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REVIEW ARTICLES

Ocular Manifestations of Obstructive Sleep Apnea

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Study Objectives: Obstructive sleep apnea (OSA) incurs a host of systemic side effects. The eyes are particularly susceptible to both mechanical and vascular sequelae of the disease. This paper outlines the ocular manifestations of sleep apnea. The authors hope to increase awareness of the ocular complications of this common disorder and increase communication and co-management between eye-care providers and sleep specialists alike.
Methods: Data were collected from PubMed and the Brown University Library Collection.
Results: Twenty-two papers were included in this review to address floppy eyelid syndrome, nonarteritic anterior ischemic optic neuropathy, central serous retinopathy, retinal vein occlusion, and glaucoma. We used three meta-analyses and several cross-sectional cohort and case-control studies that investigate the aforementioned conditions and their associations with OSA.
Conclusions: Hypoxia induced by nightly cessation of breathing increases patients' risk of coronary artery disease, heart failure, stroke, and other conditions. As with many maladies detrimental to vascular health, obstructive sleep apnea affects the eye and ocular adnexa. This paper summarizes the current evidence implicating OSA in these ocular maladies and highlights their proposed mechanisms. The authors describe ocular pathology which sleep specialists may encounter. We encourage more aggressive attention to ocular symptoms in patients with sleep apnea to prevent vision-threatening complications. Further research should investigate how sleep apnea treatment affects these ocular findings and identify which sleep apnea patients are most prone to developing ocular pathology.
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INTRODUCTION

Obstructive sleep apnea (OSA) describes a sleep disorder with nocturnal pharyngeal collapse leading to partial airway obstruction and hypopneic or apneic events during sleep.[1] Ocular manifestations of OSA derive from mechanical and vascular effects of the syndrome. These include floppy eyelid syndrome, nonarteritic anterior ischemic optic neuropathy, central serous retinopathy, retinal vein occlusion, and glaucoma. This paper describes the epidemiology of ocular manifestations in OSA, offers suggestions for sleep medicine clinicians assessing ocular involvement, and discusses proposed mechanisms. Knowledge of these ocular sequelae may facilitate triage between sleep specialists and ophthalmologists, thereby preventing ocular complications and vision loss in patients with OSA.

FLOPPY EYELID SYNDROME

Floppy eyelid syndrome (FES) describes a condition in which the upper eyelids easily evert with upward traction.[2] This leaves the eye susceptible to discomfort and visual symptoms related to exposure. In a study of 50 patients with FES, 96% experienced symptoms associated with OSA.[3] Of these 50 patients, 11 had a previous diagnosis of OSA. Seventeen patients in this cohort in whom OSA was not diagnosed underwent sleep studies, of whom 16 were then found to have OSA.[3] These data suggest most patients with FES suffer from OSA. However, some studies suggest only between 2% and 5% of patients with OSA have FES as well.[3] A prospective study of 127 patients referred for a sleep study found that 25.8% of patients with OSA had FES, and this frequency increased to 40% among those with severe OSA.[4] Miyamoto et al. and McNab have also suggested that FES in patients with sleep apnea denotes a greater severity of disease.[2,3]

Physicians caring for patients with suspected and/or known OSA may identify FES by asking about symptoms of ocular discomfort. Exposure symptoms related to FES may present as foreign body sensation, dryness, redness, or eyelid swelling. Patients with dry eyes may complain of excessive tearing, a reflexive lacrimation responding to underlying dryness. Sleep medicine physicians may ask about blurry vision, as corneal abnormalities related to dry eyes can impair visual acuity.[3] With tissue damage and eyelid eversion likely occurring at night, patients often report these symptoms being worst upon waking. Patients with such symptoms should use artificial tears for lubrication, especially at night, and referral to an ophthalmologist may help evaluate for corneal pathology.

Histologic evidence suggests mechanisms linking FES and OSA. Pharyngeal collapse in OSA occurs due to connective tissue compromise against increased neck thickness. FES histology reveals decreased elastin content and increased matrix metalloproteinase activity in lid connective tissue, demonstrating a similar connective tissue weakness.[2] Akin to the increased neck thickness in obstructive sleep apnea, patients with FES display tissue redundancy in the lateral canthal tendon.[2] Patients with FES often experience symptoms on the side

on which they sleep, corroborating the theory of mechanical stress causing the syndrome.

Lid histology in FES also reveals chronic inflammation with absent tissue atrophy.[2] This offers a second sleep apnea theory for the development of FES: pressure from sleeping on a particular side induces transient ischemia in lid tissue, exacerbated by hypoxia during apneic events. With the resumption of normal breathing, reperfusion oxidation injury may cause continuous lid inflammation.[2] Likely, this chronic inflammation and underlying connective tissue weakness both contribute to the FES seen in patients with OSA.

Adherence with continuous positive airway pressure (CPAP) may improve signs and symptoms of FES. In treating the underlying disease, McNab reports anecdotal success in reversing signs of FES.[3] Conversely, lid tightening surgery used to treat FES in patients with untreated OSA is more likely to result in recurrent disease.[3] The surgically repaired lid remains susceptible to further damage from untreated OSA. As such, sleep specialists can help mitigate the effects of FES through effective adherence counseling, especially in patients considering eyelid surgery. Further studies may better demonstrate the effect of OSA treatment on lid laxity and ocular symptoms related to OSA. Given the implications that FES and ocular surface disease may have on patients' vision and quality of life, it is important for physicians to ask patients with OSA about these symptoms at every routine visit.

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Nonarteritic anterior ischemic optic neuropathy (NAION) describes a sudden, painless, often unilateral, irreversible, and nonprogressive visual loss. Ophthalmologic examination reveals a relative afferent pupillary defect and funduscopic abnormalities.[5,6] A large cohort study by Stein et al. found a 16% increased hazard of the development of NAION in patients with untreated OSA relative to patients without OSA.[7] Another meta-analysis found that patients with NAION had a five-fold increased odds of having OSA.[6]

Physicians caring for patients with OSA may elucidate a history of NAION by asking about any instances of sudden visual loss upon waking. Patients on multiple hypertension medications are especially at risk for this ischemic optic neuropathy. Given the irreversibility of this vision loss, patients may only see well with one eye. Patients with NAION bear a 15% risk to the contralateral eye over 5 years. This suggests an urgent need to alleviate risk factors, and physicians treating OSA play an important role in preserving vision of the contralateral eye in patients with a history of NAION.[6]

NAION involves ischemia in the short posterior ciliary arteries, which supply the optic nerve. Ischemia causes edema where the nerve exits the eye, with further compression compounding vascular compromise.[5] Patients often report experiencing symptoms of NAION upon waking, suggesting a contribution of nocturnal hypotension. This further implicates OSA in its pathogenesis. Patients with OSA suffer from impaired blood flow autoregulation, with an imbalance of nitric oxide and endothelin exacerbating the hypoxic hypoperfusion of tissues.[5] Furthermore, during apneic episodes, intracranial pressure increases. This elevated intracranial pressure limits perfusion to the optic nerve and may lead to NAION.

Future studies should ascertain if initiating CPAP treatment for OSA following NAION in one eye may prevent NAION in the other eye.[3] Some link between treatment of OSA and NAION development likely exists: indeed, the previously mentioned 16% increased hazard of having NAION with OSA was absent in patients receiving CPAP.[8] Some still speculate if OSA contributes to the pathogenesis of NAION directly or occurs as a comorbid disease with other NAION risk factors such as obesity, diabetes mellitus, and hypertension.[6]

CENTRAL SEROUS RETINOPATHY

Central serous retinopathy (CSR) describes an idiopathic detachment of the retina secondary to serous fluid collection beneath the retina. A meta-analysis by Huon et al. found a statistically significant association between CSR and OSA after pooling together the results of two case-control studies.[9] A smaller study of 23 consecutive patients with CSR found that 14 of these patients (60.9%) had OSA.[10] Case reports further support the association: a 45- year-old male patient described by Jain et al. presented with bilateral CSR that rapidly improved following CPAP treatment.[11]

Patients with CSR typically present with visual abnormalities, darkening, and/or image magnification. Physicians may elucidate a history of CSR in patients with OSA by asking about visual distortions; one example would be seeing straight lines as wavy. Given the idiopathic nature of the condition, finding potential risk factors and mitigating them is paramount to preventing recurrence and permanent visual loss.

Circulating epinephrine and norepinephrine levels increase in patients with OSA. This increased sympathetic tone exerts endothelial dysfunction on the blood-retinal barrier, which may lead to the accumulation of subretinal serous fluid. Few studies investigate the effect of CPAP on the duration of symptoms of CSR. Should treatment of OSA decrease the sympathetic tone incurred by apneic events, this may offer an opportunity to limit the effect of this otherwise idiopathic condition.

RETINAL VEIN OCCLUSION

Retinal vein occlusion (RVO) represents the second most common cause of blindness from vascular disease in the retina after diabetic retinopathy.[9] These occlusion events include branch retinal vein occlusion and central retinal vein occlusion, with occlusion of the branch retinal vein system the more common of the two. In a study of 40 patients having been treated for RVO, 37% of these patients demonstrated sleep-disordered breathing as measured by nocturnal pulse oximetry.[12] In another series of patients with RVO, OSA prevalence was found to be 77% among patients selected for screening based on nighttime symptoms.[13] The association between OSA and RVO has been widely suggested in the literature, and these few studies corroborate this.[9,12,13]

Sleep medicine specialists may identify patients with OSA at increased risk for RVO or patients with a history of RVO. Patients with RVO describe transient visual loss either centrally or peripherally, depending on the vascular areas involved. Such patients frequently bear other cardiovascular or hypercoagulable risk factors in addition to OSA. Patients with vein occlusions are frequently treated with intravitreal antivascular endothelial growth factor injections to prevent neovascularization of the retina. Similar to NAION, symptoms of RVO traditionally occur upon waking, which may relate in some cases to nocturnal apneic events.

Mechanisms for this correlation derive from the effect of OSA on blood flow autoregulation and microvasculature. Previous inquiries suggest venous occlusion occurs following slow retinal blood flow in OSA secondary to hypoxemia and nocturnal intracranial pressure elevations.[14] Changes in the retinal microcirculation may further explain the implication of OSA in RVO, with hemodynamic changes on the central retinal artery leading to compression of the adjacent retinal vein. Hypercoagulability, often resulting from OSA and subsequent inflammation, contributes to the development of RVO.[15]

Sleep medicine clinicians assist in addressing risk factors for this common and irreversible cause of vision loss. Further studies should investigate whether treatment prevents subsequent vein occlusions in patients with OSA and prior RVO.

GLAUCOMA

Glaucoma describes a chronic, progressive optic neuropathy with associated visual field deficits and characteristic cupping of the nerve on fundoscopic examination. It is the second leading cause of blindness worldwide. Variations of glaucoma include open angle glaucoma (OAG), normal tension glaucoma (NTG), and angle-closure glaucoma (ACG). In OAG and ACG, high intraocular pressure causes compressive neuropathy and visual field defects. Some theories in NTG (and the other types as well) suggest a vascular mechanism, with susceptible optic nerves more likely to be damaged in the setting of poor blood flow. The exact etiology remains unclear.[16]

Studies have demonstrated an association with OSA and both NTG and OAG.[5,9,17] A meta-analysis of 3 case-control studies, including 711 cases and 6,709 controls, found an odds ratio (OR) of 2.46 for the association between OSA and glaucoma. Among cohort studies, the same meta-analysis found an OR of 1.43.[18] Another meta-analysis by Huon et al. used six case-control studies with 1,122 glaucoma cases and 7,122 controls. The study found an overall OR for OSA of 1.746 among individuals with glaucoma.[9] A number of case reports have suggested the association as well. One such report describes a 60-year-old patient with NTG who displayed progressive visual field worsening despite lowering intraocular pressure with both eye drops and surgical intervention. After a subsequent diagnosis of OSA and treatment with nasal CPAP, this patient demonstrated stabilization of visual field deficits for 3.5 years of follow-up.[19]

Identifying glaucoma in asymptomatic patients remains an important challenge for ophthalmologists. Visual deficits initially occur peripherally in glaucoma. When these deficits become detectable, optic nerve damage is irreversible. Therefore, screening and identifying patients at risk for glaucoma prior to optic nerve damage is crucial. Given their increased risk, patients with OSA may benefit from ophthalmologic referral from sleep medicine clinicians. Regular eye exams assess additional risk factors for glaucoma, including both intraocular pressure (IOP) measurements and fundoscopic examination to identify optic nerve damage.

OSA may contribute to the pathogenesis of glaucoma through the vascular and/or mechanical theories of its etiology. Mechanically, IOP compresses the optic nerve, causing glaucomatous damage. Research has sought to evaluate changes in IOP during sleep utilizing wireless contact lens sensors, which continuously monitor IOP.[17] Shinmei et al. implemented this technique to monitor nocturnal IOP in patients with OSA; however, their findings seemingly contradicted the prevailing association between OSA and glaucoma, showing a statistically significant decrease in IOP during hypopneic and apneic events.[17] The authors explained that the decrease in IOP during apneic and hypopneic events likely resulted from negative intrathoracic pressure created by an attempted inspiration against a blocked airway (opposite the effect of Valsalva on IOP). OSA contributes to the pathogenesis of glaucoma less through a mechanical process and more through vascular effects.

OSA induces myriad vascular effects that may contribute to the pathogenesis of glaucoma. OSA predisposes the optic nerve head to ischemia and damage through episodes of hypoxia, hemodynamic changes to retinal blood vessels, oxidative stress, mitochondrial dysregulation, and inflammation.[18,20,21] This proclivity to damage leads to the nerve fiber dysfunction and degeneration seen in glaucoma. Patients with OSA may possess optic nerve heads more sensitive to mechanical damage given their poor perfusion and potential for ischemic changes.[18] However, the association between OSA and glaucoma remains subject to potential confounding factors, such as conditions associated with poor blood supply to the optic nerve head including obesity, hypertension, and diabetes.

Some studies suggest that treating OSA may have an effect on glaucoma progression. A cross-sectional study of 38 patients with CPAP-treated OSA, 32 patients with untreated OSA, and 36 patients without OSA found that those with untreated OSA had significantly higher IOP. Patients with untreated OSA also displayed significantly higher cup-to-disc ratios on physical examination.[22] Accompanying these differences on physical examination, the prevalence of glaucoma was 5.2%, 12.5%, and zero in the three groups, respectively. These findings suggest some adjunct role of treating comorbid OSA in the overall management of glaucoma, or in the prevention of the development of glaucoma. This emphasizes the importance of sleep medicine physicians in treating the multifactorial aspects of glaucoma. Further studies may investigate if CPAP therapy can help decrease the incidence of new glaucoma diagnoses among patients with OSA.

CONCLUSIONS

Patients with OSA bear increased risk for several vision-threatening ocular conditions. Providers treating patients

with OSA may utilize a directed review of systems to identify those displaying ocular involvement. In doing so, increased referrals between sleep specialists and ophthalmologists may lead to improved vascular and ocular health for patients with OSA. Many of the ocular conditions mentioned in this review require chronic treatment. Their treatments involve diligent mitigation of risk factors. Visual field deficits in glaucoma insidiously progress; vision loss in glaucoma, NAION, and RVO frequently prove irreversible. Remaining alert to the potential ocular sequelae of OSA may better prevent permanent vision loss in these patients.

ABBREVIATIONS

ACG, angle closure glaucoma
CPAP, continuous positive airway pressure
CSR, central serous retinopathy
FES, floppy eyelid syndrome
IOP, intraocular pressure
NAION, non-arteritic anterior ischemic optic neuropathy
NTG, normal tension glaucoma
OAG, open angle glaucoma
OR, odds ratio
OSA, obstructive sleep apnea
RNFL, retinal nerve fiber layer
RVO, retinal vein occlusion

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