Sleep Disorders and the Eye

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During the past decade, associations between sleep disorders and certain ophthalmologic disorders have been increasingly recognized. To review the literature on these important associations, we conducted a PubMed search using combinations of the following terms: *sleep disorders*, *sleep apnea*, *circadian rhythm disorder*, *continuous positive airway pressure*, *eye disease*, *floppy eyelid syndrome*, *glaucoma*, *ischemic optic neuropathy*, *papilledema*, *nocturnal lagophthalmos*, and *vision loss*. We limited our search to articles published in English that involved human participants. All available dates were included. One of the most common sleep disorders, obstructive sleep apnea, has been associated with a variety of eye diseases, including glaucoma, nonarteritic anterior ischemic optic neuropathy, floppy eyelid syndrome, papilledema, and continuous positive airway pressure–associated eye complications. Nocturnal lagophthalmos manifests during sleep and is defined as the failure to fully close the eyelids at night. Finally, blindness is associated with increased risk of circadian rhythm disorders. On the basis of the existing published literature, we discuss these rarely recognized associations, potential pathophysiologic mechanisms, and the effect these associations have on the clinical management of patients. The knowledge of these associations is important for the primary care physician, ophthalmologist, and sleep physician so that underlying sleep disorders or ophthalmologic disorders can be detected.

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CPAP = continuous positive airway pressure; ICP = intracranial pressure; IOP = intraocular pressure; MMP = matrix metalloproteinase; NAION = nonarteritic anterior ischemic optic neuropathy; NTG = normal-tension glaucoma; OSA = obstructive sleep apnea/hypopnea syndrome; POAG = primary open-angle glaucoma; RDI = respiratory disturbance index

Absolute sleep deprivation is well known to lead to a decline in mental function, including cognitive and behavioral performance and, if prolonged sufficiently, personality changes, psychosis, and death.[1,2] During the past 2 decades, disorders of sleep have become better recognized and characterized, and it has become apparent that both quality and quantity of sleep are important. Although sleep historically has been thought to primarily serve the brain, more recent evidence has suggested that sleep disorders also influence extracerebral physiologic function. Downstream effects include cardiovascular disease, cerebrovascular disease, and even metabolic derangements possibly increasing the risk of obesity and diabetes mellitus.[3]

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Given these known physiologic consequences of sleep disorders, it is not surprising that important associations exist between ophthalmologic and sleep disorders. In this review, we discuss the rarely recognized associations between specific ophthalmologic disorders and specific sleep disorders, the potential pathophysiologic mechanisms of these associations, and the effect these associations have on the clinical management of patients.

The literature search for this review was conducted through PubMed. An initial exploratory search was performed using the search terms *sleep disorders and eye disease*. On the basis of the results from this search and preliminary review of the literature, additional searches were performed using the following terms: *floppy eyelid syndrome and sleep apnea*, *glaucoma and sleep apnea*, *ischemic optic neuropathy and sleep apnea*, *papilledema and sleep apnea*, *continuous positive airway pressure and eye disease*, *nocturnal lagophthalmos*, and *circadian rhythm disorder and vision loss*. Searches were limited to articles published in English that involved human participants. All available dates were included. Case reports, editorials, and nonrelevant articles were excluded except when pertinent for historical or background information or when larger studies and case series were unavailable. Bibliographies of relevant references were also scanned, in a process referred to as pearling, to identify additional articles not identified in the database searches.

OBSTRUCTIVE SLEEP APNEA–ASSOCIATED EYE DISEASES

Obstructive sleep apnea/hypopnea syndrome (OSA) is characterized by repetitive episodes of upper airway occlusion during sleep combined with symptoms, most commonly excessive daytime sleepiness. Airflow obstruction results from loss of normal oropharyngeal tone during sleep. Critical narrowing usually occurs at the level of the soft palate or at the base of the tongue. Apneas can last from 10 seconds to 2 minutes and are terminated by microarousals or full arousals from sleep. Hypopneas occur because of partial pharyngeal airway collapse and are defined by at least a 30% reduction in airflow accompanied by at least a 3% to 4% oxygen desaturation and/or an arousal. The average number of apneas/hypopneas per hour is referred to as the apnea/hypopnea index, and the number of respiratory-related arousals per hour is referred to as the

TABLE 1. **Severity of Obstructive Sleep Apnea/Hypopnea Syndrome Based on the Apnea/Hypopnea Index**[a]

Severity	Score
Normal	<5
Mild	5-15
Moderate	15-30
Severe	>30

[a] The apnea/hypopnea index indicates the average number of apneas plus hypopneas per hour of sleep.

respiratory disturbance index (RDI).[4-7] Table 1 lists the standard grading system, based on the apnea/hypopnea index, for OSA severity.[8] Oxyhemoglobin desaturation may vary from mild (low of 90%) to very severe (<30%). In addition to arousals and desaturations, the termination of apneas and hypopneas leads to increased sympathetic activity and spikes in blood pressure, which, over time, may lead to a loss of the normal diurnal dip in the mean blood pressure.[5]

The prevalence of OSA diagnosis has been increasing in the United States because of both increasing rates of obesity and increased awareness of the disorder. Multiple observational studies have identified OSA as an independent risk factor for the development of high blood pressure, cardiovascular disease, and cerebrovascular disease.[5,9,10] The Sleep Heart Health Study reported a dose-response relationship between the RDI in patients with OSA and vascular disease, heart failure, and stroke.[11] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure identified OSA as a treatable secondary cause of hypertension.[12] In addition, OSA has been strongly linked to increased risk of myocardial infarction, cardiac arrhythmias, pulmonary hypertension, cardiac-related mortality, and all-cause mortality.[4-6,9]

Table 2 summarizes the symptoms and clinical signs associated with OSA. The presence of any of these symptoms, particularly when combined with any of the clinical examination features or pertinent comorbidities, such as hypertension, heart disease, or stroke, should prompt the physician to recommend further evaluation. Polysomnography is necessary for diagnosis. Treatment typically requires nasal continuous positive airway pressure (CPAP), in which the optimum pressure is determined during a therapeutic polysomnogram. Conservative options include weight loss and sleep position restriction in patients with milder forms of the syndrome. Oral mandibular advancement devices and surgery are used in select patients or in patients in whom CPAP treatment fails.

TABLE 2. **Symptoms and Clinical Examination Features Associated With Obstructive Sleep Apnea/Hypopnea Syndrome**

Symptoms
Snoring
Excessive daytime sleepiness or fatigue
Witnessed apneas by a bed partner
Morning headaches
Waking up choking or short of breath
Insomnia
Clinical examination features
Obesity
High Mallampati classification[a]
Large neck circumference (men, >17 in; women, >16 in)
Tonsillar hypertrophy
Retrognathia

[a] On the basis of the oropharyngeal structures that can be visualized with maximal mouth opening and tongue protrusion. Decreasing levels of visualization result in a higher score.

Given the vascular consequences of OSA, it is not surprising that ophthalmologic manifestations exist, although not all can be directly linked to these pathophysiologic mechanisms. Obstructive sleep apnea has been associated with the following ophthalmologic conditions: floppy eyelid syndrome, primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG), nonarteritic anterior ischemic optic neuropathy (NAION), papilledema, and CPAP treatment–associated eye complications.

Floppy Eyelid Syndrome

Floppy eyelid syndrome was first described in 1981 by Culbertson and Ostler[13] in middle-aged obese men. Floppy eyelid syndrome is characterized by easily everted (ie, turned inside out such that the underlying tarsal conjunctiva is exposed) floppy eyelids and papillary conjunctivitis. Since that time, multiple case reports and large case series have led to a better description of the disorder, although its pathophysiology remains obscure.[13-19] Symptoms of floppy eyelid syndrome include watering, stickiness, discomfort, and blurred vision in the involved eye(s). Symptoms are usually worse on wakening. Persons afflicted may report that their eyelids spontaneously evert during sleep. Symptoms usually correspond to the eye on the preferred, dependent sleeping side. If both eyes are affected, the patient usually alternates sides during sleep or sleeps prone.[17]

Physical examination findings include rubbery, floppy, and easily everted eyelids (Figure 1). Application of upward traction to the upper eyelid margin will often result in spontaneous eversion and/or exposure of the underlying tarsal conjunctiva in the involved eye.[18] Mild ptosis, downward pointing eyelashes, or inversion may be present. Papillary conjunctivitis is apparent in the involved eye. Corneal involvement is common and may include punctuate keratopathy, gross surface scarring, ulceration, or increased vascularization.[16] Keratoconus (ie, noninflammatory thinning and bulging of the cornea causing a distortion of the normal shape of the cornea and resulting in extreme myopia and/or astigmatism) and infectious keratitis have also been described.[14,15,17]

The pathophysiologic mechanism is not well investigated. Some authors have suggested the role of mechanical

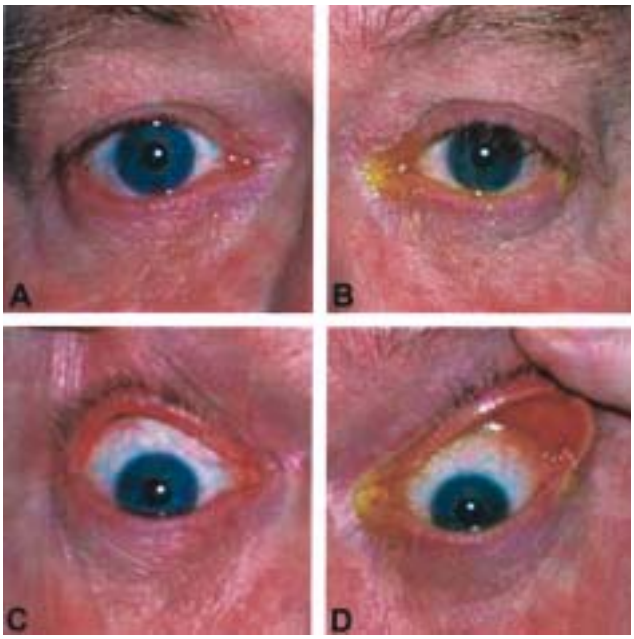

FIGURE 1. Patient with floppy eyelid syndrome involving the left eye. A, Unaffected right eye. B, Left-sided, mild, upper eyelid ptosis with partially inverted eyelashes. C, Unaffected right eye without eversion after upward traction. D, Abnormal eversion of the left eyelid with exposure of the underlying tarsal conjunctiva after gentle upward traction.

stress (rubbing and stretching of the eyelid against the pillow or bed while asleep) and/or alternating periods of ischemia and reperfusion resulting in tissue inflammation.[16,18] Netland et al[20] found a loss of elastin fibers in the tarsal plates of affected patients. A more recent study found an increase in the immunoreactivity for the elastolytic processes, particularly an increase in matrix metalloproteinases (MMPs), which likely accounts for this loss of elastic tissue.[21] Increased MMPs can be seen with mechanical stress and with ischemic reperfusion injury in other tissues.[18] Finally, Taban et al[22] retrospectively studied 11 patients with floppy eyelid syndrome and found elevated blood leptin levels, which correlated with body mass index. Leptin is known to affect angiogenic processes in endothelial cells and increase MMP expression and activity.[23,24]

Since its initial description, floppy eyelid syndrome has been linked to a variety of systemic disorders, including obesity, hypertension, diabetes mellitus, ischemic heart disease, and psoriasis.[17,18] However, the most well-established association is with OSA. Most of the early cases described in the literature occurred in obese men, some having pickwickian syndrome (characterized traditionally by a combination of obesity, alveolar hypoventilation, excessive daytime sleepiness, and OSA). In a series of 3 cases, Woog[19] was the first to suggest an association with OSA. Since then, several case series have examined the association and prevalence of OSA and floppy eyelid syndrome.[17,25-28] All studies reported to date are limited, and no large longitudinal cohort study has clarified the actual prevalence of the association between these 2 disorders. The studies are summarized in Table 3.[17,25-28] The prevalence of OSA in patients with floppy eyelid syndrome ranged from 96% to 100% in the 2 retrospective case reviews performed by McNab.[17,26] The largest review included 50 patients, 96% of whom had symptoms suggestive of OSA. Forty-three were men (86%) and 44 (88%) were obese. Twenty-seven of these patients underwent polysomnography, 26 (96%) of whom were confirmed to have OSA.[26] Two studies evaluating the prevalence of floppy eyelid syndrome in patients with OSA demonstrated a relatively low prevalence, ranging from 4.5% to 5.0%.[17,25] The correlation between parameters of OSA and parameters of floppy eyelid syndrome has also been evaluated. Mojon et al[27] found that the RDI positively correlated with the presence or absence of floppy eyelids, eyelid distraction distance, and lacrimal gland prolapse and negatively correlated with tear film break-up time. Others have also shown that OSA is associated with increased eyelid hyperlaxity.[28] McNab[18] found that floppy eyelid syndrome may be an indicator of severe OSA, and there may be a predilection for younger patients with OSA.

TABLE 3. **Prevalence Studies Investigating the Association Between Floppy Eyelid Syndrome and OSA**[a]

Reference	Study design	No. of patients	Type of condition	Findings
McNab,[17] 1997[b]	Retrospective case review	17	Floppy eyelid syndrome	8 of 8 studied with polysomnography had OSA
	Cross-sectional	20	OSA	5% had floppy eyelid syndrome
McNab,[26] 2005	Retrospective case review	50	Floppy eyelid syndrome	96% had symptoms of sleep apnea; 26 (96%) of 27 studied with polysomnography had OSA
Karger et al,[25] 2006	Masked cross-sectional	59	OSA	4.5% (95% confidence interval, 0.5%-15.1%) prevalence of floppy eyelid syndrome
Mojon et al,[27] 1999	Prospective case series	72	Referred for OSA evaluation	RDI correlated positively with eyelid distraction distance (P=.05) and presence of floppy eyelids (P=.01)
Robert et al,[28] 1997	Cross-sectional	69	Evaluated for sleep disorders	Increased eyelid hyperlaxity was observed in OSA

[a] OSA = obstructive sleep apnea/hypopnea syndrome; RDI = respiratory disturbance index.
[b] This study included 2 separate study groups.

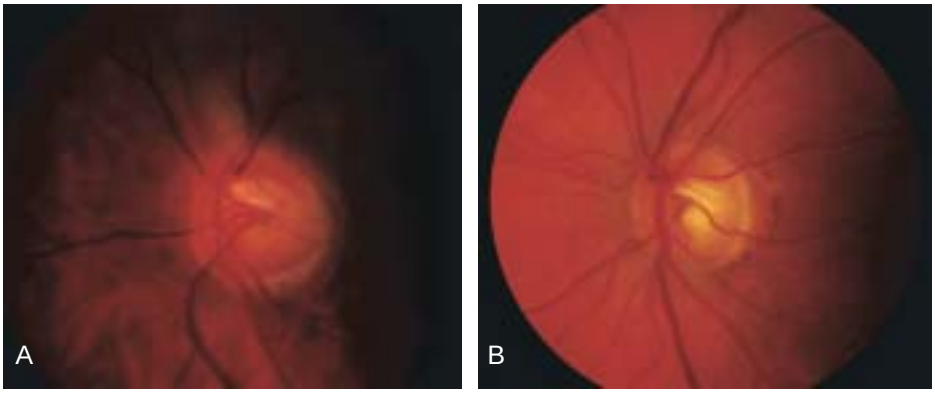

FIGURE 2. Funduscopic images from patients with primary open-angle glaucoma. A, Left optic nerve showing thinning of neuroretinal rim with associated peripapillary atrophy inferior temporally and increased cupping. B, Left nerve showing increased cupping, mild peripapillary retinal pigment epithelial changes, and thinning of the neuroretinal rim at the 5 o'clock position.

The actual pathophysiologic mechanism linking the 2 disorders is unknown. Both plasma leptin and MMP levels are reported to be elevated in patients with OSA.[29,30] Intermittent hypoxia may also trigger an increased MMP level in patients with OSA, and some have hypothesized that ischemic reperfusion–type injury during apneas may have a role.[31,32]

Patients with suspected floppy eyelid syndrome should be referred for a full ophthalmologic evaluation. If floppy eyelid syndrome is confirmed, patients should strongly be considered for evaluation of OSA. Treatment of floppy eyelid syndrome can consist of conservative measures, including weight loss, eye shields or other protective devices, lubricants, and occasionally corticosteroids or antibiotics based on ophthalmologic findings.[16,18] Resolution after treatment of OSA has been well documented.[33] Surgical tightening of the eyelids can be performed in medically refractory cases, but high recurrence rates after surgery have been documented in patients with untreated OSA. This observation further stresses the importance of managing OSA in these patients.[18]

Glaucoma

The term *glaucoma* refers to a group of distinct ophthalmologic disorders characterized by progressive optic neuropathy with slow progressive degeneration of retinal ganglion cells and their axons, resulting in a distinct appearance of the optic disc and an associated pattern of visual field loss.[34] Glaucoma is the second most common cause of blindness and the most common cause of irreversible blindness. Types of glaucoma include acute angle–closure glaucoma, POAG, and other miscellaneous forms related to inflammatory conditions or congenital defects.[35] Obstructive sleep apnea/hypopnea syndrome has been linked to POAG.[36]

The most common form of glaucoma is POAG. Risk factors include increased age, genetic factors, a thin cornea, and an intraocular pressure (IOP) higher than 21 mm Hg.[37-40] Symptoms are slow and progressive and primarily consist of visual loss. Because central vision is spared early in the disease, by the time most patients notice a loss of vision, severe damage has occurred.[35] Many cases are discovered during routine eye examinations. The diagnosis of POAG is based on a funduscopic examination that reveals characteristic changes in the optic nerve (Figure 2) and/or characteristic visual field loss. Optic disc changes in POAG include large cup-to-disc ratio, progressive optic disc cupping, asymmetry of optic disc cupping, hemorrhage of the optic disc, parapapillary retinal pigment epithelial changes, segmental thinning of the optic nerve rim that may result in acquired pit of the optic nerve, and retinal nerve fiber layer defects.[34] If IOP is normal but the characteristic optic nerve and visual field findings are present, it is frequently termed *normal-tension glaucoma*. This is thought to represent a spectrum of POAG because these patients also respond to lowering of the IOP.[35]

An increase in IOP is thought to be one of the primary pathophysiologic mechanisms, although the complete biologic basis is not fully understood and ischemia may also have a role. Elevated IOP is thought to compromise retinal ganglion cell axons and lead to degeneration and cell death through both direct compression and from deformation of the optic disc, leading to stretching and remodeling.[41-43] Other processes may contribute to the death of retinal ganglion cells and optic nerve fibers, including dysfunctional blood flow autoregulation that results in ischemia and hypoxia, oxidative stress with the formation of inflammatory cytokines and free radicals, and aberrant immunity.[44-46]

In 1982, Walsh and Montplaisir[47] were the first to describe the occurrence of POAG and OSA in the same

TABLE 4. **Prevalence Studies Investigating the Association Between POAG/NTG and OSA**[a]

Reference	Study design	No. studied	Type studied	Findings
Mojon et al,[48] 2000	Cross-sectional	30	POAG	20% had OSA based on trend overnight oximetry studies
Mojon et al,[49] 2002	Cross-sectional	16	NTG	44% had OSA, 63% (5/8) of those older than 64 y
Onen et al,[50] 2000	Case-control	212	POAG	Patients with POAG had a higher prevalence of snoring (47.6%, *P*=.04), snoring plus excessive daytime sleepiness (27.3%, *P*=.01), and snoring plus excessive daytime sleepiness plus insomnia (14.6%, *P*=.01)
		218	Controls	
Girkin et al,[51] 2006	Retrospective nested case-control	667	Glaucoma	Patients with glaucoma were more likely to have previous OSA diagnosis, which was of borderline significance (*P*=.06) and disappeared when controlled for other potential risk factors
		667	Controls	
Marcus et al,[52] 2001	Case-control	23	NTG	Positive sleep history was seen in 57% of patients with NTG, 43% of patients with suspected NTG, and 3% of controls (*P*=.001); OSA was verified in 9 of 13 patients with NTG, 4 of 4 patients with suspected NTG, and 0 of 1 control[b]
		14	Suspected NTG	
		30	Controls	
Tsang et al,[53] 2006	Case-control	41	OSA	4 times higher incidence of glaucomatous disc changes and increased subnormal visual field indices were seen in the OSA group compared with the control group
		35	Controls	
Mojon et al,[54] 1999	Cross-sectional	114	Referred for polysomnography	5 (7%) of 69 patients diagnosed as having OSA had PAOG or NTG
Bendel et al,[55] 2007	Cross-sectional	100	OSA	27% diagnosed as having POAG/NTG
Geyer et al,[56] 2003	Cross-sectional	228	OSA	2% had POAG (same as general population)
Sergi et al,[57] 2007	Case-control	51	OSA	5.9% of the OSA group had NTG, whereas 0% of control group had NTG
		40	Controls	

[a] NTG = normal-tension glaucoma; OSA = obstructive sleep apnea/hypopnea syndrome; POAG = primary open-angle glaucoma.
[b] The 1 control patient had upper airway resistance syndrome.

family. The severity of glaucoma appeared to correlate with the number and duration of apneic episodes. McNab[17] and Robert et al[28] also noticed the occurrence of POAG in their groups of patients with OSA and floppy eyelid syndrome. Since then, several studies have examined the prevalence of OSA in patients with POAG and vice versa (Table 4).[48-57] In these studies, the prevalence of OSA in patients with POAG or NTG ranged from 20% to as high as 57%. Mojon et al[49] suggested that age may influence the prevalence of OSA, with OSA being less prevalent in younger age groups with NTG and higher (up to 63%) in patients older than 64 years with NTG. Many of these studies are limited by the lack of matched controls, use of historical controls, and reliance on symptoms, questionnaires, or trend oximetry studies to diagnose OSA. One retrospective study suggested no increase in prevalence of OSA in patients with glaucoma when adjusted for other potential risk factors.[56]

Studies of patients with OSA have estimated a POAG and NTG prevalence that ranges from 2% to 27%, which compares to an expected 2% in the general population (Table 4). The higher end of this range came from our study in which we screened 100 patients with polysomnographically confirmed OSA for glaucoma within 2 days of their sleep study and before treatment with CPAP. Twenty-seven (27%) were found to have glaucoma.[55]

Two studies have examined specific clinical features of glaucoma and their correlation with OSA: one found a high incidence of visual field defects in patients with moderate to severe OSA, and another found decreased retinal nerve fiber layers in patients with OSA, the severity of which correlated with the severity of the patients' OSA.[53,58] Mojon et al[54] reported that IOP, glaucomatous disc changes, and the diagnosis of glaucoma all correlated with the RDI. Not all studies, however, have found a connection.[51,56] Geyer et al[56] reported that only 2% of 228 patients who had been previously diagnosed as having OSA by polysomnography (RDI >10) had POAG.

Several proposed pathophysiologic mechanisms may link OSA to glaucoma, although most theories have not received adequate scientific testing. These mechanisms include direct hypoxic injury to the nerve, disrupted autoregulation of blood flow to the optic nerve from periods of hypoxia and hypercapnia, and disruption of blood flow from periods of hypotension during apneas.[36] Some have theorized that increased IOP was associated with apnea; however, one study examined this and found no change in IOP after apnea events.[59]

Given the evidence of a possible link between OSA and glaucoma, it is reasonable to recommend that all patients diagnosed as having sleep apnea be screened for glaucoma. Conversely, in patients diagnosed as having glaucoma, physicians should consider the possibility of OSA. If symptoms or other risks for OSA are present, the patient should be referred for polysomnography. Treatment of glaucoma primarily consists of topical drug therapy to lower the IOP. Surgical and laser techniques are used when target IOP is not achieved by drug therapy alone.[34,60] Sev-

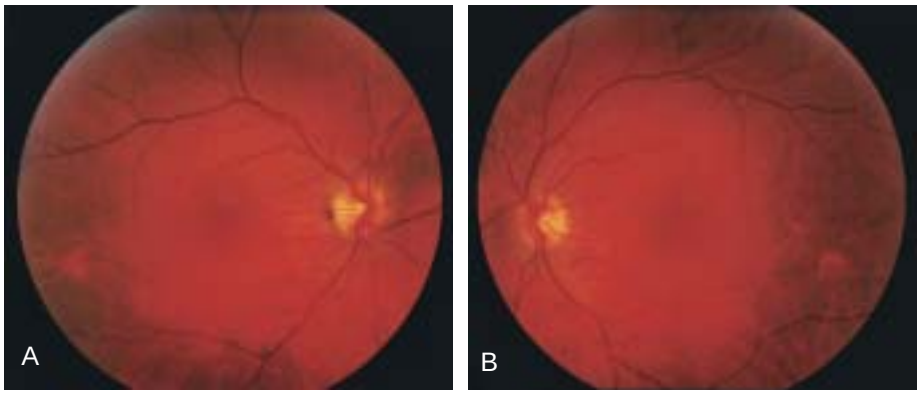

FIGURE 3. Funduscopic images from a patient with nonarteritic anterior ischemic optic neuropathy. A, Involved right eye with findings of mild disc edema superior nasally with associated hemorrhages. B, Unaffected left eye.

eral reports show a benefit of CPAP treatment in patients with both OSA and glaucoma.[61-63] Kremmer et al[61] described 2 patients with NTG whose glaucoma did not improve with medical and surgical management and stabilized only after initiation of CPAP treatment. Another report described a patient with NTG whose visual field defects improved after CPAP treatment.[63]

Nonarteritic Anterior Ischemic Optic Neuropathy

Nonarteritic anterior ischemic optic neuropathy is characterized by the sudden painless onset of unilateral visual loss. It is the most common cause of acute optic neuropathy among adults older than 50 years. Up to 6000 patients are diagnosed as having this condition annually in the United States.[64,65] Patients often notice the loss of vision on awakening in the morning. Visual loss is typically irreversible and may deteriorate further during the course of days or weeks. Clinical findings include nerve fiber bundle field defects, relative afferent pupillary defect, and optic disc edema (Figure 3).[66] In contrast to the form associated with giant cell arteritis, patients have normal erythrocyte sedimentation rates. Several risk factors have been documented and include age older than 50 years, small cup-to-disc ratio, hypertension, diabetes mellitus, atherosclerosis, and hypercholesterolemia.[67-69] The exact pathogenesis is unknown but is believed to be related to vasculopathic occlusion causing infarction. Given the known risk factors, microvascular disease has been suspected as a cause.[69] Others possible mechanisms leading to decreased blood flow in the optic disc microvasculature include optic disc crowding, optic disc compartment syndrome, systemic nocturnal hypotension, and nocturnal hypoxia.[69-71]

In 1998, Mojon et al[62] were the first to suggest a possible link between NAION and OSA. In 2002, they performed polysomnography in 17 patients with NAION and 17 matched controls. Twelve (71%) of the 17 patients with NAION had OSA compared with only 3 (18%) of the controls (P=.05).[66] Palombi et al[72] examined 27 patients with newly diagnosed NAION. All underwent polysomnography, and 24 (89%) exhibited sleep apnea with a mean RDI of 37.2. The risk ratio was 4.9 in patients with OSA compared with the general population (P<.001). Sleep apnea was 1.5 to 2 times more frequent than hypertension or diabetes, the most frequently cited risk factors. These 2 studies, as well as 1 additional study, are summarized in Table 5.[64,66,72] No studies have examined the prevalence of NAION in patients with OSA.

TABLE 5. **Prevalence Studies Investigating the Association Between NAION and OSA**[a]

Reference	Study design	No. studied	Type studied	Findings
Mojon et al,[66] 2002	Case-control	17	NAION	71% had OSA
		17	Controls	18% had OSA
Palombi et al,[72] 2006	Cross-sectional	27	NAION	89% had OSA, risk ratio of 4.9 vs general population
Li et al,[64] 2007	Case-control	73	NAION	Symptoms consistent with OSA were more common
		73	Controls	(OR, 2.62; 95% CI, 1.03-6.60)

[a] CI = confidence interval; NAION = nonarteritic anterior ischemic optic neuropathy; OR = odds ratio; OSA = obstructive sleep apnea/hypopnea syndrome.

Several potential mechanisms for NAION in OSA have been proposed.[66] These mechanisms include impaired optic nerve head blood flow autoregulation secondary to the direct effects of repetitive apneic episodes, apnea-induced blood pressure variations, or an imbalance between nitric oxide, a vasodilator, and endothelin, a vasoconstrictor. In addition, direct hypoxic effects on the optic nerve may have a role. Finally, episodic increases in intracranial pressure (ICP) (subsequently transmitted to the eye via the cerebrospinal fluid within the optic nerve sheath), associated with hypercapnia during apneic episodes, may act on the optic nerve head either through direct compression or impaired circulation.

No effective treatment is available for NAION. Recurrences in the ipsilateral or contralateral eye are not uncommon. Patients are often given aspirin or other antiplatelet treatment for vascular disease prevention, although the benefits of this approach are unproved. Atherosclerotic disease risk factor modification is routinely recommended.[65] Given the high incidence of OSA in this population, it is reasonable to screen all patients with NAION for symptoms or physical features associated with the presence for OSA. Patients in whom OSA appears to be a valid clinical concern should undergo polysomnography. No one has demonstrated that treatment of OSA reduces the risk of occurrence or recurrence of NAION. At least 1 study documented the occurrence of NAION in 3 patients despite CPAP treatment, although adherence to treatment was not discussed.[67]

Papilledema

Papilledema refers specifically to bilateral optic disc swelling in the setting of increased ICP. It can be seen in association with a variety of conditions, including intracranial lesions or masses and obstructive hydrocephalus, and should be differentiated from other causes unrelated to increased ICP, such as optic neuritis and NAION, which can occur unilaterally.[73] Papilledema occurs when the elevated ICP is transmitted to the eye through the optic nerve sheath. The elevated pressure mechanically disrupts axoplasmic flow within the optic nerve, leading to swelling of the axons and leakage of water, protein, and other cellular contents into the extracellular space.[74] Venous obstruction, nerve head ischemia, and telangiectasis develop secondarily. When the underlying origin leads to more acute or subacute increases in ICP, patients more typically present with symptoms of increased ICP as opposed to visual symptoms. These symptoms include headache, nausea, tinnitus, and vomiting. With slow, more long-term elevations in ICP, patients may also present with visual symptoms, including transient obscuration of vision and tunnel vision with arcuate visual field loss. Over time, blindness may result. Figure 4 demonstrates the funduscopic findings in a patient with papilledema. When a cause of increased ICP cannot be found, it is referred to as *idiopathic intracranial hypertension*. The idiopathic form is most commonly seen in middle-aged obese women and referred to as *pseudotumor cerebri*.[75]

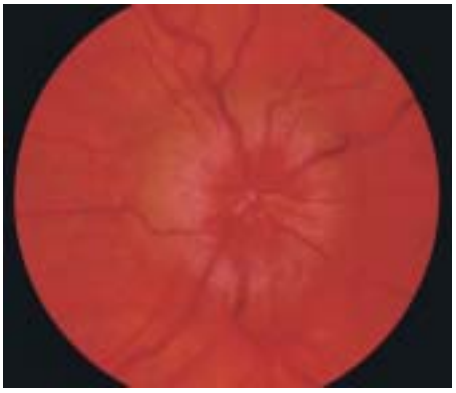

FIGURE 4. Funduscopic image from a patient with papilledema demonstrating marked optic disc swelling.

Bucci and Krohel[76] reported the first case of bilateral papilledema identified in a patient with OSA. They described a 46-year-old overweight man with headache, fatigue, episodic visual disturbances, and papilledema on funduscopic examination. Lumbar puncture revealed an ICP of only 170 mm H_2O (reference range, <250 mm H_2O). The patient had clinical symptoms of OSA, which were confirmed on polysomnography. The patient underwent rhinoplasty, uvulopalatopharyngoplasty, and temporary tracheostomy. After this surgical management of his OSA, his papilledema resolved. Wolin and Brannon[75] reported a case of a 46-year-old woman with OSA, pickwickian syndrome, and papilledema that resolved with nocturnal nasal bilevel positive airway pressure. In 2000, Purvin et al[77] reported 4 cases of papilledema in patients with OSA, all with normal opening pressures on lumbar puncture, who also improved after treatment. Finally, Lee et al[78] examined 6 cases of idiopathic intracranial hypertension in men with OSA. All had documented increased ICP noted by lumbar puncture, bilateral optic disc swelling, enlarged blind spots, and optic disc edema. Papilledema resolved after CPAP treatment in 3 patients and improved in the other 3 patients. Five patients had normal visual field examination findings after CPAP treatment; 1 patient had persistent visual field loss. Only 1 case-control study analyzed the prevalence of papilledema in patients with OSA. Peter et al[79] questioned 35 successive patients with OSA regarding visual symptoms suggestive of papilledema and then had all undergo a funduscopic examination; 40% reported symptoms suggestive of papilledema, but all had negative funduscopic examination results. The authors concluded that papilledema

is not a frequent finding in patients with OSA but recommended screening in those who have symptoms.

In 1985, Sugita et al[80] monitored continuous ICP in patients with OSA. All patients had normal daytime ICP measurements. These authors found large increases in the ICP during sleep that correlated with apneic events. The degree of increase in ICP correlated with the duration of the apnea and the decrease in oxyhemoglobin saturation. This evidence has led most to hypothesize that papilledema in patients with OSA is secondary to transient hypercapnia and the resultant transient increases in ICP. This explains why some patients have normal daytime ICP, whereas patients with more severe OSA, particularly with daytime hypercapnia, have elevated ICP even during the day.

In patients who have papilledema, either secondary to idiopathic intracranial hypertension or in the setting of normal ICP, and no other identifiable cause, the possibility of OSA should be considered and appropriate clinical history obtained. Although improvements have been reported with CPAP treatment in selected case reports and case series, most have recommended treatment with acetazolamide, at least initially, until symptoms resolve.[81]

CPAP Treatment–Associated Eye Complications

The first line of treatment of OSA is CPAP because of both its efficacy and its safety. The most common complications of CPAP treatment are nasal irritation and dryness, skin irritation, skin breakdown, and ulceration secondary to pressure from the mask. Nasal dryness and irritation are usually managed with added humidity. Skin irritation and breakdown require modifications of the mask to improve fit. Ophthalmologic problems or complications are also occasionally seen. In 1984, Stauffer et al[82] described a patient with bacterial conjunctivitis after CPAP use. In 2006, Ely and Khorfan[83] reported a case of a woman with OSA who developed unilateral periorbital swelling with CPAP treatment that resolved when she stopped CPAP treatment. She was ultimately found to have a fracture of the right superior aspect of the orbit with a sinus communication. Harrison et al[84] reported 3 cases of patients with eye complications while undergoing CPAP treatment. Patient 1 wore hard contact lenses and developed vascularized limbal keratitis, which improved after changing to soft lenses, although with somewhat poorer vision correction. Patient 2 presented with recurrent unilateral corneal ulcers secondary to bacteria. Patient 3, who also wore hard contact lenses, developed increased dryness, increased mucus in the eye in the morning, and recurrent episodes of bacterial conjunctivitis. The authors theorized that eye complications from CPAP treatment arose from 2 possible mechanisms. The first, and probably most common, is from an air leak around the superior portion of the mask, resulting in air blowing into the eye. The second may be retrograde movement of air and mucus from the nasal passage through the nasolacrimal duct and into the eye.

Nocturnal lubrication or artificial tears provide relief to patients who develop morning eye dryness while receiving CPAP treatment. Proper mask fit should be verified to prevent air leaks. Switching from a nasal mask to an intranasal interface may alleviate areas of pressure and air leakage near the eyes. If a patient develops substantial eye irritation that persists into the day or has signs of infection, early ophthalmologic consultation is required to exclude corneal disease. Given the possibility of increased risk of eye infections, it is reasonable to advise against extended-wear contacts. In patients who develop recurrent eye infections or depend on contact lenses and cannot tolerate CPAP treatment secondary to eye irritation, alternative therapy to CPAP treatment may need to be considered.

OTHER SLEEP-RELATED EYE CONDITIONS

Nocturnal Lagophthalmos

Nocturnal lagophthalmos refers to the inability to fully close the eyelids at night. Common symptoms include pain, irritation, dryness, foreign body sensation, and excessive watering. Lagophthalmos is also associated with poor sleep due to arousals from eye-related symptoms. Risk factors include neurogenic conditions (such as cranial nerve palsies, eg, Bell palsy), myopathies, thyroid-related eye disease, lid deformity, cosmetic eyelid surgery, botulinum toxin, excessive alcohol intake, and the use of hypnotics.[85,86] Genetic and ethnic factors also have a role. The condition can be asymptomatic and subclinical. One study of 500 Chinese medical students found an incidence of 5%; all were asymptomatic.[87] Why some patients develop symptoms and others do not is unclear but may be related to eye position during sleep (eyes up or the Bell phenomenon, theoretically, being protective) and adequacy of the tear film during sleep (with deficiency of the tear film possibly increasing the risk of symptoms). Diagnosis is made by a focused clinical history and slitlamp examination. The most common physical examination finding in 1 study was superficial punctate staining of the cornea. One third of patients with this finding also had associated epithelial cell loss.[86] Corneal scarring can also occur. Treatment of symptomatic cases is multifaceted and can include avoidance of alcohol and hypnotics; nocturnal use of natural, topical, or oral agents; insertion of punctal plugs; and performance of minor surgical procedures to the eyelid.[85]

CIRCADIAN RHYTHM DISORDERS OF THE BLIND

Circadian rhythms are found in all living organisms. Although the sleep-wake cycle is the most apparent circadian

rhythm in humans, many other important functions are also regulated by a circadian rhythm, including body temperature, hormone secretion, cardiopulmonary function, cognitive performance, and mood.[88] Without environmental cues, the sleep-wake circadian rhythm in humans runs approximately 24.5 hours.[89] Several environmental cues help entrain this cycle to the 24-hour day and night cycle, including light, physical activity, temperature, meal times, and melatonin. Light and melatonin are the most influential. The suprachiasmatic nucleus is thought to be the master circadian clock in the body. Optic pathways exist that travel from ganglion cells in the retina (distinct from rods and cones) to the suprachiasmatic nucleus via the retinohypothalamic tracts. The suprachiasmatic nucleus regulates the secretion of melatonin from the pineal gland.[88]

Not surprisingly, one of the circadian rhythm manifestations of blindness is the development of a free-running or irregular circadian rhythm due to the absence of light synchronization of the internal clock. On the basis of multiple case reports, Lewy and Newsome[90] defined the distinct melatonin secretory rhythms seen in blind patients. They found some to be normally entrained (synchronized with the 24-hour day and night cycle), some to have no distinct rhythm, and some to be free running (unsynchronized and running independently of the 24-hour day and night cycle). Lockley et al[91] later showed that the type of circadian rhythm was directly related to the amount of light perception. They studied 49 registered blind patients, 19 of whom had some light perception and 30 of whom had no light perception. Fourteen (74%) of the 19 patients with light perception maintained a normal circadian rhythm. Twenty-three (77%) of the 30 patients with no light perception had an abnormal circadian rhythm, with 17 (74%) of the 23 patients characterized as having a free-running circadian rhythm. Others have found similar correlations.[92-94] Why some patients without light perception maintain a normal circadian rhythm is unclear but may be related to an increased susceptibility to entrainment by other environmental cues, a circadian clock that runs close to the natural 24-hour clock, or some persistent input from the retinohypothalamic tract. This last possibility is supported by the study by Lockley et al[91] in which all patients who had undergone bilateral enucleation had free-running rhythms.

The consequences of these free-running or disrupted circadian rhythms in blind patients have been well described. Tabandeh et al[94] noted a substantially higher incidence of sleep disturbances in blind patients when compared with controls (48.7% vs 9.1%). Das et al[92] found a similar frequency (44.6% vs 15.7%). Symptoms include daytime sleepiness and periodic insomnia, characterized by delayed sleep onset, shortened sleep duration, and increased spontaneous arousals. The diagnosis is evident in many cases by clinical history. Sleep diaries and actigraphy (a small sensor, worn by the patient like a wristwatch, which measures activity levels for 1 to 2 weeks and can be used to objectively estimate a patient's sleep-wake cycle) may also be helpful in the evaluation. Measurements of serum melatonin or urinary 6 hydroxymelatonin may help with the diagnosis and determine the patient's phase abnormality.[95,96] However, these tests are not readily available.

Currently, treatment with properly timed melatonin has been shown to be the most beneficial approach. In 2000, Sack et al[97] performed a randomized, double-blind, placebo-controlled trial in 7 blind patients with laboratory-confirmed free-running circadian rhythms. In 6 of the 7 patients, administration of melatonin resulted in entrainment of the circadian rhythm ($P<.001$). Placebo had no effect. Patients in the treatment group spent less time awake after initial sleep onset and demonstrated improved sleep efficiency (time asleep divided by time in bed). The starting dose of melatonin was 10 mg/d orally. In a subsequent trial, the dose was tapered to 0.5 mg/d orally after initial entrainment with continued benefit. The effectiveness of lower doses has also been supported in a trial from Hack et al.[98] The timing of melatonin administration is important and best begun during the advanced phase of the circadian rhythm (when the patient desires to go to bed too early or wake up too early). This can be determined through laboratory measurements or clinical history. One author advocates starting melatonin therapy during the period when the patient reports the best sleep because this likely represents the time when his or her circadian rhythm is most synchronized with normal day and night cycle.[99] Further studies are needed to verify the minimum doses required at initiation and for maintenance.

CONCLUSION

During the past decade, the association between specific eye disorders and specific sleep disorders has become more apparent. Our understanding of the exact pathophysiologic mechanisms that link these disorders is minimal. However, the recognition of these associations is important for primary care physicians, ophthalmologists, and sleep physicians. It is hoped that a cooperative effort will reduce the morbidity and mortality of the underlying disease processes. For patients with OSA, a routine eye examination to evaluate for early signs of glaucoma, particularly in the setting of visual loss or change, should be recommended. Patients with ophthalmologic diseases known to be associated with sleep apnea should be screened clinically for sleep apnea and referred to a sleep center for polysomnog-

raphy if signs or symptoms suggestive of sleep apnea are present. For patients with floppy eyelid syndrome, NAION, or papilledema, referral to a sleep specialist may be advisable, even in the absence of clinical signs of OSA, when no other cause is apparent. Finally, for patients with blindness, whether presenting with a sleep disturbance or for routine follow-up, taking a sleep history to detect possible circadian rhythm problems followed by referral to a sleep specialist for diagnosis and management is recommended.

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