

Association Between Sleep Apnea Syndrome and Nonarteritic Anterior Ischemic Optic Neuropathy

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Objective: To determine if patients with nonarteritic ischemic optic neuropathy (NAION) have sleep apnea syndrome (SAS), an entity characterized by repetitive upper airway obstructions during sleep, inducing hypoxia and sleep disruption.

Methods: We recruited 17 patients with NAION and 17 age- and sex-matched controls from patients referred for treatment because of suspected restless legs syndrome. We performed overnight polysomnography and determined the respiratory disturbance index during night sleep, a value used to diagnose and grade SAS. We compared the proportions of patients with SAS among patients with NAION and matched controls using the χ^2 test. Additionally, we compared the proportions of patients with SAS among patients with NAION and a large SAS prevalence study using the binomial test.

Results: Twelve (71%) of 17 patients with NAION had SAS. According to the respiratory disturbance index, 4

patients (24%) had mild, 4 patients (24%) had moderate, and 4 patients (24%) had severe SAS. Only 3 (18%) of 17 controls had SAS ($P=.005$). In the 45- to 64-year age group, 4 (50%) of 8 patients with NAION had SAS; 51 (11.9%) of 430 of the random sample in the prevalence study had SAS ($P=.005$). In the group older than 64 years, 8 (89%) of 9 patients with NAION had SAS; 18 (24%) of 75 of the random sample in the prevalence study had SAS ($P<.001$).

Conclusions: We found a high prevalence of SAS in patients with NAION, which supports previous case reports suggesting that such an association exists. This association may explain why approximately 75% of all patients with NAION discover visual loss on first awakening or when they first use vision critically after sleeping. Our findings indicate that SAS may play an important role in the pathogenesis of NAION.

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NONARTERITIC anterior ischemic optic neuropathy (NAION) is a disease characterized by sudden, painless, mostly irreversible, and generally nonprogressive visual loss accompanied by nerve fiber bundle field defects, a relative afferent pupillary defect, and optic disc edema. The pathophysiologic characteristics of NAION remains unclear. Although several risk factors have been associated with this relatively common condition, the exact mechanism(s) that lead to optic nerve infarction remain unknown. Risk factors include aging, a small optic nerve head, and microvascular changes associated with diabetes and systemic hypertension.¹ No treatment is available since neither steroids nor surgical optic nerve sheath fenestration has proved to be effective. Prevention with aspirin has not been dem-

onstrated to be effective, although it is recommended.²

Many patients with NAION notice their symptoms in the morning.³ This has prompted investigations into changes in the systemic blood pressure at night in patients with NAION^{3,4} and raises the question of whether other nocturnal events may predispose patients to NAION. In a 1986 case report, optic disc edema was associated with sleep apnea syndrome (SAS).⁵ Recently, reports by Hayreh¹ and Mojon et al⁶ suggest an association between NAION and SAS. Other ophthalmologic findings in patients with SAS include floppy eyelid syndrome, keratoconus, reduced tear film break-up time, endothelial dystrophy,⁷ and glaucoma.⁸

Sleep apnea syndrome is a disease characterized by recurrent complete or partial upper airway obstructions during sleep.^{9,10} These obstructive respiratory dis-

PATIENTS AND METHODS

PATIENTS

We included all patients with NAION seen consecutively for 9 months at the Department of Ophthalmology, University of Bern, Bern, Switzerland (11 patients) and for 6 months at the New England Eye Center, Boston, Mass (12 patients). Eight (73%) of 11 patients in Bern and 9 (75%) of 12 patients in Boston agreed to undergo overnight polysomnography. The Epworth Sleepiness Scale scores were not significantly different between the group of patients not undergoing and the group undergoing polysomnography. The protocol was approved by the ethics committees of the University of Bern and New England Eye Center. All patients had partial loss of visual field, a relative afferent pupillary defect, loss of color vision, and swelling of the optic nerve head. All had crowded optic nerves with a cup-to-disc ratio of less than 0.1. None of them had symptoms, signs, or laboratory evidence of giant cell arteritis. In all patients with progressive visual loss, visual loss reached its maximum before the 10th day after onset.

POLYSOMNOGRAPHY

Overnight polysomnography was recorded during at least 6 hours in quiet, custom-built sleep laboratories. Recordings included electroencephalography, electro-oculography, electromyography, and nasal and oral airflow by thermistors. Simultaneously, inductive plethysmography (chest, abdomen, and sum) was performed and oxygen saturation was measured with a pulse oximeter.

POLYSOMNOGRAPHIC DATA ANALYSIS

The raw data were stored on a personal computer and analyzed off-line with sleep analysis software. Analysis was performed automatically by the software. Sleep apnea syndrome was diagnosed and graded according to the RDI (normal RDI, <10): mild SAS, RDI of 10 or more but less than 20; moderate SAS, RDI of 20 or more but less than 40; severe SAS, RDI of 40 or more.¹⁰

CONTROLS FOR POLYSOMNOGRAPHY

Seventeen patients referred for polysomnography because of suspected restless legs syndrome were used as controls. The controls were matched in a masked fashion for age (15 within 5 years of age, 2 within 10 years of age), sex, and participating Department of Ophthalmology (Bern or Boston). Additionally, the prevalences of SAS that we found in patients with NAION were compared with a 2-stage general random sample of men (aged 20 to 100 years) examined and previously described by Bixler et al.¹² This study represents the largest prevalence study available today. Their telephone survey included 4364 subjects; a subsample of 741 had a sleep laboratory evaluation. The subsample was grouped according to the RDI and age. Details about systemic diseases other than SAS were not provided.

STATISTICAL ANALYSIS

Prevalences of SAS in patients with NAION were compared with the matched controls and with the controls of the prevalence study using the χ^2 test or Fisher exact test and with the controls from the prevalence study using the binomial test. Comparison of the clinical and polysomnographic characteristics of the patients with NAION and matched controls was performed using the unpaired *t* test or Fisher exact test.¹³

turbances may last from 10 seconds to 2 minutes, leading to severe hypoxia and hypercapnia. Obstructions are terminated only after arousal from sleep, when upper airway muscle tone increases. Several hundreds of respiratory disturbances may occur during one night and cause severe sleep disruption with consequential daytime sleepiness. Typically, middle-aged and older, obese men with a long-lasting history of loud snoring are affected.¹¹ The repetitive sympathetic activation during arousal from sleep may cause serious cardiac arrhythmias and systemic hypertension. Such patients often show pulmonary-arterial hypertension, cor pulmonale, and, in severe forms, polycythemia. Sleep apnea syndrome is now recognized as an important risk factor for cardiovascular and neurovascular diseases.¹⁰

Sleep apnea syndrome is usually diagnosed by overnight polysomnography, including simultaneous electroencephalography, electromyography, electro-oculography, electrocardiography, oxymetry, plethysmography, and air flowmetry through the mouth and nose. From the polysomnographic data, the respiratory disturbance index (RDI), a value used to diagnose and grade SAS, is calculated. The treatment of first choice to prevent upper airway obstructions is the application of

nasal continuous positive airway pressure with a mask during sleep.¹⁰ In this study, we prospectively determined the prevalence of SAS in patients with NAION.

RESULTS

The clinical and polysomnographic data of all patients with NAION are summarized in **Table 1**. The age of the 17 patients (15 men and 2 women) ranged from 48 to 83 years.

Table 2 gives the summarized clinical and polysomnographic findings of the patients with NAION and matched controls. Except for the RDI, no statistically significant difference was found between the 2 groups. Six (75%) of 8 patients with NAION seen at the University Eye Institute of Bern had SAS (RDI ≥ 10). Six (67%) of 9 patients with NAION seen at the New England Eye Center had SAS. Twelve (71%) of all 17 patients with NAION seen at either center had SAS. All patients with SAS were men. According to the RDI, 4 patients (24%) had mild, 4 patients (24%) had moderate, and 4 patients (24%) had severe SAS. Table 2 gives the prevalences of SAS in patients with NAION (71%) and the matched controls (18%). The difference is statistically significant ($P = .005$).

Table 1. Clinical and Polysomnographic Data of All Patients With Nonarteritic Anterior Ischemic Optic Neuropathy*

Case No.	Center	Age, y	Sex	Body Mass Index†	RDI	SAS Grading	Eye(s)	Symptoms	Signs	Other Diseases
1	Bern, Switzerland	64	M	26.0	75.5	Severe	Right	Progressive LV	ODS, inferior altitudinal scotoma	Central retinal artery occlusion 1 y previously in the left eye
2	Boston, Mass	67	M	31.9	56.7	Severe	Both	Sudden LV of right eye 2 y after LV of left eye	ODS, central scotoma of right eye, optic atrophy of left eye	CS, CHD
3	Bern	68	M	27.0	51.5	Severe	Right	Progressive LV	ODS, inferior altitudinal scotoma	Hypercholesteremia
4	Boston	50	M	32.7	50.0	Severe	Left	Mild LV	ODS, superior VF depression	...
5	Bern	75	M	28.4	33.9	Moderate	Right	Sudden LV	ODS, inferior arcuate scotoma	HTA
6	Bern	81	M	22.2	37.1	Moderate	Right	Sudden LV of right eye	ODS, constricted VF	HTA, CHD
7	Boston	48	M	20.8	27.2	Moderate	Both	Progressive LV of right eye 5 y after LV of left eye	ODS, superior and inferior scotomas of right eye, inferior arcuate scotoma, optic atrophy of left eye	...
8	Boston	68	M	27.5	28.0	Moderate	Left	Sudden LV	ODS, constricted VF	PLM, CHD
9	Boston	83	M	29.2	17.0	Mild	Left	LV	ODS, inferior arcuate scotoma	CS, CHD
10	Bern	80	M	26.4	16.0	Mild	Both	Sudden LV of right eye, time of LV of left eye unclear	ODS, constricted VF of right eye, optic atrophy of left eye	HTA, right internal carotid constriction
11	Boston	49	M	25.7	14.0	Mild	Both	Sudden blurring of left eye 1 y after LV of right eye	ODS, inferior altitudinal scotoma of right eye, optic atrophy of left eye	HTA, DM, CS
12	Bern	76	M	22.6	11.5	Mild	Right	Sudden LV of right eye	ODS, constricted VF	POAG in both eyes
13	Bern	52	M	30.8	8.7	Normal	Both	Sudden LV of right eye 3 mo after LV of left eye	ODS, constricted VF of left eye, optic atrophy of right eye	HTA
14	Boston	54	F	32.2	3.0	Normal	Left	Sudden LV	ODS, superior arcuate scotoma	PLM, HTA
15	Boston	54	M	39.7	0.0	Normal	Both	Progressive LV of left eye 1 y after LV of right eye	ODS, inferior altitudinal scotoma of left eye, optic atrophy of right eye	PLM, HTA, CS
16	Bern	72	F	22.7	0.0	Normal	Right	Sudden loss in inferior VF	ODS, inferior arcuate scotoma	HTA
17	Boston	58	M	21.5	0.0	Normal	Left	Sudden blur in inferior VF	ODS, inferior and superior arcuate scotomas	PLM, HTA, CS

*RDI indicates respiratory disturbance index; SAS, sleep apnea syndrome; LV, loss of vision; VF, visual field; ODS, optic disc swelling; CS, cigarette smoking; CHD, coronary heart disease; HTA, hypertension; PLM, periodic limb movements; DM, diabetes mellitus; and POAG, primary open-angle glaucoma.
 †Calculated as weight in kilograms divided by the square of height in meters.

Also, the average RDI differed significantly between these 2 groups ($P = .04$).

The prevalences of SAS were also compared with data from a large prevalence study.¹² In the 45- to 64-year age group, 4 (50%) of 8 patients with NAION had SAS, whereas only 41 (10%) of 430 in the prevalence study had SAS. The SAS prevalence in patients with NAION was significantly higher than in the controls ($P = .005$). In the group of patients older than 64 years, 8 (89%) of 9 patients with NAION had SAS, whereas only 18 (24%) of 75 in the prevalence study had SAS. In this age group,

the difference in prevalence was also significantly higher ($P < .001$).

COMMENT

We found an increased prevalence of SAS in patients with NAION. Sleep apnea syndrome is a frequent breathing disorder caused by intermittent upper airway obstruction during sleep with concurrent hypoxia, negative intrathoracic pressure, and sympathetic activation. Since airway obstructions are terminated by repetitive arousal

Table 2. Summarized Clinical and Polysomnographic Findings of Patients With Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) and Controls

Characteristic	NAION (n = 17)	Restless Legs Syndrome (n = 17)	P Value
General			
Age, mean ± SD, y	64.6 ± 11.7	63.3 ± 11.0	.74
M/F, No. (%)	15/2 (88/12)	15/2 (88/12)	>.99
Body mass index, mean ± SD	27.5 ± 4.8	27.6 ± 3.9	.95
Cerebrovascular risk factor, No. (%)			
Hypertension	9 (53)	5 (29)	.30
Diabetes	2 (12)	3 (18)	>.99
Hypercholesterolemia	1 (6)	1 (6)	>.99
Smoking	5 (29)	4 (24)	>.99
Coronary heart disease	3 (18)	2 (12)	>.99
Polysomnographic findings			
Respiratory disturbance index, mean ± SD	25.3 ± 21.9	9.2 ± 20.8	.04
Respiratory disturbance index >10, No. (%)	12 (71)	3 (18)	.005

*Calculated as weight in kilograms divided by the square of height in meters.

reactions, normal sleep is disrupted. Long-term cardiovascular sequelae and complications include pulmonary and systemic arterial hypertension, cardiac arrhythmias, myocardial infarction, and stroke.^{9,14,15} Sometimes only episodic nocturnal systemic arterial hypertension or hypotension occurs.¹⁶

Recently, Hayreh¹ mentioned that he had anecdotal evidence of SAS in several patients with NAION. Also, Mojon and colleagues⁶ found that visual fields of patients with SAS revealed defects consistent with an optic neuropathy. More recently, SAS was found to be associated with optic disc swelling and visual field loss apparently due to intermittent increased intracranial pressure.¹⁷

In this cross-sectional study, we further investigated if an association between SAS and NAION exists. We found that approximately 70% of patients with NAION had SAS. The prevalences we found in patients with NAION were significantly higher than in age- and sex-matched controls. Regarding general characteristics and cardiovascular risk factors, the NAION group did not differ significantly from the matched controls. Also, when compared with the prevalences found by Bixler et al¹² in a large telephone random sample of men, the prevalences were significantly higher. Grouping by age is important because prevalence of SAS increases with increasing age.¹² Other studies¹⁸⁻²¹ have shown prevalences similar to those of the study by Bixler and coauthors. Because the prevalence of SAS for all ages is lower in women compared with men,²² the differences between our subjects, who were mostly men, and those in the prevalence study by Bixler and colleagues might even be greater.

Our own control group consisted of age- and sex-matched subjects with restless legs syndrome and were not age- and sex-matched healthy subjects. These pa-

tients were referred from the outpatient sections of the departments of neurology because of the clinical suspicion of restless legs syndrome and were not recruited from the sleep clinics. This group of patients had a prevalence of SAS similar to the general population, and this is consistent with other studies^{23,24} of restless legs syndrome and SAS.

Our sample size is relatively small and was obtained in 2 centers. However, all patients were prospectively recruited, and the results from the 2 testing centers were similar. There were more men than women, but when we calculated if no sex predilection existed, each 10th sample of 17 patients with NAION would be composed of 15 men just by chance. Since the restless legs control group was age and sex matched and the control group of Bixler et al¹² consisted of only men, no bias has been introduced by our high percentage of men. Since we performed a double comparison of our SAS prevalences among patients with NAION with our own and a historic control group, and since we found similar prevalences in 2 independent centers, we believe that our high SAS prevalence is real and clinically significant.

Our observational data do not allow any conclusions about a direct causal relationship between SAS and NAION. However, if we hypothesize that SAS causes NAION in some cases, the damage may result from impaired optic nerve head blood flow autoregulation,²⁵ secondary to repetitive prolonged apneas. Alternatively, optic nerve vascular dysregulation might be secondary to SAS-induced arterial blood pressure variations (episodic nocturnal hypertension or hypotension) and arteriosclerosis¹ or the imbalance between nitric oxide (a vasodilator) and endothelin (a vasoconstrictor).²⁶ Repetitive prolonged hypoxia also might damage the optic nerve directly. Because of the large stores of carbon dioxide and excellent buffering capacity of the body, changes in PaCO₂ and pH during apneas remain modest in contrast to changes in PaO₂, and, therefore, PaCO₂ variations do not seem to be harmful.²⁷ Episodic increased intracranial pressure during apnea spells¹⁷ may also have adverse effects on the optic nerve head, either directly or by compromising optic nerve circulation.

Approximately 75% of all patients with NAION discover visual loss on first awakening or at the first opportunity to use vision critically after sleeping.³ This might indicate that not only nocturnal arterial hypotension but also SAS could play an important role in the pathogenesis of NAION. Since there is no proven treatment of NAION, further studies are needed to clarify whether repetitive nocturnal upper airway obstructions might directly damage the optic nerve, whether continuous positive airway pressure treatment might help affected patients recover from NAION, and whether long-term treatment might help prevent involvement of the second eye. The recognition of SAS in any patient also may reduce the risk of cardiovascular or cerebrovascular disease.

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