EXTENDED REPORT

Non-arteritic anterior ischaemic optic neuropathy and presumed sleep apnoea syndrome screened by the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ)

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Br J Ophthalmol 2007;91:1524–1527. doi: 10.1136/bjo.2006.113803

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Accepted 1 May 2007
Published Online First
15 May 2007

Background: Two recent studies reported over 70% of the patients with non-arteritic anterior ischaemic optic neuropathy (NAION) had sleep apnoea syndrome (SAS) diagnosed by overnight polysomnography. The current study used the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) to evaluate this association.

Methods: A matched case-control study was conducted among 73 cases of NAION matched on age and gender to 73 controls without a history of NAION. Information regarding demographics, medical conditions, health behaviours and SAS was obtained via a telephone questionnaire that included the SA-SDQ. Conditional logistic regression was used to calculate odds ratios (OR) and the 95% confidence intervals (CI) for the association between NAION and the SA-SDQ.

Results: Cases were significantly more likely to report symptoms and characteristics consistent with SAS than controls (OR 2.62; 95% CI 1.03 to 6.60) when adjusted for medical and health behaviour characteristics.

Conclusions: The results of this study suggest that patients with SAS are at increased risk of NAION. Additional research in a larger population is needed to confirm the observed results and validate the use of the SA-SDQ in patients with NAION.

Non-arteritic anterior ischaemic optic neuropathy (NAION) is clinically characterised by acute painless monocular vision loss. It is the most common acute optic neuropathy among adults over 50 years of age in the USA, with an estimated 1500 to 6000 persons suffering from NAION annually.¹ Currently, the lack of treatment to improve vision loss or prevent fellow eye NAION underscores the need for a deeper understanding of its aetiology.

Several risk factors have been reported, including advanced age, systemic hypertension, diabetes, arteriosclerosis, hypercholesterolaemia, and a small optic cup-to-disc ratio.^{1–6} Moreover, the acute vision loss associated with NAION frequently occurs upon awakening,⁷ suggesting that a pathological event during sleep may trigger NAION. Several recent studies have reported links between NAION and obstructive sleep apnoea syndrome (SAS),^{8–12} though all but two^{11, 12} of these studies were case series. One recent matched case-control study¹¹ with 17 NAION cases and 17 controls identified 71% of the NAION cases had SAS diagnosed by overnight polysomnography. Another study reported an even higher prevalence of SAS among the NAION cases, with 24 of the 27 (89%) newly diagnosed NAION cases exhibiting SAS according to overnight polysomnography.¹² The study also found that patients with NAION were almost five times more likely to have SAS compared with previously published data from the general population.¹³

Both studies had several limitations including small numbers of NAION cases, over-representation of male participants and lack of appropriate adjustment for potential confounders. Given the expense of overnight polysomnography, future epidemiological studies with larger sample sizes may be financially prohibitive. Thus, the availability of an easy-to-implement screening tool for SAS is desirable. With this in mind, the current matched case-control study sought to evaluate the association between NAION and SAS using the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ), a 12-item instrument that has been validated against full polysomnography.¹⁴

METHODS

Selection of cases and controls

The study design and procedures were approved by the institutional review board of the University of Alabama at Birmingham, USA. The NAION cases and controls were identified from patients seen in the department of ophthalmology clinic of the University of Alabama at Birmingham in Birmingham, Alabama from January 2000 to February 2004. The cases were first identified by searching the clinic's electronic database for records containing the *International Classification of Diseases, Ninth Revision, Clinical Modifications* (ICD-9-CM) code 377.41 (ischaemic optic neuropathy). Medical record abstraction was then performed in order to confirm the diagnosis of NAION and collect selected demographic information (eg, age, gender, race). The diagnostic criteria for NAION include: (1) a history of sudden painless loss of vision; (2) optic disc oedema on ophthalmological exam that resolved into optic atrophy; (3) visual field defects consistent with optic-disc pathology; (4) lack of findings on physical or ophthalmological exam suggesting another disorder could be causing the symptoms; (5) exclusion of arteritic anterior ischaemic optic neuropathy by clinical presentation and erythrocyte sedimentation rate. Subjects were excluded if they had a previous diagnosis of anterior arteritic ischaemic optic neuropathy, toxic optic neuropathy or nutritional optic neuropathy. A control patient matched on age and gender was randomly selected for each case. Eighty-eight individuals with a diagnosis of NAION were initially identified as eligible and contacted for participation in the study, of whom 73 agreed (83.0%) to participate in the study.

Abbreviations: COPD, chronic obstructive pulmonary disease; NAION, non-arteritic anterior ischaemic optic neuropathy; SAS, sleep apnoea syndrome; SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire

Controls were randomly selected from patients seen in the department of ophthalmology clinic for reasons other than NAION during the same time period used to select cases (ie, January 2000 to February 2004). For each case a single control matched on age within 1 year and gender was randomly identified and contacted for participation in the study. If the first randomly selected control did not choose to participate in the study, another control was randomly selected. In total, 130 potential control subjects were contacted, of whom 42 refused to participate while 88 agreed to do so (67.7%).

Data collection and variable definitions

Subjects with symptoms consistent with SAS were identified using the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ). It has 12 items and has been validated in individuals with full polysomnography.¹⁴ Eight questions address the specific symptoms of SAS, including snoring loudly, stopping breathing during night sleep, awaking suddenly gasping for breath, sweating during night sleep, having high blood pressure, having nose block up when wanting to sleep, snoring/breathing getting worse when sleeping on the back, snoring/breathing getting worse when asleep after alcohol use. The rest of the questions are related to current weight, current smoking status, current age and body mass index. Responses to the 12 items are quantified and a total score is obtained by adding these items together; total scores range from 0 to 60 with higher numbers indicating a higher likelihood of SAS. The suggested cut-off points for identifying patients who may have SAS are 36 for men and 32 for women. Based on those cut-offs, the sensitivity and specificity for men are 0.85 and 0.76, respectively; the corresponding values for women are 0.88 and 0.81. The positive predictive value was 0.72 for men and 0.31 for women; the Cronbach's α value is 0.855. Those cut-offs were adopted by the current study.

Additional information was collected regarding the socio-demographic, health behaviour and medical characteristics that were present in participants before the development of NAION (case group) or at the time of the interview (control group). Socio-demographic information was collected with standard items addressing age, gender, race and education. Health behaviours were assessed with questions concerning cigarette smoking and alcohol consumption. Medical characteristics were obtained with questions regarding whether the respondent had ever been diagnosed with various chronic or acute conditions, including coronary artery disease, high blood pressure, elevated cholesterol, diabetes (type 1 or 2), chronic obstructive pulmonary disease (COPD), glaucoma, migraine headaches, stroke, cardiac arrhythmia and myocardial infarction.

All information not collected as part of the chart abstraction was collected via a telephone survey by a research interviewer trained in the administration of medical telephone questionnaires. The interviewer was not masked to the status of the subject as a case or control.

Statistical analysis

Cases and controls were compared regarding their demographic characteristics, health behaviours and disease conditions using the paired *t* test for the continuous variables and McNemar's test for the categorical variables. Conditional logistic regression models were used to calculate the odds ratios (OR) and the 95% confidence intervals (CI) for the association between NAION and sleep apnoea with or without adjustment for potential confounding characteristics. A two-sided *p*-value of 0.05 is considered statistically significant.

RESULTS

By design there was no difference between cases and controls with respect to age and gender (table 1). Neither were there significant differences with respect to smoking and alcohol consumption. The cases were more likely to be white but less likely to have college education. The history of coronary artery disease, diabetes, migraine headaches and stroke was significantly more common among cases than among controls, whereas cardiac arrhythmia, COPD and glaucoma were significantly more common among controls. A total of 35 subjects had a score on the SA-SDQ consistent with SAS, 22 (30.1%) among the cases and 13 (17.8%) among the controls (OR 1.82; 95% CI 0.87 to 3.79) (table 2). Adjusting for race in addition to the medical and behavioural characteristics in table 1 increased the OR to 2.82; however, this estimate lacked precision (95% CI 0.62 to 12.94) owing to the large number of variables in the model relative to the sample size. Adjusting only for glaucoma, high cholesterol and smoking, each of which demonstrated significant, independent associations with NAION, changed the OR only slightly but improved the precision of the estimate. Patients with NAION were 2.62 times (95% CI 1.03 to 6.60) more likely to have a score on the SA-SDQ consistent with SAS.

Table 3 compares results from the current study to the results of two previously published studies on this topic. The current study had a larger sample size than both of the other studies combined; it also had more women, although the average age of subjects was consistent across all three studies. Subjects in the current study had a slightly higher BMI. Among the NAION cases, the current study had the highest prevalence of hypertension and diabetes. Among the controls, compared with the study of Mojon *et al.*,¹¹ the current study also had a

Table 1 Demographic characteristics, health behaviours and disease conditions among NAION cases and controls

	Cases (n = 73)	Controls (n = 73)	p
Demographic characteristics			
Age (in years), mean (sd)	63.5 (11.0)	63.5 (11.1)	
Gender, n (%)			
Male	38 (52.1)	38 (52.1)	
Female	35 (47.9)	35 (47.9)	
Race, n (%)			0.008
Caucasians	68 (93.2)	57 (78.1)	
African-Americans	5 (6.8)	16 (21.9)	
Health behaviour characteristics			
Cigarette consumption			
Ever smoked 100 cigarettes, yes, n (%)	32 (43.8)	35 (48.0)	0.60
Current cigarette smoker, yes, n (%)	5 (7.0)	7 (10.0)	0.41
Alcohol consumption			
Ever consume alcohol, yes, n (%)	38 (52.1)	43 (58.9)	0.40
Number of drinks per/week, mean (sd)	3.5 (6.1)	1.7 (3.0)	0.08
Number of years drinking, mean (sd)	18.7 (15.1)	13.2 (10.7)	0.05
Body mass index	28.2 (5.98)	28.4 (5.93)	0.77
Disease conditions, yes, n (%)			
Coronary artery disease	12 (17.4)	8 (11.1)	<0.0001
High blood pressure	44 (60.3)	37 (50.7)	0.37
High cholesterol	49 (67.1)	31 (42.5)	0.46
Diabetes	21 (28.8)	19 (26.0)	0.0001
COPD	1 (1.4)	2 (2.7)	<0.0001
Glaucoma	3 (4.1)	17 (23.6)	<0.0001
Migraine headaches	8 (10.9)	6 (8.2)	<0.0001
Stroke	14 (20.0)	2 (2.8)	<0.0001
Cardiac arrhythmia	13 (18.3)	22 (30.1)	<0.0001
Myocardial infarction	41 (56.2)	31 (42.5)	0.91

Table 2 Odds ratios and 95% confidence intervals for the association between NAION and presumed sleep apnoea

	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)	Adjusted** OR (95% CI)
Sleep apnoea					
No	68 (93.2)	70 (95.9)	1.82 (0.87, 3.79)	2.82 (0.62, 12.94)	2.62 (1.03, 6.60)
Yes	22 (30.1)	13 (17.8)			

*Adjusted for race, smoking, alcohol consumption, BMI, coronary artery disease, high blood pressure, high cholesterol, diabetes, COPD, glaucoma, migraine headaches, stroke, cardiac arrhythmia, myocardial infarction. **Adjusted for glaucoma, high blood cholesterol and smoking.

higher prevalence of hypertension and diabetes. SAS was less common in the current study than reported in the Palombi *et al.* and Mojon *et al.* studies (30.1% versus 89% and 71%, respectively); although the proportion among the controls was similar between the current study and that of Mojon *et al.* (17.8% versus 18.0%).

DISCUSSION

The results of the current study suggest, as do previous studies,^{11 12} that there is an association between NAION and SAS. In the present study individuals with symptoms consistent with SAS were identified by using the SA-SDQ. The gold standard for the diagnosis of SAS is overnight polysomnography performed in sleep laboratories. Polysomnography lasts at least 6 hours and includes a variety of invasive-like recordings such as electroencephalography, electro-oculography, chin electromyography, nasal and oral airflow by thermistors, snoring by microphone, electrocardiogram, pulse oximetry and tibialis anterior electromyogram. These diagnostic procedures are costly and lengthy, which may partly explain why 82% of men and 92% of women in the USA who are likely to have moderate or severe SAS have yet to be diagnosed.^{15 19} In contrast, the SA-SDQ¹⁴ has 12 questions that can be administered over the phone by individuals who have had minimal training and it has good sensitivity and specificity to detect SAS in the general population. The successful use of the SA-SDQ in the current study supports its continued use in studies of the relationship between eye diseases including NAION and glaucoma and SAS.

It was not possible to determine the temporal relationship between NAION and SAS in the current study, and as such, inferences about cause and effect are not possible. Assuming that a relationship between NAION and SAS might exist, what might be its biological basis? Several mechanisms by which SAS may predispose one to NAION have been proposed including impaired optic nerve head blood flow autoregulation secondary to repeated apnoeas, optic nerve vascular dysregulation secondary to

SAS-induced arterial blood flow variations, and direct optic nerve damage due to prolonged hypoxia or increased intracranial pressure during apnoea among others.^{9 11}

Despite our finding of an association between NAION and SAS, the proportion of NAION cases with symptoms consistent with SAS in the current study was lower than the prevalence of SAS observed in other studies.^{11 12} There are several possible reasons for this observation. First, the cut-off points on the SA-SDQ used to identify SAS are based on results from the general population and may not be appropriate for patients with NAION. Support for this can be found in a study of patients with epilepsy for whom a lower cut-off point on the SA-SDQ was suggested.¹⁷ In fact when those cut-off points are used in the current study the proportion of cases classified as having SAS is approximately 70%, a figure much more consistent with previous reports.^{11 12} However, despite this increase in prevalence the association between NAION and SAS remains relatively unchanged (OR 2.16). Further, among the controls, the proportion of subjects reporting symptoms consistent with SAS was similar to the prevalence of SAS reported among the controls in the Mojon *et al.*¹¹ study (eg, 18%). Thus the determination of the appropriate cut-offs for the NAION population requires validation based on polysomnography.

Among the potential limitations of this study is the fact that the research interviewers were not blinded as to whether each subject was a case or control. This was because the telephone survey contained questions pertaining only to those patients with NAION. However, the research interviewers were not aware of the study hypotheses and thus there is no reason to suspect information bias. Even so, there is also the possibility that study subjects did not interpret the questions posed to them appropriately. This limitation is not unique to the present study; rather it reflects a broader limitation associated with the use of telephone surveys for collecting health-related information. However, as long as such misinterpretations do not occur systematically with respect to cases or controls, then the result would be associations that are biased towards the null. That being said, there is no reason to suspect such misinterpretations and therefore bias in the present study.

Though this is not the first study on the association between NAION and SAS, it is the first epidemiological study to explore this association using a quick, cheaper and easier screening tool to identify SAS. It is also the largest study to date on this topic. In addition to finding a positive association, this study raised several important issues regarding the use of the SA-SDQ. The recommended, population-based cut-off points may be too high for patients with NAION and individual questions on the SA-SDQ may not be sensitive enough to detect SAS among patients with NAION, many of whom did not exhibit the classical symptoms of SAS highlighted by the questionnaire. Given mounting evidence that SAS may indeed be a risk factor for NAION, future research with larger sample sizes is needed as well as validation studies on the use of the SA-SDQ in patients with NAION.

Table 3 Comparison among three studies on NAION and SAS

	Palombi <i>et al</i> ¹²	Mojon <i>et al</i> ¹¹	Current study		
	NAION N=27	NAION N=17	Controls N=17	NAION N=73	Controls N=73
Gender					
Male, n (%)	18 (67)	15 (88)	15 (88)	38 (52)	38 (52)
Female, n (%)	9 (33)	2 (12)	2 (12)	36 (48)	35 (48)
Age	65.0±8.0	64.6±11.7	63.3±11.0	63.5±11.0	63.5±11.0
BMI	27.2±3.8	27.5±4.8	27.6±3.9	28.1±5.9	28.4±5.9
Hypertension (%)	49	53	29	60	51
Diabetes (%)	26	12	18	29	26
SAS (%)	89	71	18	30.1	17.8

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Funding: This research was supported by National Institute on Aging Grant R01-AG04212, National Eye Institute Grant R21-EY14071, Research to Prevent Blindness, Inc., and the EyeSight Foundation of Alabama. CO is a Research to Prevent Blindness Senior Scientific Investigator.

Competing interests: None declared.

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