



Neuro-Ophthalmological Manifestations of Obstructive Sleep Apnea: Current Perspectives

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Abstract: Obstructive sleep apnea (OSA) is a disease of obstructed airways during sleep that significantly impacts the quality of life and increases the risk of various systemic diseases. OSA has been studied as a risk factor for a number of neuro-ophthalmic conditions and a strong relationship has been established with non-arteritic anterior ischemic optic neuropathy (NAION). The incidence of glaucoma and stroke have also been significantly associated with OSA and are conditions that may also be seen by neuro-ophthalmologists. Patients with NAION have a significantly higher incidence of OSA and OSA diagnosis significantly increases the risk for NAION development. Non-compliance with continuous positive airway pressure (CPAP) in OSA patients has also been found to be a risk factor for fellow-eye involvement and there is increasing evidence to suggest that every patient with NAION should be formally evaluated with polysomnography. The relationship between OSA and idiopathic intracranial hypertension (IIH) has also been studied, but the relationship between these two conditions is less clear. There is insufficient evidence to recommend routine eye examinations in OSA patients for papilledema and conducting a sleep study for a newly diagnosed IIH patient should be left to the discretion of the clinician based on other symptoms and risk factors of OSA.

Keywords: ischemic optic neuropathy, non-arteritic anterior ischemic optic neuropathy, idiopathic intracranial hypertension, optic nerve, glaucoma, stroke

Case Vignette

A 63-year-old man with no known medical conditions was seen in neuro-ophthalmology consultation for bilateral vision loss. He noticed blurred vision in his right eye 3 weeks prior to presentation and blurred vision in his left eye 5 days prior to presentation. He denied symptoms suggestive of giant cell arteritis and did not use any medications. He had a visual acuity of 20/400 (right) and 20/60 (left) with a right relative afferent pupillary defect. Humphrey 24-2 SITA-Fast visual fields showed severe generalized depression (right) and an inferior altitudinal defect (left). Dilated fundus examination demonstrated bilateral optic disc edema (Figure 1). Blood pressure was 128/80 mmHg and body mass index was 28.9kg/m². Review of symptoms was significant for daytime sleepiness, frequent snoring, and witnessed episodes of choking and gasping for air at night by his wife. Informed written and verbal consent was obtained from the patient for inclusion of clinical details and images in this study.

Introduction

Obstructive sleep apnea (OSA) is defined as episodes of upper airway collapse that occur during sleep. These events lead to episodic reduction or cessation of

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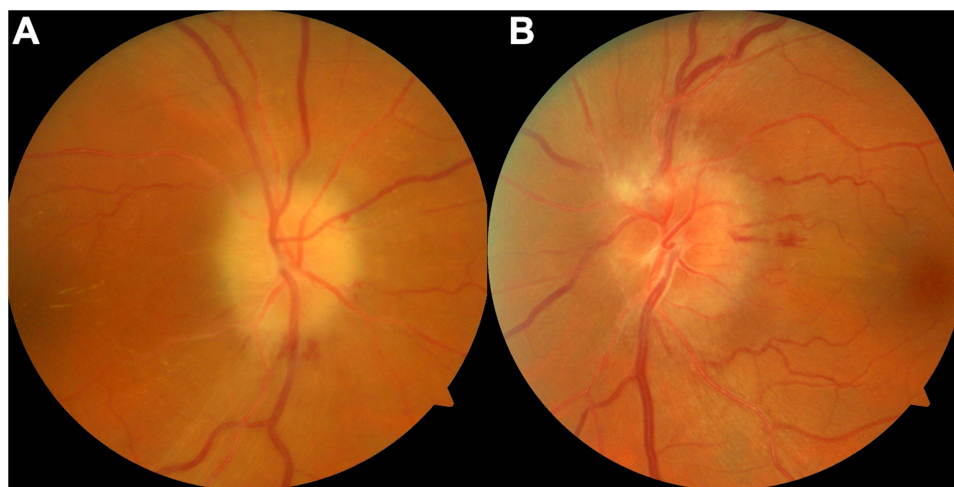


Figure 1 Fundus photography of the (A) right and (B) left optic nerve of the patient at presentation revealing bilateral optic disc edema. The right optic nerve has resolving, pallid edema whereas the left optic disc edema appears more recent with a temporal peripapillary hemorrhage.

ventilation, resulting in hypoxia, hypercapnia, or sleep arousal.¹ OSA can significantly impact quality of life and increase the risk of cardiovascular disease, stroke, diabetes, hypertension, and hypercholesterolemia.² The incidence of OSA has been estimated to be 3–50% in the general population depending on age, sex, and body mass index (BMI); often, individuals are unaware that they have this condition.^{3,4} The incidence of OSA globally does not follow a geographical trend. In men it has been the lowest in Hong Kong (8.8%) and highest in Switzerland (83.8%); while in women, New Zealand and Singapore have the lowest and highest reported rates at 3.4% and 62.3%, respectively.⁵

Conditions that influence the diameter of upper airways during sleep are risk factors of OSA. Obesity and high BMI have been associated with higher degrees of OSA since an increase in the amount of adipose tissue in the tongue or in the upper respiratory pathway can cause airway collapse.² Male sex is another major risk factor for OSA with an unclear pathophysiology, although the risk appears to be similar in postmenopausal women.^{6,7} It has been hypothesized that progesterones help maintain an appropriate airway diameter and androgens increase pharyngeal muscle mass, increasing the likelihood of airway closure.^{2,8} Less established risk factors include smoking, family history of OSA and a variety of medical conditions such as hypertension, type 2 diabetes, congestive heart failure, hypothyroidism, acromegaly, and certain craniofacial anatomical abnormalities.^{2,9}

OSA often manifests as daytime sleepiness, snoring, choking or gasping during sleep, and morning headaches.

It may also present with complications including erectile dysfunction, neuropsychiatric symptoms, or nocturnal cardiovascular events. However, the correlation of symptoms to the severity of the disease is relatively poor.¹⁰ Currently, the gold standard diagnostic test for OSA is polysomnography to determine the apnea-hypopnea index (AHI).^{2,10,11} Apneas are defined as episodes of almost total obstructed airflow of more than 10 seconds during sleep, while hypopneas are decreased airflow and oxyhemoglobin saturation by 3% or arousal from sleep.¹⁰ The AHI score can be used to both diagnose and assess the severity of OSA. An AHI score of 5 or above is indicative of OSA diagnosis. AHI scores of 5–15 are considered mild, 16–30 are considered medium, and above 30 are considered severe OSA.¹¹ In addition to polysomnography, multiple questionnaires have been developed to assess for OSA that are more accessible and less expensive, including the Berlin questionnaire (BQ), STOP-BANG questionnaire (SBQ), STOP questionnaire (STOP), and Epworth sleepiness scale (ESS). In a meta-analysis of OSA diagnostic questionnaires, SBQ was found to have the highest accuracy and sensitivity compared to the others.¹²

Positive airway pressure such as continuous positive airway pressure (CPAP), which keeps the airways open both during inspiration and expiration while the patient is sleeping, is an effective and commonly used treatment.^{2,10} However, patient adherence to CPAP therapy is low due to cost and inconvenience. Weight loss is another effective treatment that has been shown to improve outcomes in patients with OSA. In a meta-analysis of 4 randomized controlled trials, a weight loss of 14 kg was shown to

reduce the AHI score by 16 points.¹³ Other treatment options include oral appliance to protract the mandible, avoiding supine sleeping, and surgical intervention to reduce the collapsibility of the pharynx and upper airways.¹⁰

Neuro-ophthalmology refers to a subspecialty of ophthalmology and neurology that concerns itself with central nervous system pathology affecting vision. An increasing amount of evidence has implicated OSA as a significant risk factor for optic nerve disorders (referred to as optic neuropathies). These include non-arteritic anterior ischemic optic neuropathy (NAION) and to a lesser extent idiopathic intracranial hypertension (IIH). This review will examine the evidence for OSA as a risk factor for neuro-ophthalmological conditions with a focus on NAION and IIH.

OSA and NAION

Non-arteritic anterior ischemic optic neuropathy (NAION) occurs due to infarction of the optic nerve head due to hypoperfusion of the short posterior ciliary arteries.¹⁴ This condition manifests as painless vision loss and the optic nerve becomes edematous after the initial insult and the optic disc edema persists for about 6–11 weeks after which optic disc atrophy develops.¹⁴ It is seen in patients with small optic nerves and a small or absent physiological cup (so-called “disc-at-risk”). NAION commonly affects individuals above the age of 50 and is associated with vascular risk factors such as hypertension and type 2 diabetes. Other associated risk factors include dyslipidemia, smoking, and systemic atherosclerosis, but few rigorous population studies exist to establish these factors.¹⁵ We used a systematic search strategy (Table 1) and identified 18 articles that have explored the association between OSA and NAION (Table 2).

The relationship between OSA and optic disc edema was first described by Bucci et al in a 46-year-old obese male with OSA.³⁴ This patient had an extensive workup including a lumbar puncture that revealed a normal opening pressure and following the placement of a permanent tracheotomy for the treatment of his OSA symptoms, his optic disc edema resolved. This observation encouraged Mojon et al to systematically investigate the association between OSA and NAION for the first time.¹⁶ They examined the frequency of OSA by polysomnograms in patients with NAION and compared it to age- and sex-matched controls who had restless leg syndrome. They showed that

Table 1 Search Strategy Used for OVID MEDLINE (1946 to February 2020 Week 1) to Identify Studies That Investigated the Relationship Between OSA and NAION

#	Searches	Results
1	exp Optic Neuropath, Ischemic/	1620
2	Optic Nerve Diseases/	8819
3	Non-arteritic anterior ischemic optic neuropathy.tw.	181
4	Nonarteritic anterior ischemic optic neuropathy.tw.	435
5	NAION.tw.	487
6	Arteritic anterior ischemic optic neuropathy.tw.	235
7	exp Sleep Apnea, Obstructive/	20,406
8	Obstructive sleep apnea.tw.	22,456
9	Obstruct* Sleep Apnea*.tw.	22,522
10	Sleep apnea syndrome.tw.	6738
11	OSA.tw.	13,639
12	1 or 2 or 3 or 4 or 5 or 6 or 7	10,601
13	8 or 9 or 10 or 11 or 12	32,996
14	12 and 13	55
15	limit 14 to (English language and humans)	50

NAION patients had significantly higher rates of OSA diagnosis at 71% compared to the controls at 18%.¹⁶

Another study conducted phone questionnaires of 73 NAION patients and 73 age- and gender-matched controls, and assessed the OSA status of the participants based on the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ).¹⁹ Even though they used a different, indirect method of assessing for OSA, they found higher rates of OSA in NAION patients than the controls, 30.1% versus 17.8%, consistent with other studies.¹⁹

Unlike other prospective studies that matched the control group based only on age and sex, two studies matched them based on the diagnoses of diabetes and hypertension as well.^{21,24} The results were consistent in finding that the rate of OSA was 85% (17/20 patients) and 55.5% (15/27 patients) in NAION patients, which was significantly higher than the controls at 65% (13/20) and 22.2% (6/27), respectively.^{21,24} These studies demonstrated that even after controlling for all major risk factors of NAION including age, diabetes, and hypertension, OSA still appears to be strongly associated with NAION.

Conversely, other studies have investigated the frequency of NAION in patients with OSA. Comparative retrospective studies of OSA patients versus controls have shown higher incidences of NAION diagnosis in OSA patients at 0.92% and 0.36% compared to the controls at 0.42% and 0.20%, respectively.^{30,31} In addition, after adjustments for comorbidities, OSA patients had

Table 2 Studies Identified Using Our Search Strategy That Investigate the Relationship Between OSA and NAION

Authors, Year	Number of Patients	Type of Study	OSA Diagnostic Test	Findings
Mojon et al ¹⁶ 2002	17 NAION patients and 17 age- and sex-matched controls	Prospective comparative	PSG	12/17 (71%) of NAION and 3/17 (18%) of controls had OSA
Behbehani et al ¹⁷ 2004	108 patients with OSA	Prospective observational	PSG	3/108 (2.78%) of the patients had NAION
Palombi et al ¹⁸ 2006	27 NAION patients	Prospective observational	PSG	24/27 (89%) of the patients had OSA
Li et al ¹⁹ 2007	73 NAION patients and 73 age- and gender-matched controls	Prospective comparative	SA-SDQ	OSA diagnosis based on a phone questionnaire 22/73 (30.1%) of NAION patients and 13/73 (17.8%) of the controls had OSA
Stein et al ²⁰ 2011	2,259,061 patients, 156,336 of whom diagnosed with OSA	Retrospective comparative	Medical history	OSA patients who did not use CPAP had an NAION diagnosis rate of 0.07% as opposed to 0.05% in the controls
Arda et al ²¹ 2012	20 NAION patients and 20 age- and sex-matched controls with similar rate of hypertension and diabetes	Prospective comparative	PSG	17/20 (85%) of the NAION patients and 13/20 (65%) of the controls had OSA
Blaivas et al ²² 2013	1	Case report	PSG	Patient with bilateral NAION was found to be having underlying OSA due to a substernal goiter
Kolb et al ²³ 2013	17 NAION patients	Prospective observational	PSG	11/17 (64.7%) of the NAION had OSA
Bilgin et al ²⁴ 2013	27 NAION patients and 27 age- and sex-matched controls and similar systemic risk factors	Prospective comparative	PSG	15/27 (55.5%) of the NAION patients and 6/27 (22.2%) of the controls had OSA
Mohamed et al ²⁵ 2014	30 OSA patients	Prospective observational	PSG	4/30 (13.33%) OSA patients had NAION
Lacharme et al ²⁶ 2014	17 NAION patients	Prospective observational	PSG	12/17 (70.6%) of the patients had OSA
Aptel et al ²⁷ 2015	89 NAION patients	Prospective observational	PSG	67/89 (75%) of the patients had OSA.
Ghaleh Bandi et al ²⁸ 2015	19 NAION patients and 31 controls	Prospective comparative	PSG	18/19 (95%) of NAION and 13/31 (41.9%) of controls had OSA
Morsi et al ²⁹ 2019	80 OSA patients and 20 controls	Retrospective	PSG	No patient had NAION
Sun et al ³⁰ 2019	8488 OSA patients and 33,952 controls	Retrospective	Medical history	Rate of NAION diagnosis was 0.36% in the OSA group and 0.2% in the controls
Yang et al ³¹ 2018	919 with OSA, 9190 matched non-OSA	Retrospective	Medical history	10-year incidence probability of NAION in the OSA group (0.92%) was higher than the non-OSA group (0.42%)
Chang et al ³² 2019	119 patients with unilateral NAION	Retrospective	Medical history	Over a 5-year period, 24.4% of the patients developed NAION in the other eye, with CPAP non-compliance being a major risk factor
Lei et al 2019 ³³	1	Case report	PSG	Young patient with NAION who had undiagnosed severe OSA

Abbreviations: OSA, obstructive sleep apnea; NAION, non-arteritic anterior ischemic optic nerve; PSG, polysomnogram; SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire; CPAP, continuous positive air pressure.

a significantly higher risk of developing NAION than patients without OSA over an 18-year period, with a reported hazard ratio of 1.66.²⁶ Thus, OSA appears to be highly prevalent among NAION patients while NAION is much less common among OSA patients. This is likely a result of the multifactorial nature of NAION including the importance of a disc-at-risk. In addition, since OSA is consistently more prevalent in patients with NAION compared to controls, it suggests that OSA is a risk factor for NAION development.

A meta-analysis of 4 case-control studies,^{16,19,21,24} involving 137 subjects showed that OSA was significantly associated with the development of NAION with a pooled odds ratio of 3.126 ($P < 0.001$) in the OSA group.³⁵ Likewise, another meta-analysis of 5 studies,^{16,18,19,21,24,27} found a strong link between NAION and OSA with a pooled odds ratio of 6.18 (95% CI 2.00–19.11) versus non-OSA controls.³⁶ In subgroup analysis, only matched-control studies showed a significant association between NAION and OSA with an odds ratio of 5.0 (95% CI 2.22–11.25), compared to studies that did not.³⁶ This difference could be explained by the fact that NAION is a multifactorial disease.

A few studies have also reported the potential for CPAP therapy to minimize the risk of developing NAION in patients with OSA. Chang et al retrospectively studied 119 patients with unilateral NAION and OSA.³² Over a 5-year period, 29 of these patients developed NAION in the other eye as well. They found that poor adherence to CPAP was a major risk factor in developing bilateral NAION.³² This emphasizes the importance of treating OSA when present to prevent fellow-eye involvement, which often has a tremendous impact on their quality of life.

The exact mechanism of how OSA causes NAION is not fully understood but various hypotheses have been proposed. Many studies in the literature suggest that recurrent episodes of apnea lead to vascular dysregulation, compromising the ability to provide constant blood flow to the vessels supplying the optic nerve head.^{16,21,37} This dysregulation has been thought to be a result of prolonged hypoxia, production of reactive oxygen species, and an imbalance in the production of vasoactive substances.^{16,27} Vascular endothelial growth factor (VEGF) has been reported to stimulate the progression of cardiovascular disease and a meta-analysis of six studies found that levels of VEGF were significantly reduced in OSA after CPAP treatment.³⁸

Given the strong association between OSA and NAION, there is increasing evidence that polysomnography should

be performed in all patients with a new diagnosis of NAION.³⁹ This is important since there is some evidence, as outlined above, that CPAP non-compliance is a risk factor for developing bilateral NAION.³² OSA should be of particular concern in patients that have a clear diagnosis of NAION, but no other risk factors for this condition. OSA is also a concern in younger patients below 50 years of age and NAION has been found to be the presenting condition of severe sleep apnea in younger individuals.³³ Although there is no established treatment for NAION, efforts should be focused on identification and optimization of risk factors including OSA to reduce the likelihood of fellow-eye involvement, which can be devastating for these patients.

OSA and IIH

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, refers to increased intracranial pressure (ICP) of unknown cause.⁴⁰ It is most commonly seen in obese females of childbearing age and may present with headache, diplopia, or vision loss.⁴¹ IIH is diagnosed by the modified Dandy criteria and treatment is initiated to reduce the risk of permanent vision loss and help in reducing systemic symptoms. These treatments include weight loss, pharmacological treatments such as acetazolamide, or surgical intervention in severe cases.⁴⁰ Studies have shown that in patients with OSA, ICP was relatively normal during wake times with morning ICP values significantly higher than the evening values (20.7 mmHg versus 17.7, $p < 0.02$).⁶⁰ However, this value was increased as much as 90 mmHg during apnea episodes. This correlation was highly significant and was associated with a decrease in PO_2 .^{60,61} Since IIH is a syndrome of raised ICP, this sparks the question of a potential relationship between IIH and OSA. Table 3 summarizes the 19 articles that have explored the association between OSA and IIH (Table 3). OSA has been reported to occur between 4% and 60% of IIH patients.^{47,49} Many cases have been described in the literature describing patients with OSA who were also diagnosed with IIH at presentation, proposing a possible link between the two conditions. However, unlike NAION, the evidence for an association between IIH and OSA is less conclusive.

Thurtell et al conducted polysomnograms on 24 patients with a diagnosis of IIH and found that 8 of these patients had OSA.⁵³ The mean AHI score of these individuals was compared to a model developed by sampling the AHI scores of 1741 random individual and corrected for age, sex, race, BMI, and menopausal status. The results

Table 3 Studies Identified Using Our Search Strategy That Investigate the Relationship Between OSA and IIH

Authors, Year	Number of Patients	Type of Study	OSA Diagnostic Test	Findings
Doyle et al ⁴² 1991	1	Case report	Medical history	Obese patient with OSA and IIH presenting with unilateral vision loss who improved following a lumboperitoneal shunt and tracheotomy
Purvin et al ⁴³ 2000	1	Case report	Medical history	Obese patient with a 2-year history of OSA presenting with unilateral vision loss, papilledema and high ICP during sleep
Marcus et al ⁴⁴ 2001	14 IIH patients with symptoms of sleep disturbance	Retrospective	PSG	6/14 (42.9%) of the patients had OSA
Lee et al ⁴⁵ 2001	18 men with IIH	Retrospective	Medical history	6/18 (33.3%) of the patients had OSA
Thambisetty ⁴⁶ et al 2006	16 fulminant IIH female patients	Prospective observational	Medical history	None of the patients had OSA
Bruce et al ⁴⁷ 2009	721 IIH patients	Retrospective	Medical history	25/655 (4%) of the female patients had OSA as opposed to 16/66 (24%) of the male patients
Fraser et al ⁴⁸ 2010	24 IIH male patients and 48 sex-, age-, race-, and BMI category-matched controls	Prospective comparative	Berlin Questionnaire (BQ) for OSA	Following adjustments for BMI, IIH patients had a higher likelihood of having a positive Berlin questionnaire or history of OSA diagnosis
Thurtell et al ⁴⁹ 2011	30 newly-diagnosed IIH patients	Prospective	PSG and BQ	PSG: 18/30 (60%) of the patients had OSA BQ: 20/30 (67.8%) of patients were at high risk of OSA
Javaheri et al ⁵⁰ 2011	1	Case report	PSG	Female patient with IIH who was diagnosed with OSA. Her IIH improved following CPAP therapy for OSA
Stein et al ²⁰ 2011	2,259,061 patients, 156,336 of whom diagnosed with OSA	Retrospective	Medical history	OSA patients who did not use CPAP had an IIH diagnosis rate of 0.04% as opposed to 0.01% in the controls
Szewka et al ⁵¹ 2013	414 IIH patients	Retrospective	Medical history	In patients with BMI of <40, 13/256 (5.1%) had OSA as opposed to 26/158 (16.5%) in patients with BMI >40
Abraham et al ⁵² 2013	22 IIH and 12 sex- and age-matched controls	Prospective comparative	Bedside overnight respiratory monitoring	AHI scores of IIH patients higher than the control, but both values within the normal range
Thurtell et al ⁵³ 2013	24 IIH patients	Prospective observational	PSG	8/24 (33.3%) of IIH patients had OSA. The AHI scores of the IIH patients and 1741 randomly sampled individuals had no statistical difference
Wardly et al ⁵⁴ 2017	1	Case report	PSG	Patient with OSA and IIH. Her IIH went away following a clockwise maxillomandibular advancement surgery to treat OSAS
Cappuzzo et al ⁵⁵ 2018	18 IIH patients	Retrospective	Medical history	3/18 (16.7) of IIH patients had OSA

(Continued)

Table 3 (Continued).

Authors, Year	Number of Patients	Type of Study	OSA Diagnostic Test	Findings
Ardissino et al ⁵⁶ 2019	607 IIH patients and 230,792 controls all with BMI>30	Retrospective	Medical history	4/607 (0.7%) of IIH patients and 2204/230,792 (1%) of the controls had OSA
Radojicic et al ⁵⁷ 2019	219 IIH patients and 67 controls	Prospective comparative	Medical history	5/219 (2.3%) of IIH patients and 7/67 (10.4%) of the controls had OSA
Onder et al ⁵⁸ 2019a	1	Case report	Epworth Sleepiness Scale (ESS)	Patient with OSA and malignant IIH that was resolved following tonsillectomy to treat OSA
Onder et al ⁵⁹ 2019b	1	Case report	ESS	10 year-old patient with a BMI of 20, diagnosed with IIH and suspected of OSA

Abbreviations: OSA, obstructive sleep apnea; NAION, non-arteritic anterior ischemic optic nerve; PSG, polysomnogram; CPAP, continuous positive air pressure.

showed that there was no difference between the AHI scores of the two groups, indicating that IIH by itself did not increase the risk of developing OSA.⁵³ In another study, Bruce et al surveyed 721 patients with IIH and found that 5.7% of these patients also had OSA.⁴⁷ In addition, when they looked at the rate of OSA between sexes they found that males had a higher rate at 24% compared to females at 4%.⁴⁷ In a study focused on racial differences in IIH, it was found that black individuals had a higher proportion of OSA (9% vs 4%; $p=0.01$) and that OSA was more likely in patients that had severe visual loss ($p=0.002$).⁶²

A few studies have found lower rates of OSA in patients with IIH compared to the controls. In a large retrospective study, Ardissino et al found that among 607 IIH patients, only 4 of them (0.7%) had OSA.⁵⁶ Conversely, 2204 of the 230,792 controls (1%) had an OSA diagnosis.⁵⁶ Chronic IIH and increased ICP have also been shown to contribute to the development of spontaneous cerebrospinal fluid leaks (sCSF-L). sCSF-L has been associated with thinning of the calvarium with no changes to extracranial bones and is linked with obesity and OSA.^{63,64} In particular, the incidence of OSA in sCSF-L patients was reported to be 83.3% and patients with OSA have been shown to have a thinner mean calvaria.^{63,64} This suggests that there might be an indirect link between OSA and chronic untreated IIH.

Overall, there is little evidence for increased ICP in patients with OSA and fundus examination screening for papilledema in OSA patients is not warranted at this time. A few studies demonstrated a potential link between IIH and OSA, but these were small and without comparative

groups. There is therefore no strong evidence supporting routine testing for OSA in patients with IIH. However, weight loss has been shown to be an effective treatment for both IIH and is also an important treatment modality in patients with OSA.

OSA and Glaucoma

Glaucoma is a multifactorial collection of eye diseases that is characterized by degeneration of retinal ganglion cells leading to a progressive optic neuropathy and is associated with cupping of the optic disc and increased intraocular pressure. The incidence of glaucoma in patients with OSA has been reported to be anywhere between 2% and 27%.^{65,66} While some studies have found the rate of glaucoma to be the same between OSA patients and the general population,⁶⁷ others have described a higher incidence in OSA patients.⁶⁸

In a study of 69 OSA patients and 45 controls undergoing a sleep study, none of the patients in the control group had glaucoma while 7.2% of the OSA patients did, of which 40% had normal-tension glaucoma and 60% had primary open-angle glaucoma.⁶⁸ Glaucoma incidence of 7.2% in the OSA patients was also significantly higher than the 2% rate in the general population ($p<0.001$).⁶⁸

A meta-analysis of 12 studies has shown an overall increased risk of glaucoma development in patients with OSA with an odds ratio of 1.65 (CI, 1.44–1.88).⁶⁹ Sub-group analysis revealed that this significant increase was only observed in patients with primary open-angle glaucoma but not in normal-tension glaucoma. In addition, patients with severe OSA had an even more significant

increased odds (OR: 5.49) of developing glaucoma compared to patients with mild or moderate OSA.⁶⁹

The risk of glaucoma development in 1012 OSA patients and 6072 healthy controls was investigated over 5 years.⁷⁰ The incidence of glaucoma was 11.26% in patients with OSA compared to 6.76% in the controls. Even after adjustment for demographics and risk factors, OSA patients were 1.67 times more likely to develop glaucoma (95% CI, 1.30, 2.17; $P < 0.001$).⁷⁰

In addition to be correlated with a higher incidence of glaucoma development, OSA has been found to influence the anatomical progression of disease in glaucoma. In a cohort study of 32 patients, those with moderate and severe OSA had a statistically higher degree of retinal nerve fiber layer thinning than patients with no or mild OSA.⁷¹ In addition, severe OSA had an increased risk of retinal nerve fiber layer thinning by a factor of 8.448 (95% CI, 1.464–48.752; $P < 0.017$).⁷¹

Overall, the evidence suggests that patients with OSA have an increased risk of developing glaucoma. This progressive ischemia of the optic nerve could be due to chronic hypoperfusion of the optic nerve head during the apnea episodes or dysregulation of vascular modulating cytokines as a result of OSA. Investigation with polysomnography can therefore be considered in patients with glaucoma, especially if there is progression despite the achievement of target intraocular pressure.

OSA and Stroke

Stroke affecting the retrochiasmatal visual pathways is a leading cause of homonymous visual field defects and OSA has been established as a risk factor for stroke. The study by Dyken et al was one of the first studies that showed a higher incidence of OSA in patients with a recent episode of ischemic or hemorrhagic stroke.⁷² They conducted polysomnograms and found that 70.8% of the 24 recent stroke patients had OSA as opposed to 18.5% of the 27 age- and sex-matched controls. Furthermore, 54% of the patients experienced stroke during sleep, suggesting that the apnea episodes of OSA might be a cause.⁷²

Artz et al conducted a study with a retrospective cross-sectional part of 1475 patients and a prospective 4-year longitudinal part that included 1189 patients who did not have a history of stroke.⁷³ The cross-sectional study revealed that patients with an AHI score of 20 or higher have an increased odds of developing stroke with an OR of 4.33 (CI: 1.32–14.24) after adjustment for known confounding factors. Additionally, the longitudinal study

showed that patients with an AHI score above 20 have a higher risk of first-time stroke occurrence over 4 years (OR 3.08, CI: 0.74–12.81).⁷³

In another longitudinal study, a cohort of 394 non-hospitalized elderly (70 or older) subjects with no history of stroke were followed for 6 years.⁷⁴ Twenty patients experienced stroke in the duration of the study, with an average AHI score of 28 as opposed to 20.1 in individuals who did not have a stroke. Moreover, after adjustment for confounding variables, subjects with severe OSA (AHI > 30) were found to have an increased risk of stroke (HR 2.52, CI 1.04–6.01).⁷⁴ Overall, this study demonstrated that even in older patients, OSA diagnosis is associated with a higher risk of stroke occurrence. Over a 20-year period, Marshall et al recorded 31 strokes in 393 patients who were assessed for OSA using a portable home-monitoring device.⁷⁵ They found that moderate-severe OSA was associated with stroke with an HR of 3.7 (CI: 1.2–11.8).⁷⁵

Overall, various observational and longitudinal studies have demonstrated a strong association between OSA and stroke, such that the more severe OSA leads to a higher risk of stroke occurrence. This may have an impact on vision since stroke is a leading cause of homonymous visual field defects.

Conclusion

The strongest association with obstructive sleep apnea in the area of neuro-ophthalmology is with NAION. Multiple prospective studies and meta-analyses have demonstrated an increased risk of this condition in patients with NAION. There is increasing evidence that polysomnography should be strongly considered in all patients with NAION and treatment with CPAP is recommended to reduce the risk of fellow-eye involvement. There is a much weaker relationship between IIH and OSA and there is insufficient evidence to recommend routine polysomnography in this patient population at this time. Patients with homonymous visual field defects are commonly diagnosed with stroke and it is important to recognize that there is an association between stroke and OSA, which may also be the first manifestation of undiagnosed OSA.

Return to Case Vignette

The patient was diagnosed with bilateral NAION after giant cell arteritis was excluded and magnetic resonance of the brain and orbits with contrast was normal. Given the concerning symptoms for OSA, he underwent

polysomnography, which revealed severe OSA with an AHI of 48.4 per hour. He was treated with CPAP and worked on lifestyle modifications to help with weight loss. His visual function was mildly improved to 20/80 (right) and 20/40 (left) at the 6-month follow-up.

Disclosure

The authors report no conflicts of interest in this work.

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