Ricardo AMORIM

Hospital Santa Maria, LISBOA – **PORTUGAL**

★ RESUME ★

Ricardo Bastos Amorim, MD was born August 16th, 1983 in Santa Maria da Feira, Portugal. He was licensed in medicine from the University of Porto. He is currently a third year resident in Hospital Santa Maria, Lisbon. Participated in thirty-six courses and twenty-seven national and international scientific conferences.

Author and co-author of twenty-nine scientific works, with a national and an international award. He is also a committee member of the Portuguese Society Young Ophthalmologists.

OCULAR INJURY IN A SLEEP DISORDER

★ INTRODUCTION ★

During sleep, alterations occur in cardiovascular physiology that is balanced by autoregulation to maintain homeostasis. In Obstructive Sleep Apnea (OSA), the normal physiological balance is upset, leading to hypoxia and sympathetic activation. In recent years OSA is being investigated as a risk factor in the development of glaucoma1-6,9,11.

In the treatment with long-term ocular drugs as in glaucoma patients, ocular surface disease could appear due to the potential preservative toxicity that frequently causes tear film and conjunctival involvement 17-21. However, this is a multifactorial disease that could be associated with other factors 16.

The following case report describes a patient who developed ocular surface disease after treatment of glaucoma and sleep apnea.

★ CASE REPORT ★

A 68-years-old white male comes to our hospital for an ophthalmic examination routine. He has had medical history of hypertension, dyslipidemia, obesity and an episode of trombophlebitis 5 years ago. He was medicated with simvastatin 20mg id, clopidogrel id, enalapril 10mg id and lansoprazol 30mg id.
At our exam, the best corrected visual acuities (VA) were 90/100 in both eyes (OU). Pupils were equal, round and reactive to light, without any relative afferent defect. Motility examination showed no limitation, with full ductions and versions presented, without diplopia.
Slit lamp microscopy revealed a clear cornea OU, without evidences of alterations in the anterior chamber. Examination upon pharmacological dilation revealed a bilateral mild nuclear lens sclerosis; macula and peripheral retina were healthy in both eyes without evidences of disease. The optic nerves had a cup-to-disc ratio of 0.70 OU with vertical elongation and an inferior notch was identified in both optic nerves, alpha and beta peripapillar atrophy was also recorded on our exam (Fig. 1 and 2). Gonioscopy revealed open angles bilaterally (grade IV of Shaffer).
Intra ocular pressures by Goldmann applanation tonometry measured 12mmHg OU. Central corneal thickness was 516 µm in right eye (OD) and 508 µm in left eye (OS), measured by ultrasonic paquimetry.

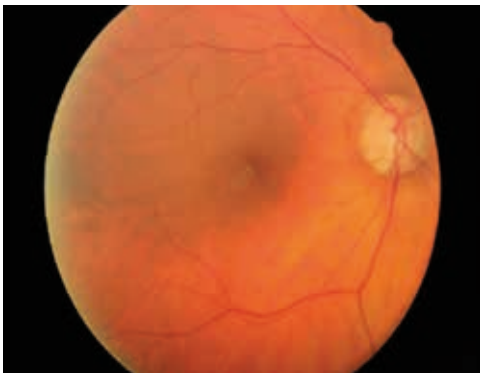


Fig. 1 – Right optic nerve head

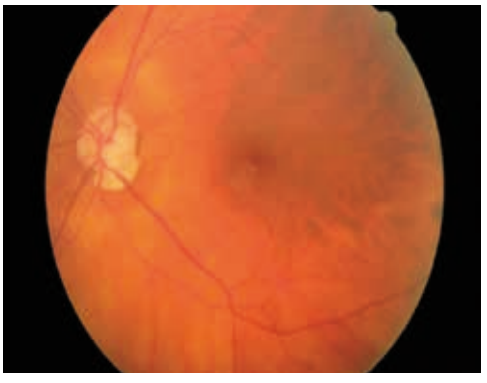


Fig. 2 – Left optic nerve head

The patient was instructed to return for an Optical Coherence Tomography – Heidelberg Spectralis® (OCT) and a threshold visual field (VF) – 101 OCTOPUS® (both performed 2 weeks later).

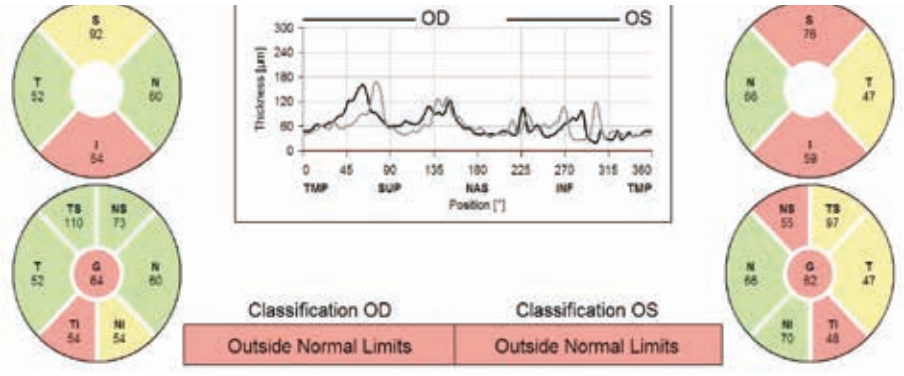
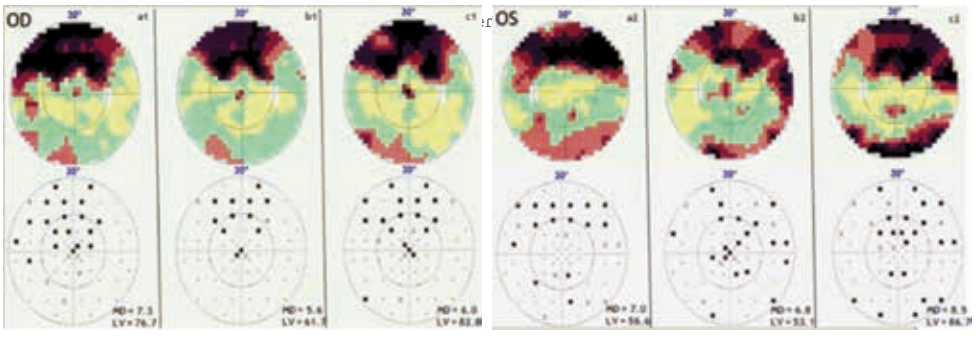


Fig 3 – Optical Coherence Tomography of both eyes.

The OCT revealed a nerve fiber layer loss in the inferior sector in OD and in OS a diminished fiber layer was noticed in the supero-inferior sectors. the average nerve fiber layer thickness was reduced in both eyes, OD – 64 µm and OS – 62 µm (Fig. 3).

The 1st visual field (Fig. 4a) showed loss of peripheral vision, demonstrating delineation of a superior arcuate scotoma in OU and possible defects closer to fixation in OD (good reliability; OD: MD 7.3 / LV 76.7 and OS: MD 7.0 LV 56.6). He repeated the visual field (Fig. 4b) 5 months after the 1st consult that confirmed the superior arcuate scotomas OU with defects near fixation point (good reliability; OD: MD 5.6 / LV 61.7 and OS: MD 6.8 LV 53.1). After the 2nd VF we decided to prescribe topical dorzolamide 2id OU.

Based on the previous findings, we initiated a work-up for Normo-Tensional Glaucoma (NTG) in this patient. We first obtained a diurnal curve to rule out possible pressure spikes occurring during the day. Intraocular pressures during the curve ranged from 10 mmHg to 12 mm Hg OU. The patient also underwent a magnetic resonance imaging of the brain, which was normal. His blood work for complete blood count, rheumatoid factor, erythrocyte sedimentation rate, anti-nuclear antibody, and syphilis was normal.



We performed a third visual field (Fig. 4c) 6 months later, that showed progression in the visual field defects, with a superior arcuate scotoma OU and a probable delineation of inferior scotoma OS with visual fields defects detected closer to fixation in both eyes (good reliability; OD: MD 6.0 / LV 82.8 and OS: MD 8.5 LV 86.7).
We referred the patient for a sleep study because his wife was complaining of loud snoring of the patient and restless sleep throughout the night. The sleep study revealed moderate obstructive sleep apnea with prolonged periods of decreased oxygen saturation, with an apnea-hypopnea index (AHI) of 28.5 in supine position v(Fig. 5).

Events

	Code	Index (#/hour)	Total Number of Events	Mean duration (sec)	Max duration (sec)	Events by Position	
						Supine (#)	Non-Supine (#)
Central Apneas	CA	0.9	3	12.5	15.5	0	3
Obstructive Apneas	OA	17.3	55	25.5	70	53	2
Mixed Apneas	MA	0	0	0	0	0	0
Hypopneas	HY	6.3	20	23.1	51	19	1
Total		24.5	78	24.4	70		
					Time in Position	151.6	39.4
					AHI in Position	28.5	9.1

Fig 5 – Sleep Apnea Study (Table of Events)

He was started on Continuous Positive Airway Pressure (CPAP) and was reportedly sleeping better. A visual field was performed 5 months after starting CPAP treatment showed a relative improvement in visual fields in both eyes (OD: MD 5.5 / LV 69.0; OS: MD 5.8 / LV 56.5) with a possible partial recovery in the inferior scotoma OS.

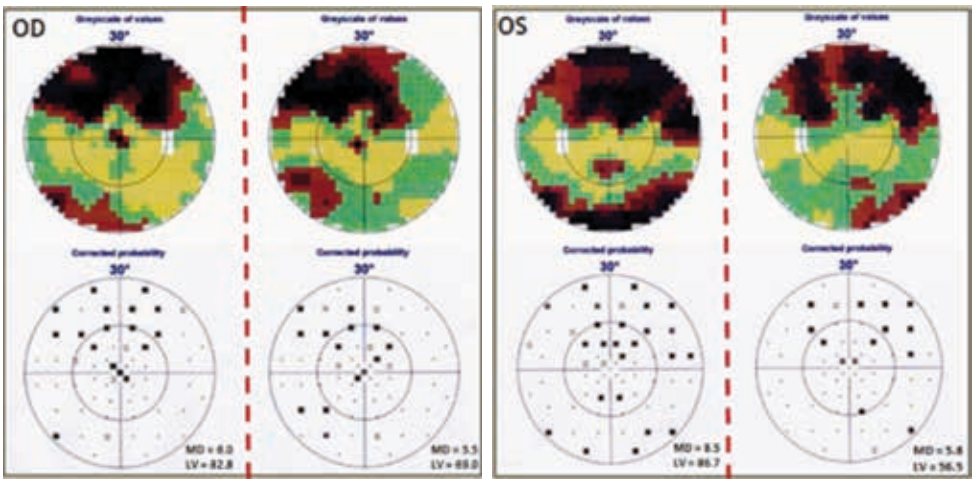


Fig 6) Visual fields - before CPAP treatment and 5 months after CPAP treatment.

A few weeks later, the patient returned to our office with complains of "red eye" and foreign body sensation, without relief during the day. We performed a new ophthalmologic observation exam and we noticed conjuntival hyperemia (Fig. 7), and mild punctuate bilateral queratitis with a tear break-up time (BUT) reduced to 4 seconds (Fig. 8). The remaining ophthalmic examination was similar to previous observations.

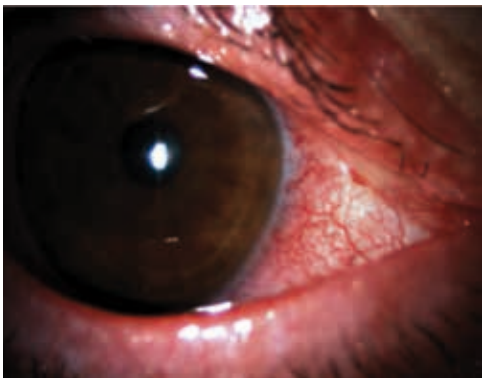


Fig 7 - Conjuntival hyperemia

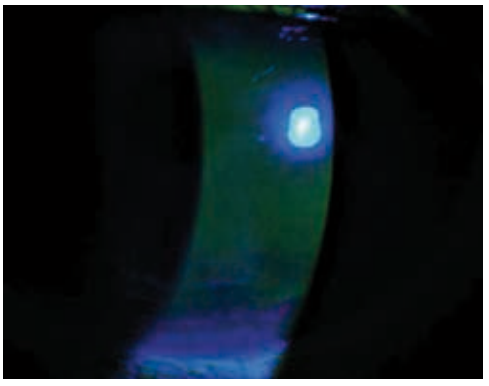


Fig 8 - mild punctuate queratitis

We decided to give him preservative-free lubricants and refer him to a technician for adjustements in CPAP mask. We also change the medication for a prostaglandin preservatives-free for a better compliance and symptoms relief. We reevaluate him 2 months later and we noticed an improvement in the cornea healing with a very few punctuate defects, however a mild hyperemia persisted.

★ DISCUSSION ★

Glaucoma & Sleep Apnea

A possible connection between glaucoma and OSA was first described in 1982 (by Walsh et al) and after that, numerous studies had been perfomed. The prevalence of glaucoma in individuals with sleep apnea was reported to be from 5,7% to 27%.1-2.4-6,11 Several studies have identified OSA in patients with glaucomatous optic disc cupping and associated visual field defects who do not respond to medical or surgical IOP-lowering treatments, but whose visual fields stabilize when treated with CPAP 1,6.

In 1999 Mojon et al. reported the prevalence of glaucoma [both primary open angle (POAG) + NTG] among 69 patients with obstructive sleep apnea to be 7.2%. One year later, Mojon reported the prevalence of "abnormal" overnight oxygen levels to be higher among 30 patients with primary open angle glaucoma (20%) compared to controls (11%) 14.

In 2002 Mojon et al. reported the prevalence of OSA among their patients with normotensive glaucoma to be 44%. They stated that their study only demonstrated an association between NTG and OSA, but did not provide any indication of the mechanism 15. There have been a few theories as to how obstructive sleep apnea could possibly cause (or contribute to) glaucoma 1, 9:

1) Obstructive sleep apnea results in impaired vascular autoregulation of the optic nerve's circulation.
2) Obstructive sleep apnea induces arteriosclerosis and arterial hypertension, which in turn induce optic nerve vascular "dysregulation".
3) Repetitive hypoxia directly damages the optic nerve.
4) Obstructive sleep apnea causes an imbalance between nitric oxide and endothelin (vasodilatory and vasoconstrictive factors), which in turn results in normotensive glaucoma.
In Waller et al. study of 100 patients with obstructive sleep apnea, they found the prevalence of glaucoma (POAG or NTG) to be 27% (2008) [4].
In a 2012 article, Aref reviewed the possible pathophysiology of glaucomatous damage that occurs overnight, contributing to the development or progression of the disease. The factors believed to contribute to reduced ocular perfusion overnight included an increased intraocular pressure overnight, a faulty vascular autoregulation, nocturnal systemic hypotension and obstructive sleep apnea [9].
Lin PW et al. discussed vasogenic theories for normotensive glaucoma and postulated that OSA may contribute to poor perfusion at the optic nerve head. They studied the prevalence of normotensive glaucoma among 209 patients with OSA compared to 38 controls with no OSA. They also sought a correlation between the severity of OSA and the risk for glaucoma and found the overall prevalence of normotensive glaucoma to in OSA patients to be 6%, a higher prevalence compared to controls (0%); Among their 12 patients with normotensive glaucoma, 8 (two-thirds) had "severe" OSA, 3 (1/4) had "moderate" OSA, and one had "mild" OSA. They recommended that glaucoma be considered in patients with moderate or severe OSA and that patients with normotensive glaucoma be screened for OSA [12].
Lin CC et al. concluded from their study that patients with OSA were at increased risk for open angle glaucoma (2013) [11].

In investigating any patient with NTG, it is important to rule-out possible secondary causes as we have outlined previously. An overlooked cause of NTG may be sleep apnea. It has been estimated that 93% of women and 82% of men with moderate to severe obstructive sleep apnea are undiagnosed [3]. Careful patient history can help determine which patients need referral to a sleep study center for polysomnography. An individual is considered to have an OSA syndrome if they demonstrate an AHI of at least 5 with the presence of daytime symptoms or AHI of 15 or more independent of symptoms, is used in sleep studies to grade apnea. The respiratory disturbance index has been shown to correlate positively with IOP, visual field loss variance, glaucomatous optic-disc changes, and the diagnosis of glaucoma [1, 9, 11]. Our patient had an AHI of 28.5 (moderate OSA), which was mandatory to start CPAP treatment, no further glaucoma progression has been noted 5 months later. Some reports showed some visual field stabilization after CPAP treatment [1,6], however there is one report (Kiekens et al) of CPAP usage resulting in increased intraocular pressure overnight [10]; another report (Stein et al) found no effect of CPAP on progression of glaucoma [1].
Since obesity is one of the primary risk factors for OSA in adults, weight loss is also an important factor in managing sleep apnea [3].

Ocular Surface Disease

Dry eye syndrome refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation that is associated with ocular discomfort and/or visual symptoms and may cause disease of the ocular surface[19].

CPAP

Continuos Positive airway pressure (CPAP) is a mode of respiratory ventilation used primarily in the treatment of sleep apnea. For some patients, the improvement in the quality of sleep and quality of life due to CPAP treatment will be noticed after a single night's use. Often, the patient's sleep partner also benefits from markedly improved sleep quality, due to the amelioration of the patient's loud snoring [3,6].

The CPAP machine blows air at a prescribed pressure (also called the titrated pressure). The mask required to deliver CPAP must have an effective seal, and be held on very securely. Common problems with CPAP include a leaky mask, trouble falling asleep, and a dry mouth or nose. A leaky or ill-fitting mask may not deliver the full air pressure needed, and may irritate the skin. It can also release air into the eyes, causing them to become dry or teary [7,8].
Hayirci et al (2012) studied 40 patients diagnosed with OSA and found increase in Schirmer 1 score, suggestive of increased ocular surface irritation; reduced tear breakup time and squamous metaplasia (demonstrated by impression cytology)[8].
It is postulated that air pressure could induce dry eye by forcing air though the tear puncta openings. Punctal plug occlusion can be tried with temporary collagen punctual plugs to rule out this possibility. CPAP induced dry eye will be worse upon awakening and improve as the day progresses while dry eye syndrome usually worsens as the day progresses [7].
In our patient, "red eye" and foreign body sensation only started after CPAP treatment, but an improvement during the day was not noticed. In this case was unclear if the ocular surface complications seen were from leakage of air into the eyes causing drying or from air passing from the nose into the eye via the nasolacrimal duct, associated with CPAP.
A possible management of CPAP-induced dry eye may include instillation/application of ocular lubricants at bedtime and upon awakening and adjustment of the mask or refitting with a different type of mask to reduce air leak [8].

Sleep apnea patients also have an increased frequency of floppy eyelid syndrome. Due to a loose eyelid the lid flips up exposing the conjunctival tissue lining. This constantly rubs on the pillow case causing mechanical irritation and exposes the tissue to any allergens that are on the pillowcase. The conjunctival tissue can become chronically inflamed with papillary conjunctivitis and a red eye upon awakening, but in this patient floppy eyelid syndrome was not detected [13].

Long exposure to Benzalkonium Chloride (BAK)

Baudouin et al, recently reviewed their extensive experience and the literature from over the past 20 years, which showed that topical ocular medications containing BAK caused tear film instability, ocular surface changes, conjunctival inflammation, epithelial apoptosis, and subconjunctival fibrosis [20].
A study of 9,658 patients, found significantly more signs and symptoms of ocular surface disease in patients taking glaucoma medications with preservatives (95+% using BAK) than those using preservative-free formulations. Dry eye sensation was reported as twice as common, foreign body sensation three times, and stinging and burning two and a half times as common in the preservative group as compared to the preservative-free group [20].
Rossi et al., showed a higher incidence of dry eye in patients taking topical ocular medication containing BAK than controls. Dry eye was found in 40% of those taking 2-3 drops per day compared to 11% once a day and 5% for no eye drops [18].

Leung et al., using the Ocular Surface Disease Index (OSDI) for measuring the symptoms of dry eye, show a 59% prevalence rate of dry eye in at least one eye in patients on topical ocular glaucoma medications with BAK compared to their overall prevalence rate of 27% in non-glaucoma patients. In glaucoma patients on topical ocular medications, there was an abnormal Schirmer's result in 61% of cases, lissamine green staining in 22%, decreased tear film break-up times in 78% and decreased tears in 65%. Each additional BAK containing eye drop was associated with 2 times higher odds of showing abnormal results on lissamine green staining test [17].

Schwab et al. showed long-term glaucoma medication with preservatives caused conjunctival foreshortening with shrinkage including conjunctival scarring. This was confirmed by Thorne et al. in a series of 145 cases in which 97.4% of these patients had antiglaucoma medication [22].

Commercial eye-drops containing BAK have caused irreversible ocular damage in several studies. The standard of proof demanded by the FDA and International Dry Eye Workshop implicating BAK and dry eye has not been yet completely clarified. In our case, after a treatment upon than one year with a glaucoma medication with BAK preservative, dry eye syndrome was detected. However, other causes could also conduce to the ocular surface disease reported in this case. Use of lubricants preservative-free and/or changing the glaucoma medication to preservative-free, could help in symptoms relief and makes part of the treatment.

★ CONCLUSION ★

Increasing evidences suggests a strong association between glaucoma and OSAS. The link between them remains controversial. Treatment of OSAS may help stabilize glaucoma and an improvement in visual field could be noticed. A lot of different reasons (for instance CPAP for OSAS or long-term eye drops medication with BAK preservative for glaucoma patients) can cause or increase ocular surface disease. The role of medications in causing or aggravating dry eye disease is complex and this paper still suffers from oversimplification and incomplete data.

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