SCIENTIFIC REPORT

Is there an association between pre-existing sleep apnoea and the development of glaucoma?

C A Girkin, G McGwin Jr, S F McNeal, C Owsley

Br J Ophthalmol 2006;**90**:679–681. doi: 10.1136/bjo.2005.086082

Aim: To determine if sleep apnoea is associated with an increased risk of developing glaucoma.

Methods: This was a nested case-control study. Patients seen at the Veterans Affairs Medical Center (BVAMC) in Birmingham, Alabama, with newly diagnosed glaucoma (cases) between 1997 through 2001 were selected (n = 667) and age matched with non-glaucomatous controls (n = 6667). Patient information was extracted from the BVAMC data files containing demographic, clinical, and medication information. An index date was assigned to the glaucoma subjects corresponding to the time of diagnosis. Patients who had a glaucoma diagnosis before the observation period of the study were excluded. 10 controls were randomly selected for each case and matched on age (plus or minus 1 year) and an encounter on or before the index date of the matched case. Ihe main outcome measures were crude and adjusted relative risks for the association between the previous diagnosis of sleep apnoea and the development glaucoma. Adjustment was performed for the associations of diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, arterial disease, and migraines.

Results: Individuals who developed glaucoma were more likely to have a previous sleep apnoea diagnosis relative to control subjects. However, this finding was of borderline significance at an alpha of 0.05 (p value = 0.06, odds ratio = 2.20, 95% confidence intervals 0.967 to 5.004). Following adjustment for other potential risk factors, no significant difference was seen (p value = 0.18, odds ratio = 1.80, 95% confidence interval 0.76 to 4.23).

Conclusions: This nested case-control study does not support a large impact of sleep apnoea on the eventual development of glaucoma relative to other putative risk factors.

While a number of risk factors associated with the development of glaucomatous optic neuropathy have been identified, the aetiology of this condition remains unclear. Sleep apnoea has been implicated as a possible risk factor for the development of open angle glaucoma[1] and normal tension glaucoma.[2] It has been suggested that repeated intermittent periods of hypoxia may influence the development of ganglion cell loss.[2] However, a causal mechanism has not been clearly identified.

While a consecutive case series of normal tension glaucoma (NTG) patients[3] and a separate series of patients with open angle glaucoma (POAG)[4] have suggested a higher prevalence of sleep disorders than expected in the general population, few case-control trials have been performed[2 5] and no large comparative study has been published determining the risk of developing glaucoma that is associated with sleep disturbances. Additionally, a recent larger series of 228 white patients with sleep apnoea demonstrated a prevalence of glaucoma no greater than would be expected in the general white population To date the literature does not provide clear evidence of a significant association between sleep apnoea and the development of glaucoma in a large cohort of subjects. Thus, the purpose of this study is to determine, in a large cohort of patients, if sleep apnoea is associated with a higher risk of developing glaucoma.

METHODS

Study population and data source

The Birmingham (Alabama) Department of Veterans Affairs Medical Center (BVAMC) is a 134 bed acute tertiary care medical facility and serves as a Veterans Hospital Administration tertiary care referral centre for Alabama. All patients who had at least one visit (inpatient or outpatient) at the Birmingham BVAMC between 1 January 1997 and 31 December 2001 were eligible for study inclusion. Because the prevalence of glaucoma is low below age 50, the study population was limited to patients aged 50 and older. Females were also excluded as they represented such a small proportion of the patient population (10.8%) that meaningful analyses were difficult.

The BVAMC provided data files containing demographic information (age, sex, race) and clinical and medication information for each patient. The clinical file contained a description of each diagnosis made at the BVAMC during inpatient and outpatient visits and the diagnosis date. All diagnoses were coded using the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9CM). The information provided pertained to all diagnoses over the course of each patient's history with the BVAMC and not just those that occurred in 1997 through 2001. All data received from the BVAMC contained no information that would allow patients to be identified. The institutional review board of the BVAMC approved the protocol.

Study design

Within the study population, a nested case-control study was conducted. Cases of glaucoma were defined using the ICD-9CM codes 365.1 (open angle glaucoma), 365.8 (other specified), and 365.9 (unspecified glaucoma). Too few patients were specifically coded as low tension glaucoma for a meaningful analysis to be performed. Information on the glaucoma diagnosis date was procured and will be referred to as the index date. Patients who had a glaucoma diagnosis before the observation period of the study (prevalent cases) were excluded.

Controls were randomly selected from the study population who did not have a glaucoma diagnosis by the end of the observation period. To be considered an eligible control for a given case, the control must have had an encounter with the

Abbreviations: NTG, normal tension glaucoma; POAG, primary open angle glaucoma

Table 1 Difference in demographic and medical characteristic between cases and controls

	Cases (n = 667)		Controls (n = 6667)				
	No	%	No	%	p Value*	OR*	95% CI*
Demographic characteristics							
Age (in years), mean	69		69		0.9223	1.043	0.938 to 1.160
Race, n (%)							
Black	190	29.8	896	14.1	0.1364	1.077	0.981 to 1.182
White	235	36.8	3031	47.5			
Unknown	213	33.4	2450	38.4			
Medical characteristics							
Diabetes	164	25.7	792	12.4	<0.0001	2.461	2.026 to 2.988
Lipid metabolism disorders	90	14.1	531	8.3	<0.0001	1.853	1.449 to 2.370
Hypertension	324	50.8	1742	27.3	<0.0001	2.863	2.418 to 3.390
Cardiovascular disease	126	19.8	1257	19.7	0.9818	1.002	0.816 to 1.231
Cerebrovascular disease	50	7.8	434	6.8	0.3275	1.166	0.858 to 1.583
Arterial disease	39	6.1	353	5.5	0.5451	1.111	0.789 to 1.563
Migraines	4	0.6	10	0.2	0.0190	4.125	1.270 to 13.576
Sleep apnoea†	7	1.1	32	0.5	**0.0601**	**2.200**	**0.967 to 5.004**
Sleep apnoea‡					**0.18**	**1.80**	**0.76 to 4.23**

*Odds ratios (OR), confidence intervals (CI), and p values for the association between sleep apnoea and glaucoma are in bold for both the unadjusted and adjusted analysis. †Unadjusted odds ratio; ‡odds ratio adjusted for intergroup differences diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, arterial disease, and migraines.

BVAMC (inpatient or outpatient) on or before the index date of the matched case. Ten controls were selected for each case and matched on age (plus or minus 1 year). Each control was assigned the index date associated with their matched case.

Information on the presence of sleep apnoea was obtained from the clinical data file based on the ICD-9CM code 244.9 (acquired sleep apnoea, unspecified). For the purposes of analysis, only diagnoses that were recorded before the index date were considered.

Information on the presence of the following conditions was extracted from the clinical data file because of previous research indicating their potential association with glaucoma: ischaemic heart disease (ICD-9CM codes 410 though 414), cerebrovascular disease (ICD-9CM codes 430 though 438), lipid metabolism disorders (ICD-9CM code 272), hypertension (ICD-9CM codes 401 though 405), diseases of the arteries, arterioles and capillaries (ICD-9CM codes 440 though 448), diabetes (ICD-9CM code 250) and migraines (ICD-9CM code 346). For the purposes of analysis, only those diagnoses that were recorded before the index date were considered.

Statistical analysis

Conditional logistic regression was used to calculate an odds ratio (OR) and 95% confidence interval (CI) for the association between the presence of sleep apnoea and the risk of developing glaucoma. These associations were calculated with and without adjustment for the potentially confounding effect of diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, arterial disease, and migraines. p Values $\leqslant 0.05$ were considered statistically significant.

RESULTS

In all, 667 incident cases of glaucoma were identified and matched with 6667 controls. There are three control subjects less than expected because 10 to 1 matching was not possible in all cases. By design, the mean age of the groups was similar (69.0 years) (table 1). The known racial distribution did not significantly differ between cases and controls. Diabetes, lipid metabolism disorders, hypertension, and migraines were all significantly more frequent among the cases than the controls; there were no differences with respect to cardiovascular, cerebrovascular, and arterial diseases. The crude odds ratio for the association between sleep apnoea and the future development of glaucoma was of borderline significance (OR = 2.20, 95% CI 0.967 to 5.004). Following adjustment for other potential confounders, no significant association was seen between sleep apnoea and the development of glaucoma (OR = 1.80, 95% CI 0.76 to 4.23).

DISCUSSION

Our study has demonstrated elevated risk of developing glaucoma in patients with a pre-existing diagnosis of sleep apnoea defined by ICD-9CM code in a large VA population using a nested case-control design. However, this crude association was only of borderline significance and, when adjusted for other risk factors available in the data set, was not significant. As discussed below, the interpretation of this result should acknowledge several characteristic of the study design that would tend to bias the estimates of relative risk towards the null.

Our analysis of this dataset has several potential weaknesses. Firstly, the study population was obtained from older male populations of patients from the Veterans Affairs. Secondly, the diagnosis of glaucoma was determined by ICD-9CM codes that introduced a potential error of miscoding and possible misdiagnosis by the individual treating physicians. However, since sleep apnoea is not an established risk factor for glaucoma, there is little reason to suspect differential misclassification. Thus, any misclassification should be non-differential and thus tend to bias our results towards the null and therefore our results are likely to underestimate any true association. Thirdly, since the identification of glaucoma was based on the first visit when glaucoma was diagnosed, the possibility of a ''left censoring'' bias is an additional potential concern. Thus, it would be expected that a few of the patients in this dataset captured early in the study during the first 2 years may have had pre-existing glaucoma and, because of our methodology, would have been included as a case of newly diagnosed glaucoma. This also should be non-differential. Overall, these weaknesses would tend to bias the results of the study towards the null owing primarily to non-differential misclassification bias.

Several previous reports have found a high prevalence of sleep apnoea in patients with POAG[4–6] and NTG.[3] The prevalence of glaucoma in patients with sleep apnoea has also been found to be higher than the general population in one small study[1] and similar to the general population in a larger series of 228 subjects.[7] While some of these studies included historical controls,[3 4] only two relatively small case-control studies have demonstrated a significant association between sleep apnoea and NTG.[2 5]

These previous studies were performed from specialty offices, which may introduce a selection bias from referral mechanisms. In our current study, no such referral bias should exist as all patients were seen in a hospital based outpatient facility. Moreover, the use of the nested case-control design allowed us to evaluate sleep apnoea antecedent to glaucoma diagnosis, thereby decreasing the likelihood that any observed association is the result of certain biases.

In summary, our study provides no evidence of a strong association between sleep apnoea and glaucoma relative to other putative risk factors. However, several issues intrinsic to a retrospective data analysis may have created some degree of bias towards the null. Given that the pre-existing literature consists of only a few small studies from poorly generalisable populations, a larger prospective study would be required to determine if there is a true association between these disorders.

Authors' affiliations
C A Girkin, S F McNeal, C Owsley, Department of Ophthalmology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA
G McGwin Jr, Department of Epidemiology and International Health, School of Public Health, and Section of Trauma, Burns, and Surgical Critical Care, Division of General Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, AL, USA

Financial support: This research was supported by NIH grant K23 EY13959-01, NIH grant R21-EY14071, Research to Prevent Blindness, Inc, and the EyeSight Foundation of Alabama. Cynthia Owsley is a Research to Prevent Blindness Senior Scientific Investigator.

Proprietary interest statement: none.

Correspondence to: Christopher Girkin, UAB Department of Ophthalmology, 1800 University Blvd, EFH 609, Birmingham, AL 35294-0009, USA; cgirkin@uab.edu

Accepted for publication 3 February 2006

REFERENCES

1 **Mojon DS**, Hess CW, Goldblum D, *et al*. High prevalence of glaucoma in patients with sleep apnea syndrome. *Ophthalmology* 1999;**106**:1009–12.
2 **Marcus DM**, Costarides AP, Gokhale P, *et al*. Sleep disorders: a risk factor for normal-tension glaucoma? *J Glaucoma* 2001;**10**:177–83.
3 **Mojon DS**, Hess CW, Goldblum D, *et al*. Normal-tension glaucoma is associated with sleep apnea syndrome. *Ophthalmologica* 2002;**216**:180–4.
4 **Mojon DS**, Hess CW, Goldblum D, *et al*. Primary open-angle glaucoma is associated with sleep apnea syndrome. *Ophthalmologica* 2000;**214**:115–8.
5 **Onen SH**, Mouriaux F, Berramdane L, *et al*. High prevalence of sleep-disordered breathing in patients with primary open-angle glaucoma. *Acta Ophthalmol Scand* 2000;**78**:638–41.
6 **Pearson J**. Glaucoma in patients with sleep apnea. *Ophthalmology* 2000;**107**:816–7.
7 **Geyer O**, Cohen N, Segev E, *et al*. The prevalence of glaucoma in patients with sleep apnea syndrome: same as in the general population. *Am J Ophthalmol* 2003;**136**:1093–6.