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REVIEW

Ocular Health in Sleep Apnea: A Comprehensive Overview

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ABSTRACT Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a chronic sleep disorder characterized by complete or partial obstruction of the airway during sleep resulting in pauses in breathing (apneas) along with loud snoring, and frequent arousals from sleep. In addition to suffering from fragmented sleep and excessive daytime drowsiness, patients with OSAHS are at risk of serious ophthalmic complications including primary open-angle glaucoma (POAG), non-arteritic anterior ischemic optic neuropathy (NA-AION), idiopathic intracranial hypertension (IIH), and floppy eyelid syndrome. Effectively treating OSAHS can minimize long-term ocular complications. The authors review the common ocular complications associated with OSAHS and emphasize the need for early screening.

KEYWORDS Obstructive sleep apnea; obstructive sleep hypopnea (OSAHS), primary open-angle glaucoma (POAG); non-arteritic anterior ischemic optic neuropathy (NA-AION); idiopathic intracranial hypertension (IIH); floppy eyelid syndrome

INTRODUCTION

The obstructive sleep apnea/hypopnea syndrome (OSAHS) is a sleep disorder that affects up to 4% of middle-aged adults.[1] It is a significant medical problem characterized by intermittent pauses in breathing, referred to as apneas, occurring throughout the sleeping period. OSAHS is diagnosed by the existence of at least 10 apneas or hypopneas per hour of sleep confirmed by polysomnography along with excessive daytime sleepiness unexplained by other causes.[2] The interrupted breathing in OSAHS is associated with increased resistance to airflow during an effort to breathe.[3] This is in contrast to central sleep apnea (CSA) in which breathing is interrupted by a lack of effort.[4] As a result of the repeated pauses in breathing, some of which last more than a minute, patients with OSAHS often suffer from fragmented sleep, excessive daytime sleepiness, and other systemic conditions.[1,3]

Populations at risk of developing OSAHS are individuals with excessive tissue surrounding the airway or structural features that result in narrowing of the airways (Table 1).[5,6] These two predisposing risk factors are often typically associated with increased body mass index (BMI).[7–9] Ethnicity is also thought to

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TABLE 1 Risk factors for the Development of Obstructive Sleep Apnea [8,9]

Obesity
Male gender
Increased tissue surrounding airway
Structural narrowing of airway
History of cardiovascular disease
History of smoking
Family history of sleep apnea
Alcohol abuse

play a role in the pathogenesis of OSAHS with, in the United States, African-Americans carrying a higher risk than Caucasians.[10,11]

The increased risk of cardiovascular and neurovascular disease associated with untreated OSAHS presents is well documented.[1,12,13] OSAHS has also been linked to decreased libido, mood changes, forgetfulness, depression, nocturia, and gastro-esophageal reflux disease (GERD).[14–17] OSAHS can also be associated with ocular dysfunction that can potentially threaten vision. Unfortunately, up to 90% of patients with suspected OSAHS remain undiagnosed making early detection of such conditions a clinical challenge.[18–20]

Among the prominent ophthalmic considerations in OSAHS are the potentially increased risks of:[21,22]

1. Primary open angle glaucoma (POAG)
2. Non-arteritic anterior ischemic optic neuropathy (NA-AION)
3. Idiopathic intracranial hypertension (IIH)
4. Floppy eyelid syndrome (FES)

The following is an overview of these four OSAHS-associated ophthalmic complications with a particular focus placed upon information that will improve the clinician's ability to establish early diagnosis and prompt referral in order to reduce morbidity and mortality as well as to improve patient quality of life.

Primary Open Angle Glaucoma (POAG) and OSAHS

Epidemiology

POAG is present in 2,000,000 Americans and in 5.9%–12.9% of patients with OSAHS.[13,23,24]

Discussion

POAG is a progressive optic neuropathy that can result in irreversible optic nerve damage and peripheral visual field loss. It is recognized as the second most common global cause of blindness and is the most common cause of blindness in African-Americans.[25] Glaucoma shares several risk factors with OSAHS including older age, a putative association with cardiovascular disease, and, in the United States, a predilection for African-Americans.[9,25,26] Although increased intraocular pressure (IOP) is one of the major risk factors for developing glaucoma, individuals with normal IOP may also develop irreversible visual impairment.[27] The two most common subsets of glaucoma are POAG and angle closure glaucoma (ACG), both occurring in association with increased IOP. In contrast, optic nerve damage in the setting of normal IOP is referred to as normal-tension glaucoma (NTG). POAG accounts for more than 90% of cases of glaucoma in the United States.[28]

Recent data suggest an increased incidence of POAG in patients with OSAHS.[22,23] Incidentally, NTG also appears to occur with higher prevalence in patients with OSAHS when compared to patients without OSAHS.[23] Given this association, the current recommendations adjure clinicians to perform a thorough and accurate sleep history in all patients diagnosed with POAG and NTG.[23] Glaucoma is often asymptomatic making detection a challenge for many primary care physicians.[18] The characteristic clinical presentation is progressive deterioration of the peripheral visual field culminating in tunnel vision and/or complete blindness in severe cases. The asymptomatic course of the disease underscores the importance of screening for early detection of optic nerve disease in at-risk populations.[29]

Pathophysiology

The estimated prevalence of glaucoma in patients with OSAHS is between 5.9–12.9%.[13,24] Recent studies have suggested that the existence of OSAHS is associated with a higher incidence of optic nerve damage and resultant visual field defects in patients with glaucoma.[30] Although the association between OSAHS and glaucoma has been established, whether OSAHS is a risk factor for the development of glaucoma remains uncertain.[31] Studies suggest that the pathogenesis of OSAHS-induced glaucoma is related to optic nerve hypoperfusion.[13] The decreased ocular perfusion is thought to be either a direct effect of the hypoxic state in OSAHS or impaired autoregulation of the optic nerve vasculature.[26]

The ocular hypoperfusion described in OSAHS is suspected to cause retinal nerve fiber thinning which

may precede clinically detectable glaucomatous optic nerve changes or visual field loss.[32] The inclusion of new diagnostic technologies such as optical coherence tomography (OCT)- capable of detecting these retinal changes- may offer promise for minimizing future complications associated with glaucoma in patients with OSAHS.[33]

Diagnosis and Management

Although there is effective medical and surgical interventions to retard the progressive visual loss in glaucoma there is as yet no cure. Thus, it is important for clinicians to identify risk factors to assist in the early diagnosis and long-term management of the disorder.[34] Screening for glaucomatous abnormalities such as visual field changes, increased corneal thickness, or optic nerve damage are crucial to preventing complications associated with glaucoma.[35–37]

Screening methods in OSAHS patients with glaucoma are analogous to those used in screening glaucoma in the general population. These methods include tonometry, optic nerve assessment, perimetry, and pachymetry.[35,36,38,39] Tonometry describes the non-invasive procedure used to measure IOP.[35] Perimetry or visual field testing is recommended in patients suspected of glaucoma and should be conducted regularly in all patients with established glaucoma to monitor disease progression and response to treatment.[36] Pachymetry is a technique used to evaluate corneal thickness which is an important indicator in accurately diagnosing IOP.[40] Corneal thickness has been shown to be a major risk factor for the development of glaucoma.[38,40] Finally, fundus examination via slit-lamp and indirect ophthalmoscopy are recommended to evaluate changes in the optic nerve (i.e.,. cupping or notching) and thinning of the retinal nerve fiber layer.[35]

Depending on the severity of the individual case, glaucoma can be treated via pharmacological therapy, laser treatment, or surgical intervention.[41,42] The primary classes of pharmacological therapy are alpha agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandins (Table 2).

Alpha agonists, Beta blockers, and carbonic anhydrase inhibitors act by decreasing the production of

TABLE 2 Pharmacologic Treatment of Glaucoma[43]*

Class	Mechanism of Action	Examples
Alpha-2-adrenergic agonists	• Result in decreased aqueous humor formation via stimulation of alpha-2 receptors of the eye	• Apraclonidine • Brimonidine
Beta-adrenergic blockers	• Block beta-2 receptors in the ciliary process to initiate decreased aqueous humor production	• Timolol • Betaxolol • Carteolol • Metipranolol • Levobunolol
Calcium Channel Blockers	• Inhibit calcium influx in vascular smooth muscles of the eye resulting in decreased vascular tone and increased blood flow.	• Diltiazem • Nifedipine • Verapamil
Carbonic Anhydrase Inhibitors (CAIs)	• Inhibit the ciliary body enzyme carbonic anhydrase resulting in decreased rate of aqueous humor formation	• Acetazolamide • Methazolamide • Dorzolamide • Dichlorphenamide
Epinephrine derivatives	• unclear	• Epinephrine • Dipivefrin hydrochloride
Hyperosmotic agents	• Reduces IOP by increasing plasma tonicity to draw water out of the eye.	• Mannitol • Glycerin • Isosorbide
Miotics	• Direct-acting cholinergic stimulation within the eye resulting in increased aqueous outflow	• Pilocarpine • Carbachol
Prostaglandin analogs	• Increase uveoscleral outflow resulting in decreased IOP	• Latanoprost • Bimatoprost • Travoprost • Unoprostone

* Table 2 adapted with permission from Hazin et al.[46]

aqueous humor while prostaglandins increase the outflow of aqueous humor.[44] Argon laser trabeculoplasty is a laser procedure which targets the trabecular meshwork to improve the outflow of aqueous humor from the eye.[45] In instances where either medications or laser procedures are ineffective, incisional filtering surgery, such as a trabeculectomy, may be warranted to improve drainage of aqueous humor.[43,46]

Nonarteritic Anterior Ischemic Optic Neuropathy (NA-AION) and OSAHS

Epidemiology

The incidence of NA-AION in the general population is approximately 8,000 per year in the United States.[47] Although a recent study concluded that up to 70% of patients with OSAHS may have NA-AION; large cohort, long-term natural history studies are needed to confirm the validity of this association.[48,49]

Discussion

NA-AION describes the medical condition of visual loss due to optic nerve damage secondary to disruption of blood flow to the optic nerve head. NA-AION is one of several subsets of ischemic optic neuropathy and is often associated with cardiovascular risk factors. NA-AION usually afflicts older adults and results in 20/200 vision or less in approximately 40% of patients.[50] Unlike glaucoma, which runs a gradual and prolonged course, NA-AION has a characteristic acute onset of visual loss.[51] Most cases involve monocular hemifield loss often in the lower half of the visual field.[52]

Some patients with NA-AION have reported visual symptoms upon awakening from sleep prompting some researchers to suggest the possibility of nocturnal hypotension as a contributing factor in the pathogenesis of NA-AION.[53] Other associated risk factors for NA-AION include diabetes mellitus, arteriosclerosis, and arterial hypertension, all of which are also closely associated with OSAHS.[26,54] The presence of OSAHS also appears to confer an increased risk of developing NA-AION.[55]

Pathophysiology

The fact that a significant number of patients with NA-AION discover visual loss upon awakening from sleep has suggested OSAHS may play a role in the pathophysiology of the disease.[56] The true mechanism underlying the pathogenesis of NA-AION is not clearly understood but it is believed to be a microvasculopathy of the posterior ciliary arteries that supply the optic nerve head.[57,58] The onset of ischemia results in swelling and as the swelling progresses the vascular circulation is further compromised resulting in damage to the optic nerve.[57,58]

Diagnosis and Management

Although visual loss from NA-AION is irreversible, prompt recognition and diagnosis can minimize the risk of further damage to vital ocular structures from the systemic risk factors associated with the disease. Failure to address underlying medical issues in patients with NA-AION may result in future visual loss in the unaffected eye or systemic complications.[59] Once viewed as a standard therapy for treating NA-AION, optic nerve sheath fenestration is no longer advocated as a suitable treatment of the condition.[60]

Idiopathic Intracranial Hypertension (IIH) and OSAHS

Epidemiology

It has been estimated that less than 200,000 people have IIH in the general population of the United States.[61] There is no information on the incidence or prevalence of IIH in patients with OSAHS.[62] There is no known racial or age predilection for the coexistence of IIH and OSAHS.[62,63] Although IIH afflicts young females more than males, there appears to be no known gender predilection for the existence of IIH in patients with OSAHS.[62,63]

Discussion

IIH (also known as benign intracranial hypertension or pseudotumor cerebri) is a condition associated with signs and symptoms that arise from elevated intracranial pressure (ICP) in the presence of normal neuro-imaging and cerebrospinal fluid composition.[64,65] Obesity is a risk factor for the development of IIH.[65,66]

Papilloedema (PA) refers to bilateral optic nerve swelling secondary to increased ICP (Figure 1).[67] PA can be a manifestation of a space-occupying lesion of the brain as well as IIH.[67,68] Other etiologies of PA include hydrocephalus, venous sinus thrombosis, meningitis, medications, and elevated blood pressure. PA is present in the majority of IIH cases.[69,70] The absence of PA in a case of IIH is referred to as 'atypical intracranial hypertension.'[71] The presentation of PA is most often

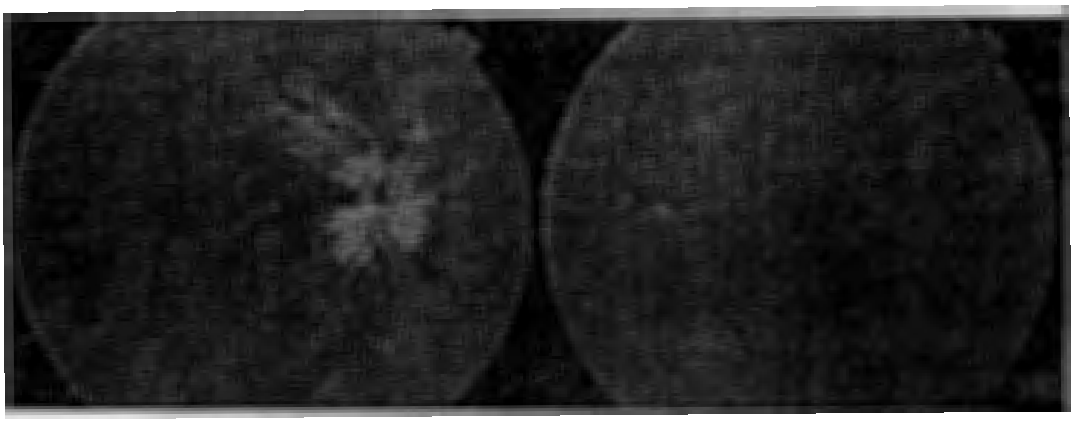

FIGURE 1 Fundus photograph of papilledema. There is bilateral optic nerve edema with hemorrhages due to raised intracranial pressure.

bilateral and its development has no predilection for a particular race or gender.[62,63] Regardless of etiology, PA is the hallmark sign of intracranial hypertension and therefore constitutes a potentially fatal condition.[72] Therefore, a thorough medical evaluation and immediate attention to the underlying cause of PA is necessary to minimize potential complications.[64,71]

Although no epidemiological data exist on the relationship between IIH and OSAHS, it is believed that patients with sleep apnea run a greater risk of developing IIH than the general population.[65,66,73,74] The hypoxemia that characterizes periods of sleep apnea in OSAHS patients is thought to exacerbate IIH and lead to significantly elevated ICP.[75] A recent study demonstrated that patients with OSAHS had markedly elevated ICP while asleep in comparison to when they were awake underscoring the need to effectively treat OSAHS.[75] Other studies have suggested that sleep-related breathing problems or other situations such as obesity resulting in nocturnal hypoxemia lead to IIH.[76]

The most common clinical features of IIH are headache, PA, and visual disturbances such as visual loss, blurred vision, and diplopia (Table 3).[77–79] The loss of peripheral vision in IIH is often gradual and can lead to progressive blindness in severe cases. Acute severe visual loss can occur but is very rare. For those patients that lose vision, often do so because the condition remains unrecognized for an extended period of time. The importance of early recognition is underscored by the fact that up to 94% of patients with IIH will experience visual loss.[80] Nonetheless, some patients with IIH can have normal visual acuity and color perception on presentation and during the course of the disease.[80]

TABLE 3 Symptoms of IIH and PA

Headache
Vomiting
Nausea
Transient loss of vision
Blurred vision

Pathophysiology

The pathological mechanism responsible for IIH remains poorly understood.[66] It has been proposed that brain edema and the resulting symptoms in IIH occur as a result of a dysfunctional hematoencephalic barrier.[81] This dysfunction initiates a cascade of events within the central nervous system (CNS) that culminates in the hyperproduction of interstitial fluid leading to extracellular brain edema and the resultant clinical symptoms.[81] This may explain why repeated lumbar punctures and CSF diversion procedures have yielded positive results in such patients.[81]

These events also lead to the development of PA which is thought to result from decreased cellular conduction along the optic nerve.[82] Axoplasmic stasis, or slowed cellular conduction along the optic nerve, results in the accumulation of intracellular fluids within the optic nerve. The subarachnoid space of the optic nerve is surrounded by the optic nerve sheath and as CSF pressure gradually increases in IIH the pressure is transferred to the optic nerve further decreasing optic nerve conduction and leading to edema of the optic nerve head.[83] This state of neural stagnation can also result from inflammatory conditions, demyelinating diseases, vascular hypoperfusion, and physical compression of the nerve.[26,84,85]

Diagnosis and Management

A thorough history and physical examination are recommended in patients suspected of IIH in order to rule out malignant hypertension or other conditions with similar clinical presentations. IIH is a diagnosis of exclusion and radiological evaluation is recommended to exclude an intracranial lesion.[77,86] Thus, a reflective differential diagnosis may facilitate early treatment and reduce the likelihood of misdiagnosis (Table 4). Ophthalmologic testing of visual acuity and color vision should yield normal results in such patients.[80] Notwithstanding, since most cases of visual loss in PA are asymptomatic, objective measurement of visual fields using perimetry can be instrumental in determining the course of therapy.

The most common visual field defects associated with IIH are loss of the inferonasal field, enlargement of the physiologic blind spot, and general constriction of the peripheral visual field.[87,88] African-American men, patients with pre-existing glaucoma, pre-existing arterial hypertension, and those with recent weight gain may be at increased risk for severe visual loss in the setting of IIH.[80] Prompt diagnosis of IIH is critical in preventing visual loss and minimizing associated complications.[89,90] Immediate institution of treatment yields improvement in approximately 50% of patients with IIH.[80]

Dilated examination and the use of indirect ophthalmolscopy should reveal PA.[72,80] Following initial evaluation, neuroimaging via computed tomography (CT) and magnetic resonance imaging (MRI) with a contrast agent are warranted in order to exclude intracranial masses, abscesses, or hydrocephalus as causes of PA.[87] Negative imaging studies in the setting of suspected PA necessitates lumbar puncture to rule out neoplastic, inflammatory or infectious causes of raised ICP.[87] Regular, coordinated consultations with a neurologist is encouraged in all patients in whom lumbar puncture reveals elevated CSF pressure (>20–25 mmHg).[80,87]

In patients with concomitant OSAHS and IIH, treating the underlying pulmonary issue often leads to significant improvement of the ocular and neurological symptoms.[94–96] If arterial hypertension or an infectious etiology are confirmed aggressive treatment of these underlying conditions are needed.[12,14,74] In the presence of visual loss, surgical intervention via optic nerve sheath fenestration or a CSF diversion procedure are options but often medical therapy (acetazolamide) is successful.[97] OSAHS should be considered in the diagnostic evaluation of patients with IIH because treatment of the underlying causes of OSAHS can be more effective than traditional IIH therapies.[98,74]

TABLE 4 Diagnosis for IIH[89–94]

Intracranial mass
Increased cerebrospinal fluid (CSF) production, i.e., hydrocephalus or choroid plexus papilloma
Decreased CSF absorption, i.e., cerebral venous infarction
Arteriovenous fistula
Malignant hypertension
Medications (i.e., tetracycline, Vitamin A preparations)
Inflammation (i.e., neurosarcoidosis)
Meningitis (i.e., cryptococcus)

Floppy Eyelid Syndrome (FES) and OSAHS

Epidemiology

The incidence of FES in the general population is unknown.[99,100] However, approximately 0.05%–2.3% of patients with OSAHS will exhibit FES at sometime during the course of their illness.[101,102]

Discussion

FES, or lax eye syndrome, describes a relatively rare condition characterized by easily evertable upper eyelids, eyelid laxity, chronic irritation of the ocular surface and other nonspecific ocular symptoms (Figure 2).[103,104] Typical features of FES include dry eyes, foreign body sensation, ocular pruritus, blurred vision, ocular discharge, ptosis, ectropion, dystopia, corneal ulcer, and unilateral conjunctivitis (Table 5).[105,106] Patients with FES often present to their primary care physician with non-specific chronic ocular irritation that is resistant to medical treatments.[103] Involvement of the cornea and conjunctiva are a frequent cause of morbidity.[104] Although originally described in

TABLE 5 Symptoms of Floppy Eyelid Syndrome

dry eyes
foreign body sensation
Pruritis
blurred vision
ocular discharge
Ptosis
Ectropion
Dystopia
unilateral conjunctivitis
corneal ulcer

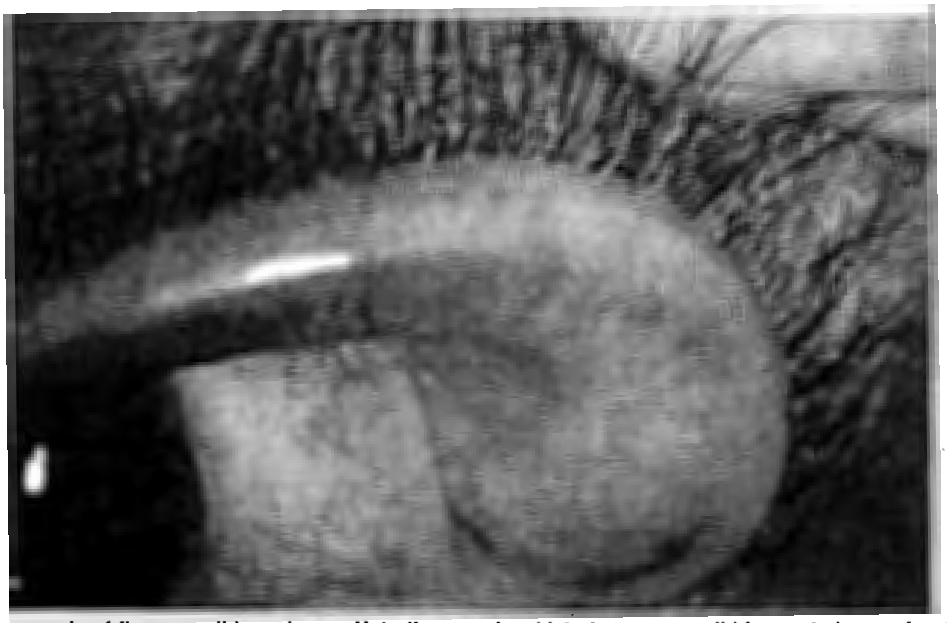

FIGURE 2 Clinical example of floppy eyelid syndrome. Note the ease in which the upper eyelid is everted exposing the underlying tarsal conjunctiva, bulbar conjuctiva, and cornea to trauma.

obese, middle-aged men, recent studies have demonstrated the prevalence of FES in non-obese male and female patients.[104,107] Notwithstanding, increased BMI may place an individual at increased risk of developing FES.[99] Thus, the diagnosis should be considered in any obese patients presenting with chronic ocular redness and discharge.[99]

Recent studies have reported a link between FES and OSAHS.[103] In some cases, FES may be the presenting symptom of OSAHS.[104] Treating the underlying obesity in patients with OSAHS can yield significant improvement of symptoms in patients with concomitant FES.[104]

Pathophysiology

Our current understanding of the pathogenetic mechanisms of FES is uncertain. Possible explanations to explain the instability of eyelid scaffolding in FES have been based on one of three premises:

[1.] The vitality of indigenous mechanical factors
[2.] The action of elastin degrading enzymes within the eyelid
[3.] Tear distribution.

The mechanical hypothesis behind FES attributes the disorder to mechanical abrasion of the ocular surface that occurs during "face down" sleeping.[26] Recent studies have suggested that levels of tarsal elastin are dramatically diminished in patients with FES.[103,108] The decreased elastin levels results in decreased tarsal plate rigidity within the upper eyelid ultimately causing spontaneous eversion of the lid.[26,103] Other studies have suggested inadequate distribution of tears and subsequent desiccation of the ocular surface as a possible cause of FES.[109]

Diagnosis and Management

FES causes significant ocular symptoms and morbidity.[99] Although surgical intervention is indicated in severe forms, most cases respond well to supportive measures such as ocular lubrication and eyelid shielding at bedtime.[99] Surgical intervention by correcting the horizontal laxity and redundant eyelid tissues can lead to resolution of symptoms particularly if associated with ptosis.[100,110] Surgical horizontal eyelid tightening has been show to improve eyelid stability and position with satisfactory long-term results.[100,110] Treatment of the underlying pathophysiologic conditions of OSAHS can lead to significant improvement in FES-associated ocular symptoms.[104]

CONCLUSIONS

Given the fact that eye disorders associated with OSAHS can result in permanently impaired vision, all patients with OSAHS should be asked about ocular

symptoms. This can hasten referral to an ophthalmologist whose assessment can prevent visual loss in at-risk patients. Further, all physicians should be aware of the primary eye disorders that are most commonly associated with OSAHS, namely POAG, NA-AION, IIH, and FES. Referral to a sleep physician for investigation and possible treatment for OSAHS is warranted in such patients since treating the underlying OSAHS can help improve the ocular impairment in most of these patients.

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