantitative variable differ between OSAHS and the control eyes.

In the second analysis, the OSAHS patients sample was divided according to the severity of OSAHS (measured by AHI) into two groups: those with mild-moderate OSAHS (Group 1, AHI ≥ 5 and < 30); and those with severe OSAHS (Group 2, AHI≥ 30). Quantitative differences between the studied variables in the three groups were compared using one way ANOVA test. Post-hoc analyses with Bonferroni adjustments were performed. We joined mild and moderate OSAHS patients assuming that severe OSAHS patients would show more differences when compared with the control group.

Results

Three of 86 people (3.5 %) did not fulfill the quality criteria for OCT. Finally, 83 individuals were included in the analisys, including 50 OSAHS and 33 healthy individuals, demographic data are summarized in table 1. Both eyes of each patient were included, except when an exclusion criteria appeared in one eye, assuming that OSAHS influence could be asimetric [28, 29]. Age showed no statistically significant difference between both groups (p=0.401, t-student test). In both groups, more men than women were enrolled, although the difference was statistically significant (p<0.05; chi-square test), gender has no effect on RNFL evaluation as previously mentioned [30]. BCVA was similar in both groups (p= 0.577). No significant differences in vascular risk factors and incidence of tabaquism among controls and cases were found (chi-square test).Table 2 summarizes polysomnographic data in OSAHS patients according severity.

1st analysis: OCT parameters in OSAHS patients versus non-OSAHS individuals

Table 3 shows the results of ONH analysis, demonstrating that VIRA, HIRW and disc area are higher in OSAHS group than those in controls. These differences were statistically significant ($p< 0.05$, t-student test). Table 4 shows a comparison between IOP, macular volume and thickness and peripapillary RNFL thickness in both groups. IOP was higher in the OSAHS group than in controls ($p< 0.001$, t-student test). Only the nasal quadrant of the peripapillary RNFL showed a statistically significant reduced thickness in OSAHS patients (74.7 µm +/- 15.8), compared with that in the control subjects (81.1 µm +/- 16.6) ($p= 0.016$, t-student test). No statistically significant differences were observed regarding the macular volume or thickness (t-student test). AHI and desaturation index showed no correlation with none of the studied parameters.

2nd analysis: OCT parameters in mild-moderate OSAHS versus severe OSAHS patients.

When dividing the OSAHS sample according to severity, age showed no statistically significant difference between the following pairs: controls (49.1 years +/- 14.3) / mild-moderate OSAHS (50.7 +/- 14.0) ($p> 0.05$, ANOVA test); controls/ severe OSAHS (51.0 ± 11.5) ($p >0.05$, ANOVA test); mild-moderate OSAHS/severe OSAHS ($p>0.05$, ANOVA test).

Severe OSAHS eyes showed statistically significant higher VIRA values than compared with the control group ($p= 0.016$, ANOVA test) (table 5). Mean values of IOP, macular thickness and volume in OSAHS subjects, classified according to IAH, are shown in Table 6. No differences in IOP were found among the three groups. Temporal inner macular thickness was significantly higher in mild-moderate OSAHS patients compared to severe OSAHS. No differences in peripapillary RNFL among the three groups were observed. Only the nasal quadrant in severe OSAHS showed a

decrease close to a statistically significant p value when comparing with controls (p = 0.057).

We found no correlation between IAH and desaturation index and the parameters when the OSAHS group was divided according to severity.

Discussion

During sleep, episodes of apnea with consequent drop in oxygen saturation leads to the activation of the adrenergic system, proinflammatory mechanisms, endothelial dysfunction, oxidative stress, procoagulant mechanisms and metabolic deregulation [31]. There is some evidences that OSAHS is a risk factor for neurovascular and cardiovascular diseases. Arterial hypertension, cardiac arrhythmia and/or ischemia, congestive heart failure and cerebrovascular disease are events more likely in the presence of the obstructive sleep disturbance [32,33]. This vascular phenomenon may in turn compromise optic nerve perfusion and oxygenation, ultimately leading to optic neuropathy.

Several authors have reported a higher prevalence of glaucomatous neuropathy in OSAHS patients [9,11], characterized by increased size of the optic disc cup and associated thinning of RNFL. Moreover, some authors have reported a significant presence of visual field (VF) defects in patients with OSAHS, even with an improvement of VF defects following treatment with CPAP in one OSAHS patient [34, 35]. This glaucomatous functional loss is thought to be preceded by thinning of RNFL in some years [36]. Thus, the first quantifiable sign of glaucomatous neuropathy in OSAHS patients is an axonal loss measured by OCT. In our study, we just included patients with normal IOP (less than 22 mmHg), normal gonioscopy and no perimetric evidence of glaucomatous neuropathy, in order to assess an hypothetical reduction of peripapillary RNFL thickness due to the alterations produced by the respiratory disorder. Our results show a significant decreased thickness in the nasal quadrant of

the RNFL in the OSAHS group, which is compatible with previous studies[12,25]. Nevertheless, this result was not confirmed when dividing the sample in subgroups, although severe OSAHS group show a “p” value close to significant value. Therefore, it is possible that an increase in the sample size might lead to a significant difference, suggesting that the presence of OSAHS would mean a risk factor for RNFL alterations. Measurement of peripapillary RNFL thickness reflects neuronal axons and would allow quantification of ganglion cell axonal loss. In the macula, the measurement of thickness and volume would reflect neurons, including bodies of retinal ganglion cells, and allowing quantification of neuronal loss. Retinal ganglion cells have been reported to be particularly sensitive to mild systemic hypoxic stress [37]. Thus, in hypoxic conditions cell death has been classified as apoptotic or necrotic. The last one presents swelling of cell body, disruption of plasma membrane and alterations in nuclear DNA [38]. It is possible that this nuclear swelling could induce an increased macular thickness preceding atrophy secondary to neurons death (reflected as a decreased peripapillary RNFL thickness). In our results, temporal inner macular thickness was significantly higher in mild-moderate OSAHS patients compared to severe OSAHS and controls. This fact would support the attractive hypothesis that a previous inflammatory edema, with increase in macular thickness, expression of VEGF, nitric oxide and other proinflammatory mediators, might precede in early stages of OSAHS to a final stage with loss of neuronal population and subsequent functional repercussion.

The significant increase in morphological ONH parameters (VIRA, HIRW and disc area) in OSAHS patients compared with those in controls, especially VIRA in severe patients (p= 0.016), might be justified by a hypothetical and slight optic nerve swelling caused by intracranial vascular dysfunction. Purvin et al. analyzed the relationship between intracranial pressure, papilledema and OSAHS. They suggested episodic hypoxia and hypercapnia as cause of papilledema in the OSAHS, which would be secondary to cerebral vasodilation phenomenon[4]. It seems that frequent changes in

the oxygenation of OSAHS patients would induce vascular problems in cerebral autoregulation, which might imply changes in intracranial volume due to vasodilation and increased brain water content[5]. Likewise, Lee et al. found an improvement of idiopathic intracranial hypertension (IIH) when nocturnal oxygenation treatment was established [6]. O'Donoghue et al.[7] reported a 4% decrease in total brain volume following treatment with positive pressure nocturnal oxygen in patients with OSAHS. The perpetuation of nerve fiber layer swelling could lead to a nerve fiber loss with the consequent thinning of RNFL as the disease progresses, this would be consistent with the RNFL nasal quadrant thinning observed in severe OSAHS group. Future studies comparing the RNFL thickness before and after treatment of sleep apnea might add more information on this point.

One of the major limitations of the present study is the relatively small sample size, mainly when OSAHS patients were divided regarding their severity. Moreover, a referral bias could be present because patients were referred for sleep disorder and, therefore, they might not be representative of the entire OSAHS population, mostly undiagnosed, and we were not able to determine the exact duration of the respiratory disease. It is possible that greater severity and longer duration of the hypoxia in SAOS will cause greater RNFL alterations.

In conclusion, changes in OCT parameters founded in OSAHS patients compared to healthy controls can suppose a new non-invasive tool to diagnose and classify OSAHS patients. Future studies would be useful to determine the usefulness of OCT as a biomarker of OSAHS syndrome.

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