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OBSTRUCTIVE SLEEP APNEA AND CENTRAL SEROUS CHORIORETINOPATHY

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Abstract

Purpose—The purpose of this study was to determine if there is an association between obstructive sleep apnea (OSA) and central serous chorioretinopathy (CSCR).

Methods—Patients with CSCR without a history of steroid use or secondary retinal disease were matched based on age/gender/body mass index with control patients and administered the Berlin Questionnaire to assess for OSA risk. Patients were scored “OSA+” if they were at “high risk” on the Berlin Questionnaire or reported a previous OSA diagnosis. Rates of OSA+ were compared between the 2 groups, odds ratio and its 95% confidence interval was calculated using exact conditional logistic regression.

Results—Forty-eight qualifying patients with CSCR were identified. There were no statistically significant differences between the CSCR and control groups by age (mean = 55 years), gender (79% male), body mass index (mean = 28.2), history of diabetes, or hypertension. Within the CSCR group, 22 patients (45.8%) were OSA+ versus 21 control patients (43.8%) (difference = 2.1%; 95% confidence interval, –18.2% to 22.2%; exact odds ratio = 1.08, 95% confidence interval, 0.47–2.49; $P = 1.00$).

Conclusion—When compared with matched controls, patients with CSCR did not have statistically significant higher rates of OSA risk or previous diagnosis. This finding contrasts with previous work showing a strong association between the diseases. The divergence is likely due to our matching controls for body mass index, a significant risk factor for OSA.

Keywords

central serous chorioretinopathy; sleep apnea

Obstructive sleep apnea (OSA) is a frequent disorder characterized by repeated apneic events during sleep frequently accompanied by transient hypoxia and hypercapnia.^{1,2} The cause of the apnea is most commonly mechanical with airway obstruction resulting from

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decreased muscle tone of the upper airway and recumbency during sleep. The most significant risk factors for OSA are obesity and aging.³

The pathogenic role of OSA in multiple conditions, most notably cardiovascular and cerebrovascular diseases, is increasingly accepted.⁴ Obstructive sleep apnea has also been shown to be associated with several ocular diseases. Examples of such associations include glaucoma, central retinal vein occlusion, and nonarteritic ischemic optic neuropathy.^{5,6} More recently, the association of OSA and central serous chorioretinopathy (CSCR) has become the focus of researchers.⁷⁻⁹

Central serous chorioretinopathy is a condition characterized by serous detachment of the neurosensory retina, usually in the macula, often multifocal, rarely with peripheral manifestations and frequently bilateral.^{10,11} It has been theorized that the underlying defect may be hyperpermeability of the choroidal vasculature and/or breakdown of the outer blood-retinal barrier.^{10,11} Although the exact pathophysiology remains unclear, there are several well-established associations that have provided some clues into possible mechanisms. Central serous chorioretinopathy is more common in middle-aged men,¹² has been associated with increased sympathetic drive,¹³ and “Type A” personality.¹⁴ It has also been associated with increased levels of serum steroids, either from exogenous administration or endogenous production as in Cushing syndrome.¹⁵ This latter association has been supported further by the resolution of serous detachments in experimental animals, and while still controversial, in humans treated with steroid antagonists.^{16,17}

Several possible pathophysiologic links between OSA and CSCR have been suggested. In both diseases, patients have increased sympathetic drive, which can cause vascular endothelial dysfunction.^{13,18-20} Additionally, it has been shown that disruptions in hormone regulatory responses result from repeated apneic episodes and can lead to increased cortisol levels,²¹ potentially increasing the likelihood of CSCR development.¹⁵

Two recent cross-sectional studies and a case report found an association between CSCR and OSA.⁷⁻⁹ The case report described a patient with bilateral CSCR who experienced dramatic and rapid resolution of the central serous detachment in both eyes after treatment with continuous positive airway pressure therapy for coincidentally diagnosed OSA. However, proving an association between a rare disease, CSCR, and a condition commonly observed in the general population, OSA, is difficult. The present work aims to evaluate the relationship between OSA and CSCR by surveying a larger number of patients with CSCR for OSA and comparing the results with a group of carefully matched controls.

Materials and Methods

Subjects

Patients were initially selected from a retrospective review of medical records of all patients seen from 2006 to 2012 at Scheie Eye Institute at the University of Pennsylvania, a tertiary level ophthalmology practice, with a diagnosis code of CSCR. Patients were included if CSCR had been confirmed by either fluorescein angiography and/or optical coherence tomography. Patients were excluded from the study if they had no current or previous

angiographic or optical coherence tomography documentation of their disease, or if serous detachments could be due to another disease such as macular degeneration or diabetic retinopathy. Patients with all forms of CSCR were included for analysis including chronic and recurring detachments, as well as patients who had only a single acute episode. Patients with a history of steroid use in the year preceding their developing CSCR were also excluded, because this may have been a confounding factor to elucidating a relationship between OSA and CSCR.²² Informed consent was given by all subjects in compliance with the Declaration of Helsinki, and the study received approval from the University of Pennsylvania's Institutional Review Board. Investigators were trained and certified in compliance of the Health Information Privacy and Portability Act.

All identified patients with CSCR were mailed consent forms and then had follow-up phone calls to obtain informed consent and complete the Berlin Questionnaire (described below). Patients could alternatively be surveyed in person if the patient was seen in clinic during the recruitment period for this study.

Berlin Questionnaire for Sleep Apnea

All consenting patients verbally completed the Berlin Questionnaire for Sleep Apnea. The Berlin Questionnaire is a validated 10-question survey that predicts a patient's risk for sleep apnea by assessing three self-reported categories: 1) snoring and witnessed apneas; 2) daytime tiredness and fatigue; and 3) obesity and hypertension. Sensitivity and specificity for the Berlin Questionnaire in a primary care setting are reported as 0.86 and 0.77, respectively.²³ A respondent is determined to be at "high risk" for OSA if they meet criteria in at least two of the three criteria listed. In addition to the questionnaire, all patients were asked about the history of steroid use, previous diagnosis of OSA, diabetes, and hypertension. The questionnaire has been previously used in assessing the association between OSA and CSCR.⁷

All study subjects were scored as positive (OSA+) if they reported a previous diagnosis of OSA or if they were at high risk on the Berlin Questionnaire.

Recruitment of Controls

The characteristics (age, gender, and body mass index [BMI]) of patients with CSCR were noted, and patients with similar demographics but without retinal disease (seen by the comprehensive Ophthalmology Practice at our institution) were contacted to participate as controls. Similar to our recruitment of the patients with CSCR, the control patients were either contacted through mail with follow-up phone calls or completed the consent and questionnaire during their visit to the clinic. Investigators were masked to the results of the Berlin Questionnaire and matched the qualifying CSCR patients with the control patients based on age, gender, and BMI.

Data Collection and Analysis

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Pennsylvania.²⁴ REDCap is a secure web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for

validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Balance was assessed for matched and nonmatched characteristics by *t*-tests for continuous variables and chi-square tests for categorical variables. Wilson score-based method²⁵ was used to calculate confidence intervals (CIs) for the difference in proportions of OSA+ between the matched pairs, exact conditional logistic regression model was used to calculate the odds ratio and its 95% CI, and McNemar's test was used to calculate the *P* value. Unconditional logistic regression model was used to assess the relationship between BMI and OSA+ by excluding the BMI component of OSA risk score. All statistical analyses were performed with SAS Software Version 9.3 (SAS Institute, Cary, NC).

Results

Three hundred and fifty-six charts were identified with the billing code for CSCR; however, 144 (40%) lacked supporting documentation (either fluorescein angiography or optical coherence tomography). Additionally, of those with documentation of subretinal fluid, 94 (26%) had another possible etiology for the fluid (e.g., diabetic retinopathy or macular degeneration). Ultimately, we identified 118 eligible patients (33%) who met criteria and had a confirmed diagnosis of CSCR with angiographic or optical coherence tomography evidence of the disease (Figure 1). Sixty-five confirmed patients (65/118) consented to participate; however, 17 (17/65) were excluded because of steroid use in the year before their developing CSCR. The remaining 48 patients with CSCR (48/65) were included in the analysis.

These 48 patients with CSCR first presented to our clinic on an average 6.3 years (median = 6.9 years) before this study. The average time since the most recent visit was 2 years (median = 1 year). Forty-one of the patients with CSCR (41/48) had active disease with subretinal fluid at the time of presentation.

Two hundred and five patients were contacted from the comprehensive Ophthalmology Practice at Scheie Eye Institute to serve as control patients. Ninety-two (92) of these control patients gave informed consent and completed the Berlin Questionnaire. Thirty-seven control patients (37/92) completed the Berlin questionnaire in person while at the clinic, and the rest (55/92) were administered the questionnaire by telephone. Forty-eight patients (48/92) were matched 1:1 to the patients with CSCR based on BMI, age, and gender.

No statistically significant differences were found between the composition of the CSCR and control groups regarding age, sex, BMI, history of diabetes, or hypertension (Table 1).

Within the CSCR group, 22 patients (22/48, 45.8%) were scored OSA+ by either having been previously diagnosed with OSA (*n* = 9) or, if not previously diagnosed, were determined to be at high risk on the Berlin Questionnaire (*n* = 13) (Table 2). Within the control group, 21 patients (21/48, 43.8%) were OSA+ by either having been previously diagnosed with OSA (*n* = 6) or, if not previously diagnosed, were determined to be at high risk on the Berlin Questionnaire (*n* = 15). There was a 2.1% difference in OSA+ between the

groups (95% CI, -18.2% to 22.2%). Conditional logistic regression showed an odds ratio of 1.08 (95% CI, 0.51–2.29; $P = 0.85$).

The data showed that increasing BMI, examined as a continuous variable, increased risk for OSA, even with the exclusion of BMI as contributing to the risk score (risk/diagnosis; odds ratio = 1.13 for 1 kg/m² increase of BMI; 95% CI, 1.03–1.24; $P = 0.01$). Additionally, when grouping patients by BMI, there were increasing rates of OSA+ in the overweight (25–29.9 kg/m²) and obese (>30 kg/m²) groups versus the normal (<25 kg/m²) BMI group (Figure 2).

Patients with persistence of the serous detachment for >6 months and/or with chronic recurrent acute detachments with widespread decompensation of the retinal pigment epithelium are generally considered chronic CSCR.¹¹ A third of our patients (15/48) could be considered within this category, consistent with the reported prevalence for this outcome and helps explain the relatively older demography of our group of patients compared with what would be otherwise expected for the typical patient with CSCR. The prevalence of OSA was slightly lower 5/15 (30%) within this subgroup compared with the control group. Given the few patients with chronic CSCR identified in this study, statistical subgroup analysis was not performed.

Discussion

Despite earlier studies that showed increased prevalence of OSA symptoms and diagnosis in patients with CSCR, this study found no statistically significant difference in risk for OSA between patients with CSCR (46%) and matched controls (44%). It is notable that these estimates of OSA risk are higher than the estimates of OSA in the general population, which is likely a result of the specific cohort of patients with CSCR studied and their matched controls.^{27,28} Leveque et al showed an association between CSCR and OSA, so an elevated proportion of OSA relative to the general population in our CSCR is not surprising (and in fact our proportion [45.8%] was lower than that of Leveque [58.6%]). However, the purpose of matching our patients with CSCR with controls on age/gender/BMI was to create a control population that reflects the CSCR population if they did not have CSCR, not to recreate the general population.

Although this study cannot conclusively exclude the possible relationship between OSA and CSCR, it does not support the previously reported strong association between the two conditions.^{7,8} The data also show the risk for OSA increased with increasing BMI—a known risk factor for OSA.^{2,3,26–28} This provides reassurance that the study captured OSA risk appropriately.

Two previous studies examined the relationship between OSA and CSCR with conclusions that run counter to what was found in this study.^{7–9} A recent case–control study by Leveque et al⁷ used the Berlin Questionnaire for sleep apnea risk to assess patients with CSCR for OSA risk. The study, which paired 29 patients with CSCR with 29 age-matched and sex-matched controls, showed an increased risk for OSA for patients with CSCR (odds ratio, 3.67; 95% CI, 1.02–13.14). The study, however, did not control for BMI, a major risk factor

for OSA. Thus, if the CSCR cohort had higher BMIs than controls, it might have biased the result toward showing a high rate of OSA among these patients.

A second study by Kloos et al⁸ surveyed 36 patients with CSCR for OSA risk using the Epworth Sleep Scale with follow-up polysomnography to confirm the diagnosis of OSA. Similar to the Berlin Questionnaire, the Epworth sleep scale is a survey instrument to determine the risk for OSA (sensitivity = 66% and specificity = 48% at an Epworth sleep scale score >10).²⁹ Fourteen of the 36 patients had an Epworth sleep scale score of >10, indicating a high risk for OSA. Of these, 8 were found to have OSA: 5 male patients (13.8%) had mild OSA, and an additional 3 male patients (8.3%) had moderate-to-severe OSA. Kloos et al⁸ concluded that these results were significantly above the prevalence of OSA in the general population, which they cited as 2% to 4% based on a 1993 study by Young et al.²⁶ However, updated epidemiologic data from the same authors argue for a higher prevalence of OSA (14.3% of men met criteria for mild OSA, and 5.8% of men met criteria for moderate-to-severe OSA).^{27,28} If the higher OSA prevalence is taken into account, then their conclusions would be more in agreement with our results.

This study used methodology similar to that of Leveque et al⁷ with the important difference of controlling for BMI and using a slightly larger cohort of patients. Although BMI is included in the risk score of the Berlin questionnaire, it is treated as a binary data point (BMI > or <30 kg/m²). In reality, BMI is a continuous measure with the risk for OSA increasing continuously.^{26–28} Consequently, the best way to control for this type of continuous variable is to use controls matched to BMI, as well as age and sex. Having controlled for BMI, the results of our study show no significant difference between case and control populations regarding the risk for OSA.

Our study relied on patient self-reports for OSA and could be strengthened through the use of objective sleep data such as polysomnography. Kloos et al⁸ used polysomnography to diagnose OSA in a cohort in patients with CSCR. The prevalence of OSA in their CSCR cohort is similar to the recent estimates of the prevalence of OSA in the general population.^{27,28} The data from Kloos et al,⁸ when viewed in the light of the updated OSA prevalence studies, are also consistent with the findings presented here.

Cross-sectional studies can only suggest an association (or lack thereof), but are usually unable to demonstrate a causal relationship or mechanism. Our patients were surveyed on an average 6.3 years after initial diagnosis of CSCR, and it is possible they had developed OSA subsequent to the diagnosis of CSCR, potentially biasing results toward finding a higher prevalence of OSA in these patients than actually existed at the time of their CSCR diagnosis. Yet, we could not find a significant difference with our age-matched controls.

Additionally, CSCR may not be a mechanistically homogeneous disease.¹¹ It could be that for a subgroup of patients, there is a strong association between OSA and CSCR. Perhaps by characterizing larger groups of patients with CSCR and by finding specific subgroups with traits that fit specific disease mechanisms, we will be able to ultimately strengthen relationships that currently seem unclear such as the association between OSA and CSCR.

This study had a relatively small cohort of patients ($n = 48$) and was not able to exclude moderate associations within the reported CI of 0.47 to 2.49. However, the study was sufficiently powered (86% power) to detect the strong association between the diseases that Leveque et al have proposed, and did not find it because we believe their association was the result of unrecognized confounding by BMI.

In summary, we did not find a statistically significant association between CSCR and OSA risk in this cross-sectional case–control study. Our result is contrary to a previous study⁷ using similar methodology that found an association between the diseases. The difference is likely explained because of our stricter control matching that accounted for BMI, a significant risk factor for OSA.^{2,3}

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References

1. Chin K, Hirai M, Kuriyama T, et al. Changes in the arterial PCO₂ during a single night's sleep in patients with obstructive sleep apnea. *Intern Med.* 1997; 36:454–460. [PubMed: 9240492]
2. Pack AI, Pien GW. Update on sleep and its disorders. *Annu Rev Med.* 2011; 62:447–460. [PubMed: 21073334]
3. Kasper, DL.; Fauci, AS.; Longo, DL., et al., editors. *Harrison's Principles of Internal Medicine.* 17. New York, NY: McGraw-Hill Medical; 2008. p. 1665-1667.
4. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005; 365:1046–1053. [PubMed: 15781100]
5. Grover DP. Obstructive sleep apnea and ocular disorders. *Curr Opin Ophthalmol.* 2010; 21:454–458. [PubMed: 20811281]
6. Glacet-Bernard A, Leroux les Jardins G, Lasry S, et al. Obstructive sleep apnea among patients with retinal vein occlusion. *Arch Ophthalmol.* 2010; 128:1533–1538. [PubMed: 21149775]
7. Leveque TK, Yu L, Musch DC, et al. Central serous chorioretinopathy and risk for obstructive sleep apnea. *Sleep Breath.* 2007; 11:253–257. [PubMed: 17457629]
8. Kloos P, Laube I, Thoelen A. Obstructive sleep apnea in patients with central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol.* 2008; 246:1225–1228. [PubMed: 18546012]
9. Jain AK, Kaines A, Schwartz S. Bilateral central serous chorioretinopathy resolving rapidly with treatment for obstructive sleep apnea. *Graefes Arch Clin Exp Ophthalmol.* 2010; 248:1037–1039. [PubMed: 20049474]
10. Gass JD. Pathogenesis of disciform detachment of the neuro-epithelium. *Am J Ophthalmol.* 1967; 63:S1–S139.
11. Levine R, Brucker AJ, Robinson F. Long-term follow-up of idiopathic central serous chorioretinopathy by fluorescein angiography. *Ophthalmology.* 1989; 96:854–859. [PubMed: 2740080]
12. Kitzmann AS, Pulido JS, Diehl NN, et al. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980–2002. *Ophthalmology.* 2008; 115:169–173. [PubMed: 18166410]
13. Bernasconi P, Messmer E, Bernasconi A, Thölen A. Assessment of the sympathovagal interaction in central serous chorioretinopathy measured by power spectral analysis of heart rate variability. *Graefes Arch Clin Exp Ophthalmol.* 1998; 236:571–576. [PubMed: 9717651]
14. Yannuzzi LA. Type A behavior and central serous chorioretinopathy. *Retina.* 2012; 32:S709.

15. Haimovici R, Koh S, Gagnon DR, et al. Risk factors for central serous chorioretinopathy: a case-control study. *Ophthalmology*. 2004; 111:244–249. [PubMed: 15019370]
16. Zhao M, Célérier I, Bousquet E, et al. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. *J Clin Invest*. 2012; 122:2672–2679. [PubMed: 22684104]
17. Nielsen JS, Jampol LM. Oral mifepristone for chronic central serous chorioretinopathy. *Retina*. 2011; 31:1928–1936. [PubMed: 21878843]
18. Kasasbeh E, Chi DS, Krishnaswamy G. Inflammatory aspects of sleep apnea and their cardiovascular consequences. *South Med J*. 2006; 99:58–67. [PubMed: 16466124]
19. Michael JC, Pak J, Pulido J, de Venecia G. Central serous chorioretinopathy associated with administration of sympathomimetic agents. *Am J Ophthalmol*. 2003; 136:182–185. [PubMed: 12834690]
20. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995; 96:1897. [PubMed: 7560081]
21. Henley DE, Russell GM, Douthwaite JA, et al. Hypothalamic-pituitary-adrenal axis activation in obstructive sleep apnea: the effect of continuous positive airway pressure therapy. *J Clin Endocrinol Metab*. 2009; 94:4234–4242. [PubMed: 19820009]
22. Gass JD, Little H. Bilateral bullous exudative retinal detachment complicating idiopathic central serous chorioretinopathy during systemic corticosteroid therapy. *Ophthalmology*. 1995; 102:737–747. [PubMed: 7777273]
23. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999; 131:485–491. [PubMed: 10507956]
24. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and work-flow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42:377–381. [PubMed: 18929686]
25. Newcombe RG. Improved confidence intervals for the difference between binomial proportions based on paired data. *Stat Med*. 1998; 17:2635–2650. [PubMed: 9839354]
26. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993; 328:1230–1235. [PubMed: 8464434]
27. Young T, Palta M, Dempsey J, et al. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin sleep cohort study. *WMJ*. 2009; 108:246. [PubMed: 19743755]
28. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013; 177:1006–1014. [PubMed: 23589584]
29. Rosenthal LD, Dolan DC. The Epworth sleepiness scale in the identification of obstructive sleep apnea. *J Nerv Ment Dis*. 2008; 196:429–431. [PubMed: 18477888]

Fig. 1.
Description of the recruitment of patients with CSCR.

Fig. 2.
Patients with OSA+ (either "high risk" for OSA or previously diagnosed OSA).

Table 1

General Characteristics of the Study Participants

	<u>Patients With CSCR</u>	<u>Control Patients</u>	
	n = 48 (%)	n = 48 (%)	P[*]
Age, years			
Mean (SD)	55 (13)	54 (14)	0.70
<50	17 (35)	19 (40)	
50–64	18 (38)	19 (40)	0.77
65	13 (27)	10 (21)	
BMI, kg/m ²			
Mean (SD)	28.1 (4.8)	28.3 (4.9)	0.86
Normal	16 (33)	13 (27)	
Overweight	17 (35)	19 (40)	0.80
Obese	15 (31)	16 (33)	
Male	38 (79)	38 (79)	1
Diabetes [†]	6 (13)	9 (19)	0.40
Hypertension [†]	18 (38)	18 (38)	1

BMI: normal, 18.5 to <25; overweight, 25 to <30; obese ≥30.

^{*} *t*-tests used for mean, chi-square tests for proportions.

[†] Diabetes and hypertension were not specifically matched for.

SD, standard deviation.

Table 2

Results From Berlin Questionnaire

	<u>Patients With CSCR</u>	<u>Control Patients</u>	
	n = 48 (%)	n = 48 (%)	P
Previous diagnosis of OSA	9 (18.8)	6 (12.5)	0.37
“High risk” by Berlin Questionnaire *	13 (27.1)	15 (31.3)	NA [†]
Total OSA+	22 (45.8)	21 (43.8)	0.85

* High risk of those not previously diagnosed.

[†] Subgroup not matched pairs, statistics not applicable for this subgroup.