GENERAL REVIEW

EYE DISEASES IN PATIENTS WITH SLEEP APNEA SYNDROME: A REWIEW

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ABSTRACT

Sleep apnea syndrome (SAS) is characterized by recurrent episodes of apnea during sleep. Mechanical upper airway obstruction is by far the most frequent form of SAS, and is named obstructive sleep apnea (OSA).

Besides giving rise to a reduced quality of life, OSA is associated with important cardiovascular morbidity and mortality if left untreated. OSA has also been associated with several ophthalmic manifestations. The purpose of this paper is to review the most important features of OSA, and to highlight the ophthalmic abnormalities recognized in these patients. Ophthalmologists should be familiar with the possibility of sleep disorders in their patients as the cause of certain eye pathologies. The ophthalmologist can often identify a patient with OSA and refer him for a sleep study. Sleep physicians, on the other hand, should be alert for the possibility of eye disorders, inform their patients and refer them for a check up.

KEYWORDS

Eyelid hyperlaxity, floppy eyelid syndrome, nonarteritic anterior ischemic optic neuropathy, optic disc edema, intracranial pressure, obstructive sleep apnea, glaucoma, normal tension glaucoma

OBSTRUCTIVE SLEEP APNEA (OSA)

OSA is characterized by partial or complete upper airway obstruction during sleep, causing apnea and hypopnea. Apnea is the cessation of airflow at the nose or the mouth for at least 10 seconds (1). Hypopnea is a 30 to 50 % reduction in airflow for at least 10 seconds and oxygen desaturation of at least 2% to 4%.

Diagnosis of sleep apnea is based on a combination of clinical features and overnight polysomnography, and requires at least 5 instances of apnea and/or hypopnea per hour of sleep, in combination with daytime hypersomnolence. This is more accurately referred to as obstructive sleep apnoe syndrome (OSAS). The total number of apneic and hypopneic episodes per hour is called the apnea-hypopnea index (AHI) or the respiratory disturbance index (RDS). An AHI of 15-30/hr is considered moderate OSA, whereas $>$ 30/hr is severe OSA.

OSA has an estimated **prevalence** in the range of 0.3 to 4%, depending on the population studied and the criteria used (2). In a random sample of employed Americans aged 30-60 years, 9 % of women and 24% of men had apnea-hypopnea index scores of 5 or more (3). Two percent of the women and 4 % of the men had complaints of daytime sleepiness and met the criteria of OSA.

Male gender and obesity are important **risk factors** for sleep apnea in people between 30 to 60 years old (3). Increased upper-body obesity, which is reflected by a large neck circumference, is a particularly good predictor of sleep apnea. Habitual snorers, both men and women, are also at risk. Extremely loud snoring or breathing pauses are even more predictive. Ret-

rognathia or tonsillar hypertrophy can also cause upper airway dysfunction.

Pathophysiology. Upper airway size and patency are determined by soft-tissue and skeletal factors. Dysfunction on the specific sites of narrowing are influenced by the underlying neuromuscular tone, the upper-airway muscle tone, and the stage of sleep (4).
As the patient falls asleep, the muscle tone in the upper pharyngeal airway decreases leading to upper airway narrowing. This produces an increase in the inspiratory effort in an attempt to overcome this narrowing, which then leads to a transient arousal from deep sleep to wakefulness or a lighter sleep phase with restoration of normal airway muscular tone and calibre. The patient then falls more deeply asleep again and the whole cycle repeats itself. This can occur many hundreds of times throughout the night leading to a fragmentation of normal sleep architecture and a reduction in quality of sleep (2).
The most common **symptoms of OSAS** are excessive daytime sleepiness, impaired concentration and nocturnal snoring. The snoring can be extremely loud, disturbing the bed partner and even the entire household, or it can be very quiet (1). The partner may have noticed cessation of breathing. The consequences of untreated sleep apnea on daily function are multiple and include impairment of cognitive function and mood daytime sleepiness, as well as personality changes. This can have serious consequences on the activities where reduced alertness is dangerous, such as driving, leading to an increased risk of road traffic accidents.
The intermittent upper airway obstruction during sleep with accompanying ineffective inspiratory efforts, results in a negative intrathoracic pressure with consequences for cardiac function (5). During the apneas, the sympathoexcitatory effect of hypoxia and the CO_2 retention result in increased sympathetic vasoconstrictor tone causing cardiac arrhythmias and systemic hypertension. Long-term cardiovascular complications include pulmonary and systemic arterial hypertension, cardiac arrhythmias, myocardial infarction and stroke.
Increased platelet activation and aggregation during sleep has also been described in patients with OSA (6).

All proposed **treatments** are based on a widening of the upper airway.
Nasal continuous positive airway pressure (CPAP) is a widely used and effective treatment of OSA. It functions as a pneumatic splint to maintain upper airway patency throughout all phases of sleep breathing (2). It operates by means of a flow generator which delivers pressure through an air tubing to a nasal mask worn overnight. Minor leaks around the mask can cause slight ocular discomfort. Most patients require lifelong treatment. It has been shown that CPAP improves not only the daytime function but also the quality of life. Furthermore it seems to improve associated cardiovascular diseases such as pulmonary hypertension and systemic hypertension, and normalize platelet activation (6).
Oral devices and *surgical approaches* can also be attempted. All of them aim at increasing the pharyngeal calibre and reducing the pharyngeal resistance during sleep (2). However reported results seem to be quite variable, and techniques are constantly evolving.

EYELID HYPERLAXITY - FLOPPY EYELID SYNDROME (FES)

One of the most common disorders associated with OSA (and other sleep-disordered breathing) is eyelid hyperlaxity (7).
Ordinary involutional changes of the eyelid include horizontal laxity of the tarsus and especially the canthal ligaments, which are common in elderly patients. When the tarsus itself has a rubbery, elastic aspect, giving rise to typical redundant, floppy, easily evertable eyelids, we refer to it as eyelid hyperlaxity or floppy eyelids (Figure 1). Robert and Adenis have suggested to define hyperlaxity as a vertical distance of more than 15 mm between the palpebral rim and the centre of the pupil, in primary gaze after manual traction on the eyelid (7). The association of eyelid hyperlaxity and marked papillary conjunctivitis corresponds to the so called floppy eyelid syndrome (FES), as originally described by Culbertson (8). Unfortunately, because there is no real consensus about how to measure the laxity and about the exact criteria for laxity or FES, quite variable prevalences of FES have been reported.

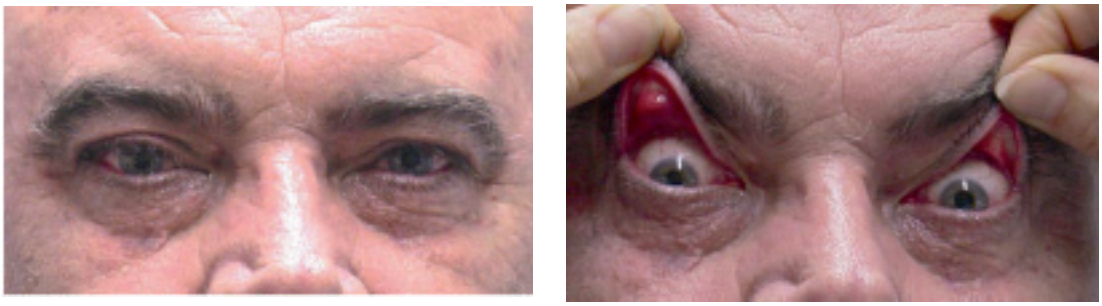

Fig. 1: Floppy eyelid syndrome can only be detected by pulling on the eyelid or lashes, demonstrating spontaneous eversion of the tarsus and redness as a sign of papillary conjunctivitis. In this patient, laxity and inflammation are more pronounced on the right side.

The reported **prevalence of eyelid laxity** among patients with OSA is very high, ranging from 29.5% of 44 SAS patients for Robert P.Y. et al, to more than 65% of 69 patients with OSAS (and other sleep breathing disorders) for Mojon D.S et al and showing spontaneous eversion after manual traction (7,9). In both studies, all patients were affected bilaterally and about half of them showed evidence of ocular involvement and symptoms of mild ocular irritation (7, 9).

The **prevalence of FES** is much lower, ranging from 1,5 % of 69 OSA patients to 4,5% of 44 OSA patients (7,10). FES is mostly found in patients with a severe degree of OSA (2). In our ongoing study, we have also found a high prevalence of hyperlaxity and FES.

The prevalence of OSA in patients with FES is extremely high. In a cumulative series of 50 patients with FES, 96% reported symptoms suggestive of OSA (11). Slightly more than half of those were willing to undergo a sleep study and 96,3 % of them were diagnosed with OSA. In other words, a patient diagnosed with FES has a big chance of having OSA.

Signs and symptoms. A typical profile for a patient with FES (and OSA) is a middle aged, obese man. FES patients usually present with prolonged symptoms of non-specific ocular irritation, often resistant to local medical treatments. Due to the horizontal laxity of the eyelid, it will evert spontaneously when the patient moves his face on the pillow. During varying periods of eversion, the palpebral conjunctiva of the eyelid and the bulbar conjunctiva and cornea may be exposed to the air and to rubbing against the pillow. Due to this recurrent exposure and mechanical rubbing, inflammatory signs will develop consisting in a papillary conjunctivitis with possible surinfection. The direct exposure of the cornea and the conjunctiva, the poor upper eyelid contact with papillary conjunctivitis and the inequal distribution of the tear film result in corneal dryness and superficial punctuate keratitis. In turn, this may generate a foreign body sensation, photophobia, redness, mucoid discharge and swelling of the eyelids. Symptoms are often worse in the morning. The most affected eye often corresponds to the side the patient preferentially sleeps on. When the patient alternates sleeping side, or sleeps face down, both eyes may be affected.

On **clinical examination**, while pulling the lashes or the skin of the upper eyelid upwards, an eyelid with FES everts spontaneously, exposing the palpebral conjunctiva, which is often inflamed with an irregular surface (Figure 1). Not only both medial and lateral canthal ligaments are very lax, but also the tarsal plate itself shows an abnormal elasticity. When it is pulled horizontally on the tarsal plate, it can be significantly elongated
Other palpebral abnormalities include eyelash ptosis (downward sloping lashes), loss of eyelash parallelism, upper eyelid ptosis, dermatochalasis, lower eyelid ectropion, hyperkeratotic skin lesions of the eyelids and the face (7,12, 13). Corneal vascularisation, scarring, ulceration and perforation have also been de-

scribed (14). Even more, corneal keratoconus has been documented in patients with FES (8,14-16). In contrast, other larger studies have found that corneal involvement in patients with OSA was very rare (7,9)

The **pathophysiology** of FES is based on an extreme horizontal laxity of the upper and/or the lower eyelid. Histopathological examinations of the affected eyelids has demonstrated loss of normal elastin fibres within the tarsal plate (17). Another immunohistochemical study had found an increase of the elastolytic protease in the areas exhibiting less elastin compared to normals. Other studies have shown that repeated minor trauma or mechanical stress in vitro can lead to similar changes (18-20). Additional possible mechanism may involve ischemia-reperfusion injury, which also upregulates MMPs in the brain, the heart and the lungs (18). In FES, tarsal elastin is affected while in OSA, palatine elastin is affected (7,21)

The **treatment** of FES aims at protecting the ocular surface during sleep and at preventing any mechanical trauma and/or further stretching. Topical treatment is based on ocular lubrification and temporarily reduction of inflammation and possible infection. Eversion of the eyelid can be avoided by wearing a soft bandage over the eyelids at night. Improvement or resolution of symptoms confirms your diagnosis. For a more permanent solution, surgical treatment is necessary and is based on a tightening of the eyelids. Correcting horizontal laxity can be done with a full-thickness pentagonal resection of a part of the eyelid or by a tarsal strip procedure and by additional reinforcing the canthal tendons. Underlying OSA should also be treated simultaneously. Maybe it might stop further progression of the laxity.
Patients with easy upper lid eversion are at risk for OSA. By recognizing the potential for OSA in these patients, the ophthalmologist may play an important role in initiating their evaluation and treatment (10).

PAPILLOEDEMA - INCREASED INTRACRANIAL PRESSURE

A few studies have demonstrated, by a continuous intracranial pressure (ICP) monitoring, that patients with OSA can have numerous episodes of tremendous ICP elevation before and during episodes of apnea or hypopnea, which was more pronounced during REM (Rapid Eye movements) sleep (22-24). In most cases, patients have normal baseline ICP that rises significantly in an episodic fashion, concomitantly to the apneic episodes.
Sustained elevation of ICP can induce papilloedema (PE) which is secondary to the obstruction of the retrograde axonal transport at the level of the optic disc. The effect of this transient elevation of the ICP is less clear. Anyway intermittent ICP elevation might be sufficient to cause morning headache that patients with ASO frequently complaint, but also tinnitus or even PE, and is often referred to as idiopathic intracranial hypertension.

Various **pathophysiological** mechanisms may contribute to the increase in ICP during apnea (25). First, hypoventilation episodes will cause hypoxia-hypercapnia and will lead to cerebral venous vasodilatation which in turn induces an increase in the intracranial vascular volume. Secondly, mechanic airway obstruction with increased respiratory effort can generate an increase of the intra-abdominal pressure and the intrathoracic venous congestion that may alter the cerebral venous drainage. Thirdly, elevated systemic arterial pressure, due to the increase of the sympathetic tone, can also be involved.

The prevalence of OSA among idiopathic intracranial hypertension has been investigated in retrospective studies. Obstructive events were found in 20-30% (26, 27).

The prevalence of PE in patients with OSA is unknown. A few case reports have been published describing OSA patients with visual decrease due to bilateral PE (23,28-30). In a prospective study by Peter L. et al, 35 patients with recently diagnosed mild and moderate OSA, have completed a questionnaire about visual symptoms (visual loss, transient visual obscuration or diplopia) and had a fundoscopy (25). Although 40 % of them had visual symptoms suggestive of PE, none were found to have PE. The authors had concluded that PE is not frequently associated with OSA, and that a sys-

tematic screening seems not to be warranted. Nevertheless, patients with visual complaints should have their fundus checked.
Older male patients with idiopathic intracranial hypertension and PE are particularly at risk of having OSA as a causative factor, and treatment with CPAP may reverse the disc swelling (19,26).

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (NAION)

NAION is characterized by an acute onset of painless vision loss. Ophthalmological examination reveals a visual acuity and visual field loss, a relative afferent pupillary defect, as well as optic disc edema evolving into optic atrophy. Despite the frequency with which this condition occurs, its exact cause is not known. Several risk factors have been suggested, including advanced age, systemic hypertension, arteriosclerosis of the carotid artery, hypercholesterolemia, diabetes mellitus, and a small cup-to-disk ratio.
Sleep apnoea was found to be 1.5 to 2-fold more frequent than the rate of the other identified risk factors typically associated with NAION (hypertension, diabetes) (31).

Several studies have reported a higher **prevalence of OSA** in patients with NAION, consisting mostly in case report series (23, 29, 31-33). Two studies have investigated the prevalence of the OSA in NAION patients with overnight polysomnography. One of them found a prevalence of 71% in 17 NAION patients (32), and the second a prevalence of 89 % in 27 newly diagnosed NAION cases (31).
In one case report series, Behbehani et al described 3 patients who developed a NAION while being treated with CPAP for SAS (34). The authors have pointed the attention to the fact that CPAP treatment did not prevent the development of NAION in these patients.

Several **mechanisms** by which OSA may increase the risk for NAION have been proposed. Among them, impaired optic nerve head blood flow autoregulation secondary to repeated apnoeas (35), optic nerve vascular dysregulation secondary to OSA-induced arterial blood flow variations (episodes of nocturnal hypertension or hypotension). Arterial hypertension and arteriosclerosis have also been incriminated (35). This dysregulation may by due to the imbalance between nitric oxide (a vasodilator) and endothelin (a vasoconstrictor). Furthermore platelet activation may cause microinfarcts in the optic nerve (33) Finally, direct optic nerve damage can occur as a consequence of repetitive or prolonged hypoxia or increased intracranial pressure during the repetitive apneic spells. The association between NAION and OSA may explain why approximately 75% of all patients with NAION discover visual loss on first awakening or when they first use vision critically after sleeping (32).Sleep apnoea is the most frequent disorder associated with NAION and should be screened in this population (31). Optimally, a questionnaire related to the obstructive sleep apnoea symptoms and the assessment of diurnal sleepiness should be systematically given to patients with NAION.

GLAUCOMA (POAG AND NTG)

Glaucoma is defined as a specific optic neuropathy characterized by typical and progressive loss of visual field and glaucomatous optic disk excavation. Most important **risk factors** of POAG are increased intraocular pressure (IOP), a positive first-degree family history, high myopia and cardiovascular diseases. Vascular factors are especially important in glaucoma with relative normal IOP (normal tension glaucoma, NTG). These may be subdivided into abnormal blood flow, vasospastic syndrome, systemic hypotension, abnormal blood coagulability and other factors such as severe blood loss or hypotensive shock (36). It is believed that a reduced flow in the blood vessels that supply the optic nerve head is an important causative factor in NTG. Blood flow in these vessels depends on various factors including blood pressure, IOP, vascular resistance and autoregulatory mechanisms (36,37).
Several publications have suggested to add OSAS to the list of risk factors for POAG and NTG.

Pathophysiology. The theories that link glaucoma to OSA are similar to those that link NAION to OSA. Alteration in the posterior ciliary circulation, that is the main source of blood supply

to the optic nerve head, is primarily responsible for the common ischemic disorders of the optic nerve head, e.g. anterior ischemic optic neuropathy and glaucomatous optic neuropathy (35).
Of course, additional IOP increase may worsen the situation. However, studies dealing with this concern are still non conclusive. IOP measurements at night in 3 SAS patients had failed to find an increase in IOP immediately after a prolonged apnea (38). Several papers dealing with NTG associated with OSA have monitored the IOP throughout the 24 hours and had not found any abnormally high IOP at night. In a prospective study, we measured the diurnal IOP every 2 hours in OSA patients, and found a moderate increase in IOP during the night (which might still be physiologic), but with a higher trough-peak difference compared to healthy young adults (39).
During the last decade, numerous reports were published on the association between OSA and glaucoma, POAG as well as NTG.

A few larger studies addressed the high **prevalence of glaucoma** within OSA patients. In 41 Chinese patients with moderate to severe OSA, the incidence of VF defects and glaucomatous optic nerve changes was 4 times higher than in the control group (40). Mojon et al have found that 7,2 % of a series of 69 patients with SAS had glaucoma (3 POAG, 2 NTG) (9). They also found that the respiratory disturbance index (RDI), was positively correlated with the IOP, the visual field loss, as well as the glaucomatous optic disc changes and the diagnosis of glaucoma (9). Similarly, Bendel had found a prevalence of glaucoma of 27% in a group of 100 patients with moderate to severe OSA (41). In our own ongoing study of consecutive patients with OSA, we also found a much higher prevalence of glaucoma than in the normal population (2%). However, one conflicting cross-sectional study involving 228 patients with OSA had reported a prevalence of POAG similar to those observed in the general population.
Several studies were conducted to determine the **prevalence of OSA** in glaucoma patients. Mojon et al have determined the prevalence of OSA with oximetry in 30 consecutive patients with POAG, and have found that as much as 20 % had SAS (42). In another study based on overnight polysomnography, they reported a prevalence of OSA in NTG patients of 50% in the age group of 45-64 years and of 63% in the group older than 64 years (32). Marcus et al looked at the prevalence of sleep related symptoms in patients with NTG and NTG suspects, and found that 57 % of 23 NTG patients and 43% of 14 NTG suspect patients suffered from symptoms suggestive for a sleep disorder, compared to only 3% in the 30 non-glaucomatous controls (27). 13 of these symptomatic patients accepted to undergo polysomnography and 11 were indeed diagnosed to have a sleep disorder (7 sleep apnea, 3 sleep hypopnea, 1 upper airway resistance syndrome). Since many OSA patients do not realize they have symptoms of a sleep disorder, and often seek help on request of their partners, these results are probably underestimated.

A few case reports have demonstrated the beneficial effect of **CPAP treatment** in patients with NTG, which finally stabilized after starting the CPAP treatment in the newly diagnosed OSA (43,44).
Although CPAP has a tremendous beneficial effect on the quality of life and on the cardiovascular comorbidity of the patients, the influence on IOP itself might not be positive. In a clinical study including 18 glaucomatous patients without OSA, Alvarez-Sala R. et al have demonstrated that IOP was increased after 15 minutes of CPAP during daytime, while patients were seated (45). In a group of 20 OSA patients without glaucoma, we measured a statically significant nocturnal IOP increase during CPAP treatment, compared to the pre-treatment values (39). The pressure-raising effect of CPAP was confirmed by the significant IOP decrease observed thirty minutes after CPAP cessation. Why CPAP therapy causes an increase in IOP is not yet understood. One could speculate that CPAP leads to an elevated intrathoracic pressure, which in turn induces a pressure elevation in the venous circulation and may reduce the aqueous humour outflow through the episcleral veins. This hypothesis is supported by the higher IOP in the lower ipsilateral eye when patients were sleeping in lateral decubitus position before IOPmeasurements. The finding correlates with the assumption that venous outflow from the lowest eye is decreased and

on the contrary, that venous outflow from the higher controlateral eye is increased, causing a reduction in IOP (46).
Based on this body of literature, we can state that POAG and NTG are associated with OSA. Therefore it is advised to ask for symptoms of OSA in all patients with NTG. If these are positive, patients should be screened by polysomnography.
Every patient with OSA should have an ophthalmological screening for glaucoma, and certainly patients treated with CPAP should be followed yearly.

DISCUSSION

Whether all the papers referred to in this review have used the same criteria for OSA is not absolutely certain. Some of them stated general criteria of OSA in their introduction, but this was rarely mentioned in the section "Material and Methods". Being symptomatic is part of the definition of OSA, more accurately referred to as OSA Syndrome or OSAS. Unfortunately the terms OSA, OSAS and SAS are variably used. Since most patients presented for investigation or treatment, we could assume that they were symptomatic, but it is most often not mentioned.
In order to demonstrate that the severity of OSA is an even stronger risk factor, larger studies taking into account the AHI, the symptoms and an estimated duration of the disease and its treatment are necessary

CONCLUSION

A growing body of literature provides evidence that patients with OSA have an increased incidence of some particular ocular disorders, including floppy eyelid syndrome, glaucoma and nonarteritic ischemic optic neuropathy. Whether all this phenomena are indirectly caused by the vascular co-morbidity associated with OSA is not exactly known.
As sleep-associated disorders become increasingly recognized, it is our responsibility as health care providers, to recognize signs and symptoms of disorders that are not directly related to our specialities, but affect the overall health of our patients.
The ophthalmologist should be alert to the possibility of sleep disorders in their patients.
In patients with eye surface disease, poorly responding to local treatment and recurring regularly, the eyelids should be inspected thoroughly. Surgical treatment of floppy eyelid syndrome is susceptible to significantly improve the quality of life in these patients.
In patients with an optic neuropathy, such as normal tension glaucoma, NAION or papilloedema, the ophthalmologist should question the patient, or his/her partner, about history of snoring, daytime sleepiness and should inspect the physical appearance of the patient, and especially search for risk factors such as obesity, male gender, large neck girth. When the patient has been suspected to have ocular disorders and another risk factor, the ophthalmologist should refer patients for a formal sleep study.
Sleep physicians should also be alert to the possibility of eye disorders in their patients. They should inform their patients and send them for regular check up. The ophthalmologist should measure the eyelid laxity, inspect the palpebral conjunctiva, thoroughly inspect the optic disc and perform a visual field in all suspect discs and in all small discs, or in every patient if the ophthalmologist is not experienced in optic disc evaluation. Early detection of glaucoma and treatment can prevent evolution to functional disabling visual field defects.

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