ELSEVIER

Sleep Medicine 3 (2002) 361–364

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Brief communication

Headache complaints in relation to nocturnal oxygen saturation among patients with sleep apnea syndrome

Glen P. Greenough*, Peter D. Nowell, Michael J. Sateia

Dartmouth–Hitchcock Medical Center, Sleep Disorders Center, One Medical Center Drive, Lebanon, NH 03756, USA

Received 25 September 2001; received in revised form 29 November 2001; accepted 11 December 2001

Abstract

Background: Morning headaches are often ascribed to patients with sleep apnea syndrome (SAS) but the etiology of headaches in SAS is unclear. Given the relationship between oxygen and other headache syndromes, nocturnal hypoxia might be one factor contributing to headaches in SAS.

Methods: All subjects 18–80 years of age who were determined to have SAS and who underwent a continuous positive airway pressure trial in our sleep laboratory between March 1, 1997 and March 18, 1998 were considered for inclusion. Subjects were grouped according to whether they endorsed that waking with headaches is a problem for them. Polysomnography and standardized questionnaires were used to test the main hypothesis that patients with SAS and headaches would spend more time at lower oxyhemoglobin levels than those SAS patients without headache.

Results: Headache and non-headache patients did not differ in the percentage of time spent with an oxygen saturation less than 90%, either in total sleep time or in rapid eye movement sleep (REM). The headache patients were more likely to be female and spend a lower percentage of time in REM sleep. The REM sleep difference was not accounted for by the use of REM suppressing medications or by depression (as measured by the Zung scale).

Conclusions: These data do not support the hypothesis that the duration of nocturnal hypoxemia relates to headache complaints in patients with SAS. The lower REM sleep percentage and higher variability in REM apnea index among the headache patients warrants further investigation.

Keywords: Sleep apnea; Headache; Hypoxemia; Nocturnal hypoxemia; Rapid eye movement sleep

1. Introduction

Many sleep disorders, including sleep apnea syndrome (SAS), have been associated with headaches that have their onset primarily during sleep [1–4]. The International Classification of Sleep Disorders lists morning headache as a feature of SAS [5]. Few studies, however, have critically evaluated the relationship between headache and SAS. Aldrich and Chauncey demonstrated that patients with a respiratory disturbance index (RDI) > 30 and frequent headaches on awakening were significantly younger, heavier and spent a lower percentage of total sleep time in rapid eye movement sleep (REM) than patients with infrequent headaches on awakening [1]. That same study, however, did not demonstrate a relationship between the RDI, or minimum oxygen saturation and headache complaints.

The duration of nocturnal desaturation and its relation to headache complaints has never been evaluated to our knowledge. Acute hypoxia from high altitude has been associated with headaches that are often worst in the morning [6]. In cluster headache, hypoxemia has been postulated as a headache trigger [7]. Since patients with SAS often have oxyhemoglobin desaturations during sleep, desaturation may contribute to morning headache complaints. Our primary goal was to determine if the duration of time spent with lower oxyhemoglobin saturation at night was related to headache complaint. An association between REM and the onset of headaches in both chronic paroxysmal hemicrania and cluster headache disorder has been described [8–10]. Consequently, our secondary hypothesis was that REM-related desaturations would be more commonly found in the headache group.

2. Methods

An open, retrospective chart review (approved by the

* Corresponding author. Tel.: +1-603-650-7534; fax: +1-603-650-7820.
E-mail address: glen.greenough@hitchcock.org (G.P. Greenough).

1389-9457/02/$ - see front matter
PII: S1389-9457(02)00006-0

Committee for the Protection of Human Subjects) of consecutive patients evaluated in the Dartmouth–Hitchcock Sleep Disorders Center between March 1, 1997 and March 18, 1998 was conducted. Patients whose clinical history and polysomnography were consistent with SAS and who then went on to have continuous positive airway pressure trials were included. Of the 173 patients identified, 116 patients met inclusion criteria. Data was extracted from polysomnography reports and clinical questionnaires. Fifty seven patients were excluded based on criteria as follows: incomplete data (29), age outside the range of 18–80 years (2), introduction of CPAP during the baseline study (18), inpatient at time of study (5), or RDI of less than five (3).

Polysomnographic parameters recorded included the following: electroencephalogram (C3-A2, C4-A1, OZ-A1), electro-oculogram, submental electromyogram, electrocardiogram, intercostal electromyogram, airflow (via a nasal-oral thermister), respiratory effort (via thoracic and abdominal strain gauges), and oxygen saturation (via pulse oximeter). Scoring was done according to conventional criteria [11]. An apnea was defined as cessation of flow for 10 s or more. A hypopnea was defined as a 30% decrease in flow associated with a four-point desaturation by pulse oximetry or an arousal. Apneas and hypopneas were scored as central or obstructive (includes mixed) based on conventional criteria [12]. The overall RDI was defined as the sum of the apneas and hypopneas of all types per hour of sleep.

The primary outcome measure was the percentage of time during sleep spent with an oxygen saturation below 90%. Group was determined based on response to a question from our standardized questionnaire asking whether the patient is currently "Waking up because of headaches". Additional variables collected included age, gender, Epworth sleepiness score, mean waking oxygen saturation, body mass index (BMI), TST, REM percentage, sleep efficiency and RDI. RDI was subdivided into an obstructive apnea index, obstructive hypopnea index and central apnea index for TST and REM. Zung scores and medication lists were obtained from all headache patients and from an equivalent number of randomly selected non-headache patients. Student's *t*-test and Mann–Whitney *U* tests were used to compare means between groups. The primary a priori hypothesis was set at an alpha level of 0.05. Secondary analyses were considered exploratory with exact *P*-values reported for each comparison.

3. Results

There are 29 patients in the headache group and 87 patients in the non-headache group. The two groups significantly differed in gender distribution and REM percentage but not on other background variables (Table 1). More men ($N = 79$) than women ($N = 37$) were diagnosed with SAS. Thirty eight percent of women with SAS reported headache but only 19% of men with SAS reported headache. Patients were labeled as being on REM suppressing medications [13] if taking one or more of the following: sertraline ($n = 7$), amitriptyline ($n = 1$), paroxetine ($n = 4$), doxepin ($n = 2$), fluvoxamine ($n = 1$), bupropion ($n = 1$), trazodone ($n = 3$), fluoxetine ($n = 4$), nefazodone ($n = 2$), nortriptyline ($n = 1$), olanzapine ($n = 2$), venlafaxine ($n = 3$) and methylphenidate ($n = 1$). Some patients were on more than one medication from the list above. The headache group and the randomly selected non-headache group subset

Table 1
Background and outcome variables[a]

	Headache group ($N = 29$)	No headache group ($N = 87$)	df	*P*-value[*]
	Mean (SD)	Mean (SD)		
Age (years)	50.03 (13.11)	53.55 (10.88)	114	0.16
Gender (% female)	48	26	1	0.05
BMI (kg/m^2)	40.26 (11.00)	36.18 (7.14)	36[b]	0.07
Waking O_2 saturation (%)	94.55 (1.74)	94.17 (2.07)	114	0.38
Sleep efficiency (%)	82 (10)	80 (12)	114	0.43
TST (min)	317.43 (60.71)	321.52 (67.41)	114	0.77
REM sleep (%)	10 (7)	14 (7)	114	0.01
Epworth score	13.24 (4.77)	14.38 (5.35)	106[c]	0.33
Zung (raw score)[d]	43.29 (9.47)	40.24 (9.81)	55	0.24
REM suppressants (% yes)[d]	48	35	1	0.42
TST with O_2 saturation <90% (%)	10 (22)	16 (24)		0.12
REM with O_2 saturation <90%(%)	20 (27)	24 (28)		0.62

[a] TST with O_2 saturation <90%; $N = 29$ Headache Group, $N = 87$ No Headache Group. REM with O_2 saturation <90%; $N = 26$ Headache group, $N = 85$ No Headache group.

[*] Unpaired *t*-test, two-tailed except Gender and REM Suppressants which was chi-squared test.

[b] Adjusted for unequal variance.

[c] Six scores missing from the No Headache Group and two scores missing from the Headache Goup.

[d] Random subset ($n = 29$) of No Heachache Group (see text).

did not significantly differ in the percentage of patients using the aforementioned medications.

The primary outcome variables recorded were the percentage of TST and REM time spent with an oxygen saturation below 90%. There was no significant difference between the two groups when comparing headache patients versus non-headache patients for these outcome variables (Table 1). Respiratory indices were compared between the headache and non-headache groups for TST and REM (Table 2). The mean central apnea indices were so low that statistical comparison was not performed. The headache and non-headache groups did not significantly differ for apnea types in TST or REM.

4. Discussion

Our study did not find a relationship between headache complaints and nocturnal oxygenation based on the percentage of TST or REM spent with an oxygen saturation below 90%. The primary hypothesis, that nocturnal desaturation leads to awakenings with headaches, was not supported by our data. These findings are consistent with Aldrich and Chauncey's finding that SAS patients with frequent morning headaches, when compared to those with infrequent morning headaches, did not differ on the basis of minimum oxygen saturation at night. These studies cast significant doubt on the hypothesis that oxygen desaturation mediates the relationship between morning headache and SAS.

Our study had several limitations. In retrospective studies, data gathered for one purpose is evaluated from a potentially different perspective. Another potential limitation was the selection of a cutoff point of 90% for the saturation. Ninety percent was chosen because the rate of change in the oxyhemoglobin saturation curve accelerates below 90%. Also, no distinction was made between early and late desaturations. The wording of the questionnaire presents other limitations. "Waking up because of headaches", could include any headache type and not just the morning headaches ascribed to OSA. The phrasing also implies some causality that the patient may not ascribe to the headaches. A more comprehensive headache assessment would be desirable in a prospective design.

Table 2
Breathing-related variables[a]

		Headache group Mean (SD)	Non-headache group Mean (SD)	*P*-value[*]
RDI	TST	41.84 (30.97)	38.96 (26.57)	0.69
	REM	43.1 (31.0)	36.2 (26.2)	0.37
OAI	TST	6.4 (10.3)	8.2 (13.0)	0.28
	REM	13.9 (27.2)	4.6 (8.7)	0.77
OHI	TST	37.03 (25.16)	29.88 (21.38)	0.17
	REM	29.22 (19.41)	30.79 (22.29)	0.85
CAI	TST	0.18 (0.29)	0.29 (0.55)	–

[a] $N = 23$ Heachache Group, 61 Non-Headache group except for TST RDI where $N = 29$ Headache Group, 87 Non-Headache group (see text).
[*] Mann–Whitney *U*, two-tailed.

In the examination of background variables, OSA patients with headaches were found to be women who spent less time in REM. In our study, 38% of the women with OSA report headaches but only 19% of men with OSA report the same problem. Aldrich and Chauncey observed a similar trend. Among patients with OSA, the tendency for women to suffer from headaches more than men is not surprising given the epidemiology of headache in the general population. Females are more likely to suffer from both tension type headache and migraine headache [14].

In populations without SAS, sleep deprivation has been associated with headache complaints [15,16]. We could not fully exclude sleep deprivation as the etiology of headache reporting in our study. TST and REM time could not be used as proxy measures of prior sleep deprivation because of an enforced wake time. Sleep efficiency, while a less than ideal measure of sleep deprivation, did not differ between the two groups suggesting that sleep deprivation was not a factor in headache generation among our patients.

A finding demonstrated by both our study and Aldrich and Chauncey's was the significant decrease in the percentage of REM in SAS patients with headache complaints. We analyzed additional variables that might account for the differences in REM between groups. The use of REM suppressing medications did not differ between the two groups. One caveat is that, analgesics and over the counter medications were not recorded. The presence of depression, as measured by the Zung Depression Scale, did not differentiate the two groups. Since the confounding influences of sleep scheduling, medications, and depression do not account for the difference in REM between the two groups, this suggests another possible relationship.

There are many possibilities as to why alterations in REM may be related to headache symptoms. The decrease in REM may be compensatory if headache generation occurs in REM as has been suggested in cluster headache and paroxysmal hemicrania [8]. Alternatively, REM fragmentation or disruption may play a role in headache generation. We did not directly measure this variable so it is possible that it might simply manifest as a decrease in REM percentage. We did assess the potential degree of REM fragmentation caused by respiratory events by measuring a REM stage RDI. There were more obstructive apneas in REM in the headache group than in the non-headache group. This difference, however, did not achieve statistical significance. Reanalysis with a greater number of patients may demonstrate a significant difference.

In summary, oxygen desaturation during sleep overall or in REM does not appear to mediate awakenings with headaches in SAS patients. We found that SAS patients with headaches are more likely to be female and to spend less time in REM than SAS patients without headaches. The

absence of confounding factors to explain the decrease in REM percentage lends credence to the idea that REM is associated with headache generation in patients with OSA.

References

[1] Aldrich MS, Chauncey JB. Are morning headaches part of obstructive sleep apnea syndrome? Arch Intern Med 1990;150:1265–1267.
[2] Pavia T, Farinha A, Martins A, et al. Chronic headaches and sleep disorders. Arch Intern Med 1997;157:1701–1705.
[3] Ulfberg J, Carter N, Talback M, Edling C. Headache, snoring and sleep apnoea. J Neurol 1996;243(9):621–625.
[4] Poceta JS, Dalessio DJ. Identification and treatment of sleep apnea in patients with chronic headaches. Headache 1995;35(10):586–589.
[5] International Classification of Sleep Disorders of the American Sleep Disorders Association. Diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association, 1990.
[6] Krasney JA. A neurogenic basis for acute altitude illness. Med Sci Sports Exerc 1994;26:195–208.
[7] Chervin RD, Zallek SN, Lin X, et al. Sleep disordered breathing in patients with cluster headache. Neurology 2000;54(12):2302–2306.
[8] Sahota PK, Dexter JD. Sleep and headache syndromes: a clinical review. Headache 1990;30:80–84.
[9] Kayed K, Godtlibsen OB, Sjaastad O. Chronic paroxysmal hemicrania IV: 'REM sleep locked' nocturnal headache attacks. Sleep 1978;1(1):91–95.
[10] Kudrow L, McGinty DJ, Phillips ER, Stevenson M. Sleep apnea in cluster headache. Cephalalgia 1984;4(1):33–38.
[11] Rechtschaffen A, Kales A. A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects. Washington, DC: US Government Printing Office, 1968.
[12] Bornstein SK. Respiratory monitoring during sleep: polysomnography. In: Guilleminault C, editor. Sleeping and waking disorders: indications and techniques, Menlo Park, CA: Addison-Wesley, 1982. pp. 196–201.
[13] Thase ME. Depression, sleep and antidepressants. J Clin Psychiatry 1998;59(suppl 4):55–65.
[14] Rasmussen BK. Epidemiology of headache. Cephalalgia 1995;15(1):45–68.
[15] Blau JN. Sleep deprivation headache. Cephalalgia 1990;10(4):157–160.
[16] Pavia T, Batista A, Martins P, Martins A. The relationship between headaches and sleep disturbances. Headache 1995;35:590–596.