

Original Investigation | July 2015

JOURNAL CLUB

Association of Nonarteritic Ischemic Optic Neuropathy With Obstructive Sleep Apnea Syndrome

Consequences for Obstructive Sleep Apnea Screening and Treatment

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JAMA Ophthalmol. 2015;133(7):797-804.

doi:10.1001/jamaophthalmol.2015.0893.

ABSTRACT

Importance The prevalence of obstructive sleep apnea syndrome (OSAS) in patients with nonarteritic anterior ischemic optic neuropathy (NAION) and its influence on second eye involvement is not well known.

Objective To evaluate the prevalence of OSAS in patients with NAION and risk factors of second eye involvement.

Design, Setting, and Participants In this cohort study, we examined 118 patients with anterior ischemic optic neuropathy referred to a tertiary care center from January 1, 2003, through December 31, 2010.

Exposures Patients underwent polysomnography to detect OSAS and were prospectively followed up to assess the risk of second eye involvement.

Main Outcomes and Measures The prevalence of OSAS in patients with NAION and the risk of second eye involvement using survival analysis based on the presence of OSAS, indication for ventilation treatment with continuous positive airway pressure, and other potential ocular and systemic confounders.

Results In 89 patients with NAION who underwent polysomnography, 67 (75%) had OSAS. Second eye involvement was found in 10 (13.7%) of 73 patients at 3 years: 8 (15.4%) of 52 patients with OSAS at 3 years and 2 (9.5%) of 21 patients without OSAS at 3 years; $P = .04$. In multivariate analysis, nonadherence to ventilation treatment with continuous positive airway pressure in patients with severe OSAS increased the risk of second eye involvement (hazard ratio, 5.54; 95% CI, 1.13-27.11; $P = .04$).

Conclusions and Relevance These results suggest that OSAS is common in patients with NAION and that polysomnography should be considered in these patients. These findings also suggest that patients with severe OSAS who are nonadherent to ventilation treatment with continuous positive airway pressure have an increased risk of second eye involvement.

INTRODUCTION

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common optic neuropathy after the age of 50 years, with an incidence of 2 to 10 per 100 000 people per year in the United States.¹ The pathophysiologic mechanisms of NAION remain poorly understood. Typically, NAION occurs in patients with an anatomical predisposition, such as a small or shallow optic cup.² The risk factors for the onset of NAION described in the literature are essentially cardiovascular, such as high blood pressure,³⁻⁵ diabetes mellitus,^{1,3-5} coronary ischemia,^{4,5} a history of ischemic stroke,^{3,5} hyperhomocysteinemia,⁶ dyslipidemia,⁴ carotid atheromatous overload, and/or smoking.^{4,7} Furthermore, certain drugs (particularly

phosphodiesterase type 5 inhibitors)⁸ and cataract surgery have also been implicated.⁹ More recently, an association between obstructive sleep apnea syndrome (OSAS) and NAION has been suggested by several authors.¹⁰⁻¹²

Obstructive sleep apnea syndrome is a common condition, estimated as affecting 5% of the general population and 18% of those older than 50 years.¹³ It corresponds to repeated episodes of complete or incomplete pharyngeal collapse. This pharyngeal collapse has 4 main effects: occurrence of desaturation-reoxygenation sequences, episodes of hypercapnia, increased respiratory effort, and the occurrence of microarousals during sleep. From these stimuli that accompany each respiratory event, mechanisms of adaptation of the cardiovascular system have been identified, including endothelial dysfunction, systemic inflammation, marked oxidative stress, coagulation abnormalities, sympathetic hyperactivity, and metabolic dysfunctions (diabetes, high-density lipoprotein dysfunction, and increased abdominal fat).^{14,15} These mechanisms induce increased cardiovascular risk, as evidenced by the more frequent occurrence of fatal and nonfatal cardiovascular events in patients with OSAS.¹⁶

The gravity of the evolution of NAION is the severity of the decline in visual function and the possibility of second eye involvement. The incidence of second eye involvement varies from 5% to 25% depending on the study.¹⁷⁻²⁵ In the Ischemic Optic Neuropathy Decompression Trial, the incidence was 15% during a mean follow-up of 5 years (n = 418), with a median time to occurrence of 1.2 years.²² Moreover, the recurrence rate of NAION was estimated at 6.4% in another series of 829 eyes, with a mean follow-up of 3.1 years.²⁶

The ventilation treatment of OSAS by continuous positive airway pressure (CPAP) is effective in reducing the mortality and morbidity associated with OSAS.^{16,27} Given the possible association between OSAS and NAION, it is essential to evaluate the effect of OSAS treatment on the risk of second eye involvement. We thus conducted a prospective study to assess the prevalence of OSAS in a large prospective cohort of patients with acute NAION and the potentially protective role of CPAP on the risk of second eye

involvement.

At a Glance

- We evaluated the prevalence of obstructive sleep apnea syndrome (OSAS) in patients with nonarteritic anterior ischemic optic neuropathy (NAION) and its influence on second eye involvement.
- In 89 patients with NAION, the prevalence of OSAS was 75% (67 of 89).
- Second eye involvement was found in 10 (14%) of 73 patients at 3 years (8 [15%] at 3 years of 52 patients with OSAS at 3 years and 2 [10%] of 21 patients without OSAS at 3 years; $P = .04$).
- In multivariate analysis, nonadherence to continuous positive airway pressure treatment in patients with severe OSAS increased the risk of second eye involvement (hazard ratio, 5.54 [95% CI, 1.13-27.11]; $P = .04$).
- Polysomnography should be considered in patients with NAION.

METHODS

A total of 118 consecutive patients referred to Grenoble University Hospital with anterior ischemic optic neuropathy were studied from January 1, 2003, through December 31, 2010 (Figure). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki on medical research in patients. This study was approved by the Comité de Protection des Personnes Sud-est 5, and patients were included after they provided written and oral informed consent.

Figure.

Flowchart of Patient Recruitment and Follow-up

AHI indicates apnea-hypopnea index; CPAP, continuous positive airway pressure; ION, ischemic optic neuropathy; NAION, nonarteritic ischemic optic neuropathy; OSAS, obstructive sleep apnea syndrome.



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The diagnosis of anterior ischemic optic neuropathy was made after the appearance (<14 days) of a painless decrease in visual acuity and/or visual field defects and a clinical examination for diffuse or sectorial optic nerve head edema, optic nerve head hemorrhages, and a variable degree of optic nerve head pallor.²⁸ The criteria for noninclusion were arteritic anterior ischemic optic neuropathy or another ocular condition that could reduce visual acuity and/or the visual field. The diagnosis of arteritic anterior ischemic optic neuropathy was made on the basis of a combination of clinical and laboratory signs: the onset of clinical signs of giant cell arteritis, elevated erythrocyte sedimentation rate and C-reactive protein level, pallid optic disc swelling, occlusion associated with the cilioretinal arteries, choroidal ischemia on fluorescein angiography, and/or positive findings on histologic examination of a biopsy specimen of the temporal artery. Patients who presented with damage to the contralateral optic nerve at inclusion were included in the study but not analyzed for risk assessment of second eye involvement.

The inclusion visit involved a comprehensive general clinical and ophthalmic examination with measurement of visual acuity, anterior segment and fundus examination, and measurement of intraocular pressure using a Goldmann applanation tonometer. Photographs (30°) of the optic nerve head were taken to measure the diameter of the disc and its cup (vertical cup-disc ratio). Ocular magnification was corrected with the Littman algorithm.

After screening, patients underwent fluorescein angiography (Topcon 50 IA camera; Topcon Corporation) and a visual field examination (Humphrey automated field analyzer 24-2 SITA-standard; Carl Zeiss AG). The visual field

was considered reliable and healthy only if the false-negative and false-positive results were below 30% and loss of fixation was less than 20%.

The assessment systematically included repeated measures of daytime blood pressure (8 times per day), laboratory tests for biological inflammatory syndrome (erythrocyte sedimentation rate and C-reactive protein), tests for dyslipidemia (total cholesterol, triglycerides, and high-density lipoprotein cholesterol), and measurement of fasting blood glucose. An examination of the carotid arteries was performed with ultrasonography of the supra-aortic trunks (HP Sonos 2500 scanner; Hewlett-Packard Development Company LP).²⁹ Smoking status was ascertained by asking about the estimated number of cigarettes smoked per day and the estimated number of years of smoking.

Nocturnal polysomnography and the Epworth Sleepiness Scale were systematically proposed to detect OSAS.³⁰⁻³² Polysomnography is the criterion standard for documenting abnormal events that occur during sleep. A continuous recording was made using C3/A2-C4/A1-Cz/01 electrodes. The air flow rate was measured using nasal pressure along with nasal and buccal thermistor measurements. The assessment of respiratory effort was made using the thoracic and abdominal movements and the transit time of the pulse. Blood oxygen saturation was measured with a pulse oximeter (Biox-Ohmeda 3700; Ohmeda Inc). *Sleep apnea* was defined as an apnea-hypopnea index (AHI) of 15 or more per hour.³⁰ The American Academy of Sleep Medicine Task Force 7 has proposed an AHI of 30 events per hour to distinguish moderate from severe OSAS.³⁰

The standard treatment for obstructive OSAS is ventilation treatment with CPAP. It consists of blowing pressurized air (at approximately 5-15 cm of water) into the upper airways using a nasal mask. An indication for ventilation treatment with CPAP was made when the AHI was greater than 30 per hour or 15 to 30 per hour when combined with daytime sleepiness, increased respiratory effort on the polysomnography, or cardiovascular morbidities. The CPAP treatment was initiated 1 month after the inclusion examination. Adherence to CPAP treatment was assessed by the number of hours of use

per night. Treatment was considered effective when used for more than 3 hours per night.³³ The duration of treatment was equal to the length of follow-up.

Follow-up consisted of ophthalmic clinical examinations and visual field examinations at 1, 3, 6, and 12 months after the episode of NAION and annually thereafter.

Statistical analyses were performed with the NCSS statistical software, version 97 (NCSS LLC) and SAS statistical software, version 9.1 (SAS Institute Inc) software packages. All tests were conducted in a bilateral manner. Differences were considered when $P < .05$.

Continuous variables were tested for normality from the computation of their skewness and kurtosis (omnibus test). The characteristics of the patients between the 2 populations were compared with the unpaired t test for normal continuous variables, the Mann-Whitney test for nonnormal continuous variables, the χ^2 test for discrete variables, or the Fisher exact test when expected counts were less than 5 (or Cramer V measure of association when expected counts were <5 and the table was larger than 2×2).

Prevalence is given as the number (percentage) of patients with OSAS, with the 95% CIs calculated using the Wilson score method with continuity correction.

The Kaplan-Meier survival method was used to construct the graphs. Cox proportional hazards regression models were used to assess risk factors for second eye involvement. Univariate Cox models were created and described in terms of the corresponding hazard ratios (HRs) with 95% CIs. Before this analysis, the hypothesis of log linearity had been checked graphically for every quantitative variable. None of the variables respected this hypothesis, so they were recoded from quartiles or the median (depending on the information). The hypothesis of proportional risks was also checked (graphic representation of $\text{Log}[-\text{Log}[S(t)]]$ according to the follow-up duration). Adherence to ventilation treatment with CPAP was considered as a time-dependent variable.

RESULTS

From a population of 118 patients with anterior ischemic optic neuropathy, 10 patients with arteritic anterior ischemic optic neuropathy and 19 patients with NAION who refused polysomnography recording were excluded. Thus, 89 patients with NAION were included in this study (58 men and 31 women; mean [SD] age, 68.0 [9.2] years; range, 55-94 years), and their general, ophthalmic, and cardiovascular characteristics are summarized in Tables 1, 2, and 3. A difference in the demographic, ocular, and cardiovascular characteristics between the groups with and without OSAS was not identified ($P > .05$) except for the AHI ($P < .001$).

Table 1. General Characteristics of Patients at Inclusion

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Table 2. Ophthalmologic Characteristics of Patients at Inclusion

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Table 3. Cardiovascular Characteristics of Patients at Inclusion

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Of 89 study participants, 85 (96%) were followed up for 3 years. One patient presenting with bilateral involvement at inclusion, 1 patient having only 1 eye, 2 patients having CPAP treatment before the first eye involvement, and 12 patients who had contralateral optic atrophy at the inclusion examination were also not included in the analysis of second eye involvement; thus, CPAP treatment was performed on 73 patients. A flowchart of patient recruitment and follow-up is shown in the Figure.

In this study, OSAS was found in 67 (75%) of 89 patients. The median AHI of the OSAS population was 40.0 (interquartile range, 28.0-48.5) events per hour. The OSAS was considered moderate in 24 patients (36%) and severe in 43 patients (64%). The prevalence of vascular risk factors for NAION is given in Table 3, with a clear predominance of hypertension (67%). None of our patients had received cataract surgery in the year preceding the episode of NAION or second eye involvement.

One patient presenting with bilateral involvement at inclusion and 12 patients who had contralateral optic atrophy at the inclusion examination were not included in the analysis of second eye involvement (performed on 73 patients). At 3 years, a risk of second eye involvement was found in 10 (13.7%) of 73 patients: 8 (15.4%) of 52 patients with OSAS and 2 (9.5%) of 21 patients without OSAS (difference, 5.9%; 95% CI, 0.2%-11.5%; $P = .04$). The median time to event was 12 months (interquartile range, 4-58 months).

Ventilation treatment with CPAP was indicated in 46 (88%) of the 52 patients with OSAS included in the second eye involvement analysis, with satisfactory adherence in 22 (48%) of 46 (Figure). Two deaths were recorded during the follow-up period (1 patient in the group with moderate OSAS and 1 patient in the group with untreated severe OSAS).

From the univariate model, the risk factors for second eye involvement with $P < .20$ and entered into the multivariate model were as follows: initial mean deviation (-16.32 or greater vs less than -16.32 ; HR, 0.10; $P = .03$), carotid stenosis (severe plus moderate vs normal; HR, 4.08; $P = .19$), smoking (yes vs no; HR, 0.18; $P = .10$), and the category of OSAS (nonadherent severe OSAS vs non-OSAS plus moderate OSAS without an indication for ventilation treatment with CPAP; HR, 4.29; $P = .07$) (Table 4). In multivariate analysis, the presence of severe OSAS nonadherent to ventilation treatment with CPAP was associated with significantly increased risk of second eye involvement (nonadherent severe OSAS vs non-OSAS plus moderate OSAS without an indication for ventilation treatment with CPAP; HR, 5.54; 95% CI, 1.13-27.11; $P = .04$). When the overall test (nonadherent severe OSAS vs all others; HR, 2.80; $P = .09$ in univariate analysis) was entered in the

multivariate model, the 95% CI extended above and below 1.0 (HR, 4.98; 95% CI, 0.91-12.41; $P = .10$).

Table 4. Univariate Survival (Cox Proportional Hazards Regression Model): Relative Risk of Second Eye Involvement as a Function of the Parameters Recorded at Inclusion

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The Kaplan-Meier graphs showing the risk of second eye involvement over time according to the OSAS group are shown in the eFigure in the Supplement.

DISCUSSION

This prospective study confirms the high prevalence of OSAS (75%) in a large cohort of patients with NAION^{5,10-12} and reveals for the first time, to our knowledge, that patients with severe OSAS who are nonadherent to ventilation treatment with CPAP have an increased risk of second eye involvement. The high prevalence of OSAS was suggested in studies^{11,12} that required systematic polysomnography, the reference test for the

diagnosis of OSAS, but with small numbers of patients (n = 17-27). A more recent study,¹⁰ based on a sleep disorder questionnaire, reported a prevalence of 30%. However, this questionnaire significantly underestimates the number of apneic patients. This underestimation is also the case with the Epworth Sleepiness Scale³² used in our study, for which no difference in score was found between the groups of apneic and nonapneic patients, suggesting that this score cannot be used as part of screening.³⁴ Our study and data from the literature indicate that it is therefore necessary to perform overnight polysomnography for the diagnosis of OSAS in patients with NAION.

The pathophysiologic mechanisms underlying the onset of NAION remain poorly understood. Identification of OSAS as a risk factor of NAION allows new pathophysiologic hypotheses to be proposed. We found that nocturnal hypotension was rare (decrease in blood pressure in 5% of patients with NAION) and ocular perfusion pressure does not significantly decrease during the night in patients with NAION.³⁵ It is well known that patients with obstructive OSAS for the most part have a “nondipper” blood pressure profile.³⁶ The mechanisms leading to cardiovascular complications in OSAS affect the autoregulation of blood flow, either metabolically (increased PaCO₂, endothelial dysfunction, plasma levels of endothelin, and sympathetic hyperactivity)^{15,37} or myogenically (increase in vasoconstriction in response to increased intravascular pressure).³⁷⁻⁴²

Currently, there is no approved treatment for NAION.⁴³ Treatments focused on one or more of the risk factors could reduce the likelihood of second eye involvement. Three retrospective studies^{21,24,44} on the efficacy of aspirin on the rate of second eye involvement, with conflicting results, do not enable any conclusions to be drawn about its protective effect. In our study, the rate of second eye involvement of 13.7% at 3 years is similar to what was reported in the Ischemic Optic Neuropathy Decompression Trial (14.7%), with a mean follow-up of 5 years. Our study explores, for the first time, the risk of second eye involvement in a population of patients with OSAS. The risk of second eye involvement was 15.4% at 3 years in those with OSAS and 9.5% at 3 years in those without OSAS. In multivariate analysis, patients with severe

OSAS nonadherent to CPAP ventilation treatment increased their risk of second eye involvement by a factor of 5.54 (HR, 5.54; $P = .04$). A difference in the frequency of the general characteristics of patients (eg, age and diabetes) between the groups with and without OSAS, which included factors already known to promote bilateralization,^{45,46} was not identified. This finding suggests that, in the future, the presence and severity of OSAS are factors that must be considered as independent risk factors of second eye involvement of NAION.

To date, the possible role of CPAP in reducing the risk of a second eye involvement has not been studied in a large series of patients. This specific treatment for sleep apnea should be considered a serious therapeutic strategy because it removes respiratory anomalies, restores sleep quality, partially or completely improves acute chronic cardiovascular abnormalities, improves vascular reactivity, and reduces systemic inflammation.^{38,40,41,47} We found in a multivariate analysis that took into account possible confounding factors that patients with severe OSAS who are nonadherent to ventilation treatment with CPAP had an increased risk of second eye involvement (HR, 5.54). A possible bias of the study is that patients who are nonadherent with ventilation treatment with CPAP may have a tendency toward nonadherence with other medications and recommendations from their physicians, which by itself may lead to an increased risk of second eye involvement. Another bias of the present study is that when the overall test (nonadherent severe OSAS vs all others; HR, 2.8; $P = .09$ in univariate analysis) was entered in the multivariate model, the 95% CI extended above and below 1.0 (HR, 4.98; 95% CI, 0.91-12.41; $P = .10$). This finding could indicate that the OSAS severity and the ventilation treatment with CPAP could influence the risk of second eye involvement and that our analysis does not distinguish the respective roles of each of these 2 factors. A randomized comparative study assessing the risk of second eye involvement in patients with OSAS treated with ventilation treatment with CPAP and patients treated with placebo would be needed to conclude on the protective effect of ventilation treatment of OSAS with CPAP on the risk of second eye involvement. However, given the need to monitor patients for at least 1 year

to assess the rate of second eye involvement and the effectiveness of ventilation treatment with CPAP on their cardiovascular comorbidities,⁴⁸ the randomization of patients with NAION and OSAS to sham CPAP treatment for 1 to 2 years does not seem feasible to us.

CONCLUSIONS

The results of this prospective cohort of 89 patients with NAION suggest that OSAS is common in patients with NAION and that polysomnography should be considered in these patients. These findings also suggest that patients with severe OSAS who are nonadherent to ventilation treatment with CPAP have an increased risk of second eye involvement. The effect of ventilation treatment of OSAS with CPAP on the risk of second eye involvement should be prospectively evaluated in a larger cohort of patients.

ARTICLE INFORMATION

Submitted for Publication: November 11, 2014; final revision received February 20, 2015; accepted March 1, 2015.

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Published Online: April 30, 2015. doi:10.1001/jamaophthalmol.2015.0893.

Author Contributions: Drs Aptel and Chiquet had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

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Statistical analysis: Aptel, Khayi, Romanet, Chiquet.

Obtained funding: Aptel, Levy, Chiquet.

Administrative, technical, or material support: Aptel, Tamisier, Romanet, Chiquet.

Study supervision: Aptel, Pépin, Levy, Chiquet.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Tamisier reported receiving an unrestricted grant for IH exposure research from Resmend Foundation. Dr Tamisier has also received a fee for consulting from Jazz Pharmaceutical. No other disclosures were reported.

Funding/Support: This study was supported by grant ETO-578 from the Fondation de l'Avenir.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Additional Contributions: N. Arnol, MSc, INSERM U1042, Hypoxia and Physiopathology Laboratory, Joseph Fourier University, Grenoble, France, performed the statistical analysis, and Alison Foote, PhD, Clinical Research Center, Grenoble University Hospital, translated the manuscript. No financial compensation was provided.

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