REVIEW ARTICLE

Ocular Manifestations of Obstructive Sleep Apnea

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ABSTRACT: Obstructive sleep apnea (OSA) is a sleep disorder resulting in periods of breathing cessation secondary to upper airway collapse during sleep. The effects of OSA on a patient's cardiovascular and metabolic health are well known, though less recognized are OSA's associations with ophthalmic disease. The effects of OSA on the eye and ocular adnexa include floppy eyelid syndrome (FES), chronic eye irritation, glaucoma, nonarteritic anterior ischemic optic neuropathy (NAION), papilledema, keratoconus, central serous chorioretinopathy (CSCR), retinal vein occlusion (RVO), and complications with anti-vascular endothelial growth factor (anti-VEGF) injections. Sleep apnea is a common sleep disorder with a slew of ocular side effects, some of which are sight threatening, and many of which merit referral to an eye care provider.

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep disorder resulting in periods of breathing cessation secondary to upper airway collapse during sleep. Apneic events in patients with OSA generally last from 10 to 30 seconds and result in numerous swings between hypoxia and reperfusion throughout the night. The effects of OSA on a patient's cardiovascular and metabolic health are well known and include an increased risk of hypertension, type II diabetes, cardiovascular disease, and changes in neurocognitive function.[1,2] Less recognized are OSA's associations with ophthalmic disease.

The prevalence of OSA is ever increasing along with the rise of obesity, societal aging, and improvements in screening and testing methods for the disorder; OSA is now considered an issue of global public health. Studies have found the prevalence of symptomatic OSA to range from 22% to 24% in men, 9% to 17% in women, and 6% in adolescents.[1,3,4] A 2014 study found 26 of 30 patients with OSA to have some form of ocular involvement.[2] The effects of OSA on the eye and ocular adnexa include floppy eyelid syndrome (FES), chronic eye irritation, glaucoma, nonarteritic anterior ischemic optic neuropathy (NAION), papilledema, keratoconus, central serous chorioretinopathy (CSCR), retinal vein occlusions, and complications with anti-vascular endothelial growth factor (anti-VEGF) injections.[5,6] Sleep apnea is a common sleep disorder with a slew of ocular side effects, some of which are sight threatening, and many of which merit referral to an eye care provider.

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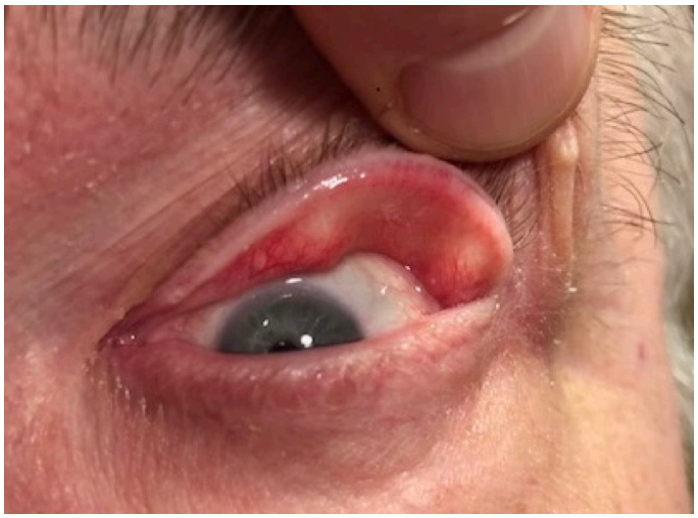
FLOPPY EYELID SYNDROME

Floppy eyelid syndrome is a condition in which the upper eyelids become more elastic and more easily everted with upward traction *(Figure 1)*. Lid eversion most commonly occurs while sleeping, secondary to traction of a pillow against the patient's eyelids. Eversion of the upper lid during sleep leaves the eye exposed and susceptible to mechanical trauma, papillary conjunctivitis, and eyelid edema. One study found 96% of patients with FES have OSA,[7] while the reported prevalence of patients with OSA who have FES ranges from 2% to 25.8%.[7,8] The likelihood of concurrent FES increases with the severity of the patient's OSA symptoms.[8]

FIGURE 1:

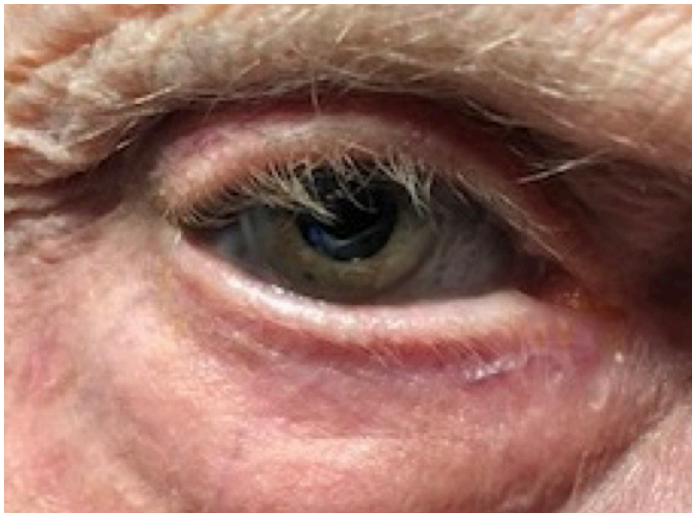
Eyelid eversion with floppy eyelid syndrome



Exposure of the cornea during sleep results in ocular surface disorders including punctate epithelial erosions, dry eye, exposure keratopathy, corneal scarring, neovascularization, ulceration, and rarely microbial infections that may lead to corneal perforation.[9-11] Eversion of the upper eyelid and rubbing of the conjunctiva against the pillow can result in conjunctival irritation and chronic papillary conjunctivitis. This mechanical trauma to the eyelid can over time result in lid edema, dermatochalasis, blepharitis, meibomianitis, ectropion, eyelash ptosis *(Figure 2)*, and trichiasis. Repeat mechanical trauma to the exposed cornea can also result in keratoconus.[10,11]

FIGURE 2:

Eyelash ptosis



Two mechanisms have been proposed to explain the etiology of FES, these being mechanical stress and transient tissue ischemia. Histological studies of affected eyelids reveal decreased elastin and increased matrix metalloproteinase (MMP) activity in lid connective tissue, and chronic inflammation.[12] Patients with FES are often more symptomatic on the side they sleep on. Traction of the lid against a pillow weakens lid connective tissue over time, providing support for the mechanical stress theory. Additionally, transient tissue ischemia secondary to hypoxia followed by periods of reperfusion that are characteristic of apneic events in patients with OSA have been shown to result in vascular damage and chronic lid inflammation.[12] The combination of these two mechanisms results in the connective tissue damage and increased lid elasticity seen in patients with FES. Eyelid laxity can be quantified through measurement of vertical eyelid pull. The eyelid is measured in resting position and at maximal manual displacement superiorly.[5] Normal eyelids can be stretched 5 to 10 mm vertically, though in eyes with FES this vertical pull ranges from 15 to 25 mm.[11]

Treatment of OSA via continuous positive airway pressure (CPAP) has been shown to improve the signs and symptoms associated with FES.[7] Treatments specific to FES should focus on treating any ocular surface disease and advising the patient against sleeping on their side or face. The patient can wear an eye shield at night to protect their lids, and use ocular lubricants and artificial tears to maintain the health of the ocular surface. Surgical intervention can be employed to shorten the upper eyelids, effectively tightening its apposition to the globe.

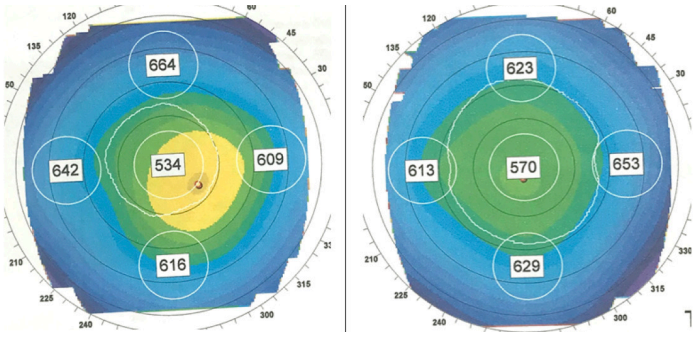
KERATOCONUS

Keratoconus is a condition characterized by progressive thinning and protrusion of the cornea, resulting in a cone-shaped corneal surface and a high degree of irregular corneal astigmatism *(Figure 3)*. These irregularities in the corneal surface result in decreased vision that is often difficult to correct without specialty contact lenses and is progressive in nature. Studies have found 18% to 20% of obese patients with keratoconus to have OSA, while the prevalence of keratoconus in the general population is cited at only 0.054%.[13,14] When obesity is controlled for, non-obese patients with keratoconus were not found to have an increased prevalence of OSA.[15]

The mechanism for developing keratoconus in patients with OSA is unknown, though it is theorized that mechanical trauma to the cornea results in the breakdown of corneal collagen fibers and progressive thinning of corneal tissue.[16] Additional theories propose that increased corneal MMP activity similarly results in chronic inflammation and tissue damage. In patients with OSA, keratoconus is seen more frequently in patients who also have FES,[17] leaving the corneal surface exposed with lid eversion during sleep. This exposure makes the cornea more susceptible to damage and provides further support for the mechanical trauma theory.

FIGURE 3:

Keratoconic corneal topography (L) versus normal corneal topography (R). Yellow center of the keratoconic cornea indicates corneal steepening.



Treatments for keratoconus include fitting the patient in a specialty contact lens such as a scleral or hybrid contact lens. In more advanced cases, surgical intervention in the form of corneal cross-linking or corneal transplant may be required to improve the patient's vision and stabilize their condition.

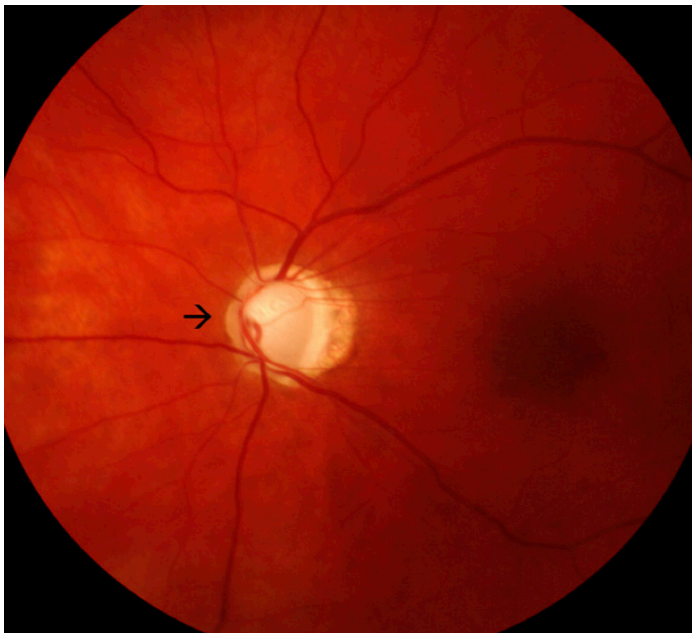
GLAUCOMA

Glaucoma is a chronic, progressive optic neuropathy resulting in thinning of the nerve fiber layer of the retina and increased cupping of the optic nerve on fundus examination *(Figure 4)*. Patients with glaucoma are often asymptomatic in the early stages

of the disease, slowly developing defects in their peripheral visual field over time as the condition progresses. Without treatment, patients develop complete loss of their peripheral field, (tunnel vision) and reduced visual acuity. Glaucoma is the second leading cause of blindness worldwide and has been shown to have a positive association with OSA.[18,19] Studies have found the prevalence of glaucoma in patients with OSA to range from 2% to 27%, while in the general population glaucoma has a prevalence of only 2% to 3%.[20]

FIGURE 4:

Fundus photo of glaucomatous optic nerve head



The mechanism for glaucomatous damage to the optic nerve remains unclear, however two leading theories exist. The mechanical theory proposes that elevated intraocular pressure (IOP) compresses the optic nerve resulting in damage to nerve fibers, while the vascular theory proposes that it is poor perfusion to the optic nerve head that results in glaucomatous damage.[5] The most likely explanation for nerve fiber loss in glaucoma is a combination of these two mechanisms, and OSA may contribute to both. A 2016 study found IOP to decrease in patients with OSA during apneic events, potentially resulting in periods of optic nerve head hypoxia.[21] Regardless the mechanism controlling glaucomatous damage, stabilization of glaucomatous visual field loss with treatment of OSA has been reported in the literature.[22] In light of the association between glaucoma and OSA, it is important that all patients with OSA undergo regular eye examinations including IOP checks and assessment of the optic nerve. Management of glaucoma involves the use of eye drops to reduce intraocular pressure. Numerous methods of surgical intervention exist that can be used to reduce eye pressure either by selectively targeting the ocular tissues responsible for creating the aqueous humor of the eye, or by promoting drainage of the aqueous humor.[6]

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Nonarteritic anterior ischemic optic neuropathy is characterized by a sudden, painless, unilateral loss of vision that occurs most frequently upon waking *(Figure 5)*.[23] NAION is caused by ischemia of the short posterior ciliary arteries that supply the optic nerve head and can result in irreversible loss of vision. Risk factors for NAION include vascular disease such as hypertension, atherosclerosis, vasculitis, and diabetes as well as the anatomical risk factors of a small optic nerve head and small optic cup.[24] The loss of vision occurring upon waking suggests that nocturnal hypotension plays a role in the development of NAION, a finding commonly seen in patients with OSA. Studies show the prevalence of OSA in patients who have had a NAION is 71% to 89%, and meta-analysis reveals patients with NAION are five times more likely to have OSA than the general population.[23,25,26]

The mechanism for developing NAION in patients with OSA is unknown though several theories exist. One theory proposes that vascular dysregulation of the optic nerve, coupled with the oxidative stresses of hypoxia and reperfusion as seen in apneic events, results in damage to the optic nerve and characteristic loss of vision.[25] Another theory proposes it is the increase in intracranial pressure (ICP) seen during these events that results in NAION.[23] The most likely etiology is a combination of these factors.

NAION is a sight-threatening condition that may result in significant visual field defects *(Figure 6)* and even bilateral blindness without proper management of risk factors. Although the presentation of NAION is generally unilateral, both eyes are at risk. Management of risk factors involves the treatment of underlying systemic disease. In patients with OSA, studies show a decreased risk of developing NAION in patients who are treated with CPAP.[27]

FIGURE 5:

Fundus photo showing localized disc edema (arrow) in a patient with nonarteritic ischemic optic neuropathy.

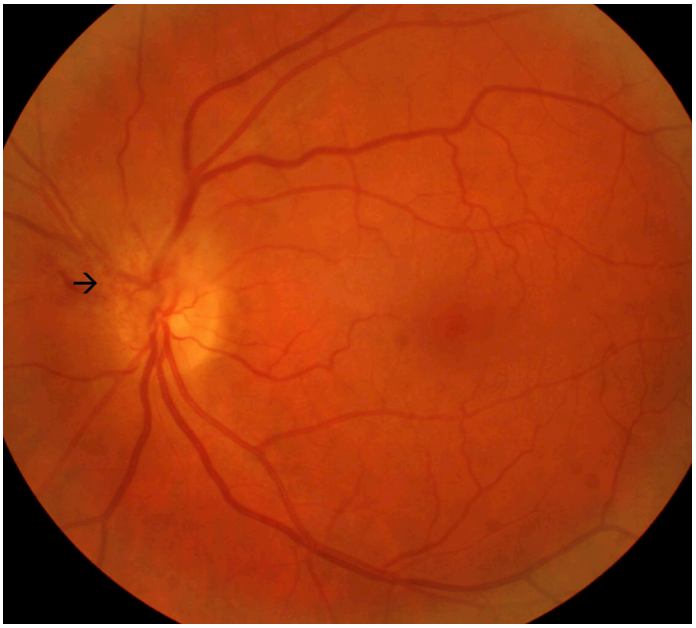
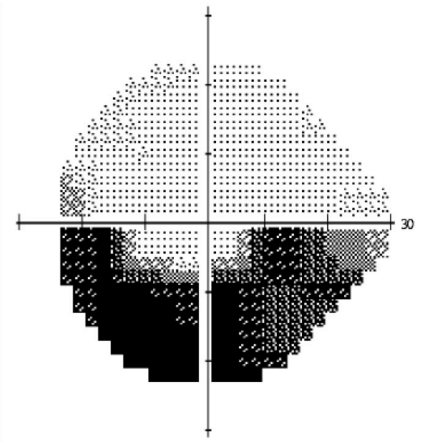


FIGURE 6:

Characteristic altitudinal visual field defect in nonarteritic ischemic optic neuropathy



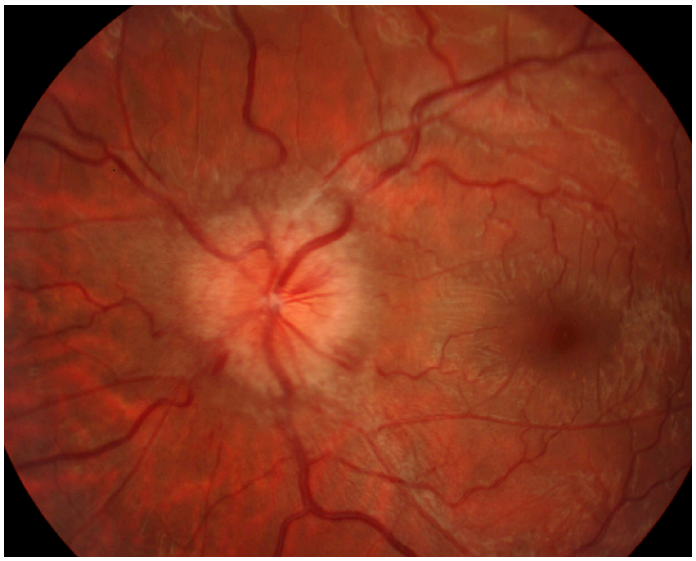
PAPILLEDEMA

Papilledema is the bilateral swelling of the optic discs secondary to increased ICP. Edematous optic discs appear elevated, with dilated capillaries and blurred disc margins *(Figure 7)*. The cause of increased ICP can be a mechanical blockage of intracranial fluid drainage (intracranial tumor), central nervous system (CNS) inflammation, or can be idiopathic in nature. Idiopathic cases are referred to as idiopathic intracranial hypertension (IIH) and are the form of papilledema associated with OSA. One study found 33% of individuals with IIH to have concurrent OSA.[27] Patients with papilledema may experience headache that is often worse in the morning, nausea, vomiting, and an increase in the size of the blind spot on formal visual field testing.

During apneic events blood oxygen levels decrease and carbon dioxide levels increase, resulting in cerebral vasodilation and a subsequent increase in intracranial blood volume. This increase in blood volume can over time result in venous sinus stenosis and the sustained increase in ICP we see in IIH.[28]

FIGURE 7:

Fundus photo of papilledema



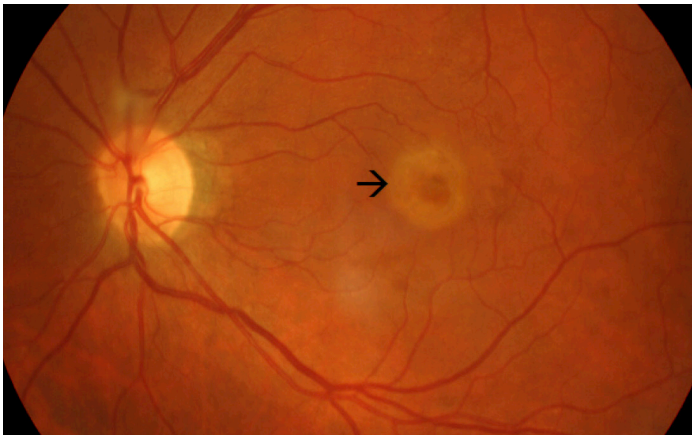
The preferred treatment for IIH is weight loss; studies show reducing body fat by 6% is generally successful in resolving IIH symptoms.[29] Diuretics such as acetazolamide, or surgical intervention by lumboperitoneal shunt or optic nerve sheath fenestration can be utilized in more severe or persistent cases to decrease ICP. Studies show that in patients with OSA and papilledema, CPAP can be used to reduce ICP.[15]

CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy is the fourth most common form of retinopathy, and is typically found in middle-aged males.[30] CSCR results in a serous detachment of the sensory retina in the location of the macula *(Figure 8)*. This can result in a mild reduction in visual acuity (20/30 to 20/60), central visual distortions, a reduction in contrast sensitivity and color vision disruption.[30] Meta-analysis has found a statistically significant association between OSA and CSCR.[31] One study found 66% of patients with CSCR to have OSA,[32] though additional research shows that when obesity is controlled for, there is no increase in the prevalence of CSCR for patients with OSA.[33]

FIGURE 8:

Fundus photo of central serous chorioretinopathy



The mechanism for CSCR is unknown, though elevated levels of endogenous cortisol have been found in affected individuals. It is theorized that vasospasm and endothelial dysregulation of choroidal vessels, as mediated by cortisol, increases vascular permeability. This allows for fluid leakage from retinal capillaries and a buildup of osmotic pressure beneath the retina. This pressure gradient pulls fluid through the retinal pigment epithelium into the choroid, resulting in CSCR's characteristic serous retinal detachment.[34] In patients with OSA, the oxidative stress of hypoxia and reperfusion results in vascular endothelial cell dysregulation and has also been shown to result in fluid leakage.

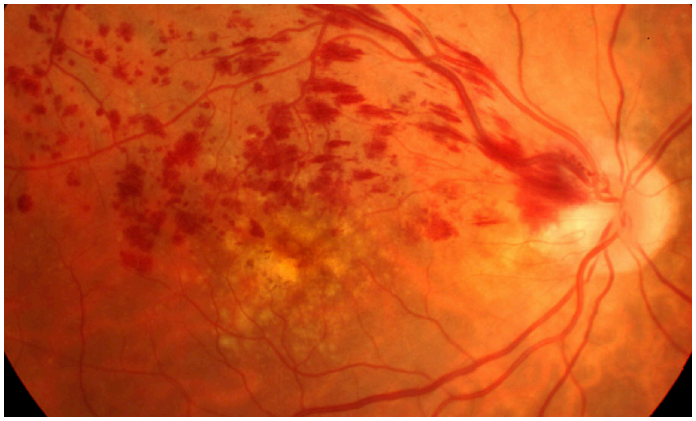
Most cases of CSCR are self-resolving, with patients recovering the majority of their visual acuity within three months.[30] If CSCR is recurrent however, permanent reduction can occur. Treatment for chronic or recurrent cases includes the use of laser and intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) to reduce retinal swelling. Systemic medications such as aldosterone inhibitors, beta-blockers, and carbonic anhydrase inhibitors have also been found to be effective in resolving CSCR.[30]

RETINAL VEIN OCCLUSION

Retinal vein occlusion (RVO) is the second most common vascular cause of blindness after diabetic retinopathy.[35] Vein occlusion most commonly presents as a branch retinal vein occlusion (BRVO) wherein only a portion of the retina is affected, though central retinal vein occlusion (CRVO) affecting the entire retina may also occur *(Figure 9)*. Patients that have a RVO often experience a sudden, painless, unilateral loss of vision or new visual field defect. These visual findings are a result of retinal ischemia following venous occlusion, as well as subsequent retinal hemorrhaging and edema. Studies suggest that there is an increased risk of RVO in patients with OSA.[35-37] A 2012 study found 37% of patients with RVOs to have sleep-disordered breathing, including sleep apnea.[36]

FIGURE 9:

Fundus photo of branch retinal vein occlusion



The mechanism for RVOs in patients with OSA is theorized to be hypercoagulability and vascular inflammation of retinal vessels secondary to increased nocturnal ICP and changes in retinal microcirculation.[37] Hypoxic conditions, as experienced in an apneic event, result in increased hematocrit levels and a predisposition for clot formation.[38] Patients with OSA have also been found to have an increase in blood viscosity independent of cardiovascular risk factors such as hypertension.[39]

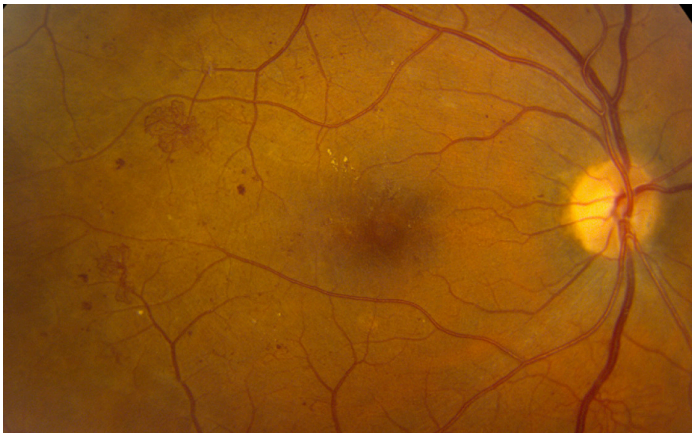
A study conducted in 2001 found that consistent use of a CPAP machine in patients with OSA reduced blood hypercoagulability, thus reducing the patient's risk of developing a stroke including a BRVO.[40] Treatment of RVOs after they have occurred consists of laser photocoagulation for patients with macular edema, as well as intravitreal steroid or anti-VEGF injections.[37]

COMPLICATIONS WITH ANTI-VEGF

Studies have found an increased prevalence of diabetic macular edema (DME) in patients with OSA.[41] Macular edema is the buildup of fluid within the macula, the area of the retina responsible for central vision. Damage to retinal blood vessels results in fluid leakage and swelling of the macula *(Figure 10)*. Patients with DME may experience reduced visual acuity and visual distortions, known as metamorphopsia. The treatment for DME is intravitreal injections of anti-VEGF. Studies have shown that patients with OSA are more resistant to this anti-VEGF treatment.[42,43] Hypoxia experienced during apneic events results in oxidative stress, inflammation, and vascular endothelial cell dysfunction of retinal vessels, all of which encourage the release of VEGF. Anti-VEGF resistance in patients with OSA is likely due to this increased retinal VEGF secretion.

FIGURE 10:

Fundus photo of diabetic retinopathy with macular edema



Although the link between OSA and other causes of intraretinal edema and neovascularization has not been studied, anti-VEGF resistance has implications for the treatment of numerous ocular diseases. Conditions such as exudative age-related macular degeneration and RVOs are also treated with intravitreal anti-VEGF injections. Management of OSA with CPAP however, has been shown to decrease retinal anti-VEGF resistance.[43]

CONCLUSION

Sleep apnea is a common sleep disorder associated with numerous ophthalmic conditions that merit co-management with eye-care providers.[1,3,4] Physicians should be aware of the many ocular side effects of OSA, some of which are sight threatening, so that appropriate referrals can be made, and damage to the patient's ocular health and vision prevented.

AUTHOR DISCLOSURES:

No relevant financial affiliations

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