Neurobiology of Aging, Vol. 10, pp. 343–346. © Maxwell Pergamon Macmillan plc, 1989. Printed in the U.S.A.

0197-4580/89 $3.00 + .00

Sleep Apnea in Alzheimer's Disease[1]

DONALD L. BLIWISE,[2] JEROME A. YESAVAGE, JARED R. TINKLENBERG AND WILLIAM C. DEMENT

Sleep Disorders Center, Department of Psychiatry and Behavioral Science
Stanford University Medical School, Stanford, CA 94305

Received 7 October 1988; Accepted 22 March 1989

BLIWISE, D. L., J. A. YESAVAGE, J. R. TINKLENBERG AND W. C. DEMENT. *Sleep apnea in Alzheimer's disease.* NEUROBIOL AGING 10(4) 343–346, 1989.—Mental deterioration accompanying sleep apnea has been noted frequently. Because sleep apnea increases with age, such deficits raise the possibility that dementia in the elderly could be related to sleep apnea. In this study we investigated this possibility cross-sectionally by comparing respiration during sleep in 28 patients with Alzheimer's disease (AD) and 25 nondemented controls. We hypothesized that higher levels of sleep apnea would be present in AD patients. Our results indicated no significant differences between AD patients and controls but those few AD patients who desaturated during sleep experienced morning confusion. The findings imply that AD and sleep apnea are two separate conditions which may still interact in the aged.

Sleep apnea Alzheimer's disease Sleep and aging Mental status Hypoxemia Neuropsychology

THE clinical presentation of sleep apnea frequently involves dementia-like symptoms of memory loss, inability to concentrate, and mental confusion, often on morning awakening (18). Because the prevalence of sleep apnea increases with age (1, 3, 6, 11, 12, 33), the possibility exists that dementing illnesses of the senium could be caused or hastened by the presence of untreated sleep apnea. As one test of this hypothesis, we studied cross-sectionally sleep-related respiratory disturbance in 28 patients with presumed Alzheimer's disease (AD) and compared them to nondemented controls.

METHOD

Subjects

AD patients were 28 ambulatory men (N = 18) and women (N = 10) with a mean age of 67.6 (SD = 8.65) with a diagnosis of definite (i.e., confirmed by autopsy or biopsy) (N = 4), probable (N = 19) or possible (N = 5) AD following criteria (24) established by the National Institute of Neurological Disorders and Stroke. Mean duration of dementia was 5.0 ± 3.3 years. Mean Folstein Mini-Mental State Exam (MMSE) score (16) (17.96 ± 6.87) and Hachinski rating scale (34) score (1.58 ± 1.46) suggested mild dementia and relatively few signs of multi-infarct dementia, respectively. An analysis of sleep stage data for these patients has been reported elsewhere (9). Only 3 AD patients regularly used psychotropic medications. One patient had been receiving haloperidol; this was suspended one month prior to the laboratory night. The other two patients regularly used benzodiazepines (alprazolam and triazolam, respectively) and these were suspended one week prior to the laboratory night. The latter patient became agitated after awakening during the lab night and was administered triazolam (0.25 mg) at that time.

Nondemented controls were 25 subjects (mean age = 75.2, SD = 8.0; 23 M, 2 F) selected from a previously described cohort of 198 elderly research volunteers evaluated in a study of sleep disordered breathing (6,7). Controls were significantly older than the AD patients ($t = 3.30$, $p < 0.01$), but there were no differences between the groups in Bod; Mass Index (weight/height^2) (lb/inches) (33.1 vs. 33.3, $t = 0.25$, NS). Mean MMSE score was 28.1 (SD = 1.6), which was significantly higher than the AD patients ($t = 7.58$, $p < 0.001$).

Both AD patients and controls refrained from alcohol intake on the laboratory night and the night before. Among the AD patients, caregivers of 6 patients reported very light (e.g., occasional glass of wine with dinner) use of alcohol; the remaining 22 patients did not drink at all. Fifteen of the controls reported nightly usage of alcohol ranging from a glass of wine to several shots of hard liquor. Our rationale for not employing a longer period of abstinence from alcohol prior to the lab night was based partly on enlisting cooperation of subjects and partly on other practical considerations. Particularly for the AD patients, we believed that we would enhance the likelihood of participation if we required as little disruption of their evening routine as was possible. Additionally, from a pragmatic perspective, based on our prior experiences (8), we were skeptical that subjects would actually abide by instructions to discontinue alcohol for a period of, for example, two weeks. Unless we were able to take blood alcohol levels to confirm such abstinence (which we were not), we felt our best

[1]Supported by NIA AG-06066, NIA AG-04558, and NIMH MH-40041.
[2]Requests for reprints should be addressed to Donald L. Bliwise, Ph.D., Sleep Disorders Center, Stanford University Medical Center, Stanford, CA 94305.

approach would be to make what subjects would experience as more realistic demands in the hope of enlisting greater cooperation.

Two of the AD patients and none of the controls smoked at the time of the study, but 15 patients and 13 controls were former smokers. Spirometry performed on 24 of the 28 AD patients who could follow verbal instructions showed a trend for less airway obstruction relative to controls (Forced Expiratory Volume in 1 second divided by Forced Vital Capacity = 77.1% vs. 71.0%, $t = 1.92$, $p < 0.10$).

Procedures

Patients underwent one night of polysomnography following standard procedures for electroencephalography, electrooculography and surface mentalis electromyography (30). Controls were studied with similar procedures for two nights but only data from the first night are included here. Sleep stages were scored in 30 second epochs. Respiration during sleep was recorded with respiratory inductive plethysmography (13) except in the case of a few of the controls where mercury-filled capillary strain gauges were used. Nasal/oral thermistors recorded airflow. Oxygen saturation was recorded with an ear oximeter (Biox Model III). Impaired respiration in sleep was defined by episodes of apnea and hypopnea of at least 10 seconds in duration. We divided the total number of apneas and hypopneas by the total sleep time for the night to yield an Apnea/Hypopnea Index (AHI). Oxygen saturation data were analyzed for the number of desaturations of falls of greater than both 4% and 10%. Both of these sums were corrected for Total Sleep Time (TST) to yield a SaO_2>4% Index ($SaO_2$4I) and a SaO_2>10% Index ($SaO_2$10I). The lowest oxygen saturation during the night (Low SaO_2) was also analyzed.

AD patients were administered a 10 item Mental Status Questionnaire (MSQ) (20) and 2 consecutive 10 trial presentations of the Face Hand Test (FHT) (with eyes closed) (20,21) immediately before lights were turned off. Immediately after lights were turned on in the morning, the same examiner again administered the MSQ and FHT. Scores were the number of items correctly recalled on the MSQ and the total number of errors (displacement, exosomesthesia, extinction) noted on the FHT. We obtained complete evening and morning tests for all but 3 patients. In addition, we did not include FHT/MSQ data from the one patient receiving triazolam during the night. That patient showed no overnight change in MSQ or FHT score. This left 24 patients with complete overnight MSQ and FHT data. Supine systolic and diastolic blood pressures were taken immediately after MSQ and FHT each evening and morning.

RESULTS

Table 1 summarizes the nocturnal respiration results for the patients and controls. There were no statistically significant differences between the groups on any of the four respiratory variables (AHI, $SaO_2$4I, $SaO_2$10I, Low SaO_2). Male and female AD patients did not differ on AHI (13.5 vs. 12.0, $t = 0.30$, NS), $SaO_2$4I (1.1 vs. 3.0, $t = 1.07$, NS), $SaO_2$10I (0.63 vs. 0.55, $t = 0.18$, NS), or Low SaO_2 (87.6 vs. 84.4, $t = 1.24$, NS).

Table 2 shows the results from the overnight change in MSQ and FHT in relation to oxygen saturation measures. Of the 24 patients administered the FHT at night and in the morning, 4 had unchanged scores, 12 made errors (mean = 2.9, SD = 1.5) and 8 made fewer errors (mean = 4.5, SD = 3.4) in the morning. Of the 24 patients administered the MSQ at night and in the morning, 9 subjects had unchanged scores, 2 made more errors, and 13 made fewer errors (mean = 1.5, SD = 0.9). Overnight change in FHT (but not MSQ) was significantly related to lowest SaO_2 (rho = −0.40, $p < 0.052$) and $SaO_2$10I (rho = 0.48, $p < 0.02$) but not $SaO_2$4I (rho = 0.23, NS). In short, patients who desaturated

TABLE 1

NOCTURNAL RESPIRATION IN AD PATIENTS AND CONTROLS

	Mean (SD) AD Patients (N = 28)	Mean (SD) Controls (N = 25)	Comparison
Apnea/ Hypopnea Index (AHI)	12.8 (13.5)	13.0 (16.3)	$t = 0.02$, NS
Desaturations Greater Than 4% per Sleep Hour ($SaO_2$4I)	1.74 (3.56)	2.70 (4.70)	$t = 0.84$, NS
Desaturations Greater Than 10% per Sleep Hour ($SaO_2$10I)	0.26 (0.66)	0.18 (0.58)	$t = 0.47$, NS
Lowest Desaturation During Sleep (Low SaO_2)	86.5 (6.6)	88.4 (4.2)	$t = 1.23$, NS

TABLE 2

OVERNIGHT CHANGE IN FHT AND MSQ AND NOCTURNAL HYPOXEMIA (N = 24)*

Patient	FHT Errors (a.m.-p.m.)	MSQ Correct (a.m.-p.m.)	Low SaO_2	$SaO_2$4I	$SaO_2$10I
1	2	4	92	0	0
2	0	1	87	1.20	0
3	−9	1	90	0.56	0
4	3	0	75	5.08	1.24
5	3	0	84	0.85	0.24
6	−3	0	93	0	0
7	4	1	76	2.64	0.73
8	6	1	87	0.02	0
9	3	1	78	6.86	1.11
10	−1	0	93	0	0
11	−10	0	94	0	0
12	−2	0	89	0.66	0
13	0	1	93	0	0
14	2	−1	93	0	0
15	−6	2	80	3.27	0.15
16	3	1	94	0	0
17	−2	1	82	0.82	0
18	1	1	86	0	0
19	5	2	75	15.8	3.09
20	0	0	93	0	0
21	2	0	87	0	0
22	1	2	89	0.34	0
23	−3	0	90	0.25	0
24	0	−1	79	0.85	0

*Complete a.m. and p.m. data on 24 of 28 patients (see the Method section).

overnight were more likely to be more confused in the morning. Although evening and morning supine systolic/diastolic blood pressures were statistically different (121.3 vs. 136.3, $t=3.34$, $p<0.005$; 68.6 vs. 79.3, $t=3.90$, $p<0.002$) there was no relationship between overnight change in pressures and change in FHT errors (rho $=-0.22$ and -0.13, respectively, both NS).

DISCUSSION

Our data support those from Moldofsky and associates (26) whose 6 cases demonstrated that nocturnal hypoxemia was associated with confusion on morning awakening. In our study, the change was unrelated to other aspects of physiology (i.e., blood pressures), showing diurnal variation (29,32) and known correlations with mental function (14). Moldofsky and colleagues (26) noted that hypoxemia related to overnight change both on an attentional, computerized tracking test and on the MSQ. In our study, only the FHT showed this pattern. Other more objective measures of mental function should be used to characterize this pattern more completely.

Despite the fact that nocturnal hypoxemia related to overnight change in the FHT, there were no differences between AD patients and controls in various measures of nocturnal respiration. These findings imply that AD and sleep apnea are probably two separate conditions prevalent in the geriatric population. If sleep apnea somehow caused AD (e.g., chronic nocturnal hypoxemia hastening CNS deterioration), if AD caused sleep apnea (e.g., primary neuronal dysfunction in sleep/respiratory centers) or if both were caused by a common degenerative process, we would expect to find higher levels of sleep apnea in AD. This did not occur. Our results were consistent, however, with the possibility that both conditions could overlap by chance. When that situation occurs, the presence of sleep apnea could further compromise mental function. In our study and that of Moldofsky (26), AD patients who were more confused upon awakening were those patients who also had some evidence of sleep apnea.

Our data do have several weaknesses. The single night of polysomnography may tend to underestimate the levels of sleep apnea which would be seen on two or more recording nights (5), though it is unclear if that would differentially affect the lack of apparent differences between the two groups. Perhaps a more serious problem is that our control group is predominantly male and somewhat older relative to our AD patients and they appear to more readily use alcohol as well. All of these factors could serve to inflate the levels of sleep apnea observed in the controls (6,37) and thereby minimize differences between patients and controls. In fact, in a preliminary report of our work in which we compared our 28 AD patients to 28 age- and sex-matched controls (10), we noted higher AHI's in the patients; but unfortunately, oximetry was not recorded in these controls. A post hoc comparison of oximetry data from 18 male and 11 female nondemented aged controls published elsewhere (2), however, also suggested a higher number of desaturations of greater than 4% in controls (mean $=28.0$, SD $=41.6$) relative to our AD patients (mean $=$ 12.8, SD $=13.5$) ($t=1.95$, $p<0.06$). Thus, there appears to be no strong evidence that our AD patients, as a group, are markedly hypoxemic during sleep.

The possibility remains that other forms of dementia common in old age could be causally associated with sleep apnea. For example, several epidemiological surveys have noted associations between snoring and cardiovascular and cerebrovascular disease (22, 23, 27, 28). Consequently, the possibility that sleep apnea could play a role in multi-infarct dementia has been raised recently (15). Obviously, whether sleep apnea can be linked to any specific subtype of dementia will depend upon neuropathological verification. Until such evidence is obtained, the existing literature will be likely to conflict regarding the role of sleep apnea in dementia (4, 15, 17, 19, 25, 26, 31, 35, 36, 38).

REFERENCES

1. Ancoli-Israel, S.; Kripke, D. F.; Mason, W. J.; Kaplan, O. J. Sleep apnea and periodic movements in an aging sample. J. Gerontol. 40:419–425; 1985.
2. Berry, D. T. R.; Phillips, B. A.; Cook, Y. R.; Schmitt, F. A.; Gilmore, R. L.; Patel, R.; Keener, T. M.; Tyre, E. Sleep disordered breathing in healthy aged persons: possible daytime sequelae. J. Gerontol. 42:620–626; 1987.
3. Berry, D. T. R.; Webb, W. B.; Block, A. J. Sleep apnea syndrome: a critical review of the apnea index as a diagnostic criterion. Chest 86:529–531; 1984.
4. Billiard, M.; Touchon, J.; Passouant, P. Sleep apneas and mental deterioration in elderly subjects. Sleep 1980. 5th Eur. Congr. Sleep Res. Amsterdam; 1980:400–402.
5. Bliwise, D. L.; Carey, E.; Dement, W. C. Nightly variation in sleep-related respiratory disturbance in older adults. Exp. Aging Res. 9:77–81; 1983.
6. Bliwise, D. L.; Feldman, D. E.; Bliwise, N. G.; Carskadon, M. A.; Kraemer, H. C.; North, C. S.; Petta, D. E.; Seidel, W. F.; Dement, W. C. Risk factors for sleep disordered breathing in heterogeneous geriatric populations. J. Am. Geriatr. Soc. 35:132–141; 1987.
7. Bliwise, D. L.; Ingham, R. M.; Nino-Murcia, G.; Pursley, A. M.; Dement, W. C. Five-year follow-up of sleep related respiratory disturbance and neuropsychological variables in elderly subjects. Sleep Res. 18:202; 1989.
8. Bliwise, D.; Seidel, W.; Greenblatt, D. J.; Dement, W. C. Nighttime and daytime efficacy of flurazepam and oxazepam in chronic insomnia. Am. J. Psychiatry 141:191–195; 1984.
9. Bliwise, D. L.; Tinklenberg, J.; Yesavage, J. A.; Davies, H.; Pursley, A. M.; Petta, D. E.; Widrow, L.; Guilleminault, C.; Zarcone, V. P.; Dement, W. C. REM latency in Alzheimer's Disease. Biol. Psychiatry 25:320–328; 1989.
10. Bliwise, D. L.; Tinklenberg, J.; Yesavage, J. A.; Davies, H.; Pursley, A. M.; Petta, D. E.; Widrow, L.; Guilleminault, C.; Zarcone, V. P.; Dement, W. C. Sleep patterns in Alzheimer's Disease (AD). Sleep Res. 15:49; 1986.
11. Block, A. J.; Boysen, P. G.; Wynne, J. W.; Hunt, L. A. Sleep apnea, hypopnea and oxygen desaturation in normal subjects. N. Engl. J. Med. 300:1382–1385; 1979.
12. Catterall, J. R.; Calverley, P. M. A.; Shapiro, C. M.; Flenley, D. C.; Douglas, N. J. Breathing and oxygenation during sleep are similar in normal men and normal women. Am. Rev. Respir. Dis. 132:86–88; 1985.
13. Cohn, M. Respiratory monitoring during sleep: respiratory inductive plethysmography. In: Guilleminault, C., ed. Sleep and waking disorders: Indications and techniques. Menlo Park, CA: Addison-Wesley; 1982:213–223.
14. Elias, M. F.; Streeten, D. H. P., eds. Hypertension and cognitive processes. Mount Desert, ME: Beech Hill Publishing Co.; 1980.
15. Erkinjuntti, T.; Partinen, M.; Sulkava, R.; Telakivi, T.; Salmi, T.; Tilvis, R. Sleep apnea in multiinfarct dementia and Alzheimer's Disease. Sleep 10:419–425; 1987.
16. Folstein, M. F.; Folstein, S. E.; McHugh, P. F. Mini-mental state—a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12:189–198; 1975.
17. Frommlet, M.; Prinz, P.; Vitiello, M. V.; Ries, R.; Williams, D. Sleep hypoxemia and apnea are elevated in females with mild Alzheimer's disease. Sleep Res. 15:189; 1986.
18. Guilleminault, C.; van den Hoed, J.; Mitler, M. Clinical overview of the sleep apnea syndromes. In: Guilleminault, C.; Dement, W., eds. Sleep apnea syndromes. New York: Alan Liss; 1978:1–12.
19. Hoch, C. C.; Reynolds, C. F., III; Kupfer, D. J.; Houck, P. R.; Berman, S. R.; Stack, J. A. Sleep-disordered breathing in normal and pathologic aging. J. Clin. Psychiatry 47:499–503; 1986.
20. Kahn, R. L.; Goldfarb, A. I.; Pollack, M.; Peck, A. Brief objective

measures for the determination of mental status in the aged. Am. J. Psychiatry 117:326–328; 1960.
21. Kahn, R. L.; Hilbert, N. E. Assessment of altered brain function in the aged. In: Storandt, M.; Siegler, I.; Elias, M., eds. The clinical psychology of aging. New York: Plenum; 1978.
22. Koskenvuo, M.; Kaprio, J.; Partinen, M.; Langinvainio, H.; Sarna, S.; Heikkila, K. Snoring as a risk factor for hypertension and angina pectoris. Lancet ii:893–896; 1985.
23. Koskenvuo, M.; Kaprio, J.; Telakivi, T.; Partinen, M.; Heikkila, K.; Sarna, S. Snoring as a risk factor for ischaemic heart disease and stroke in men. Br. Med. J. 294:16–19; 1987.
24. McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, E. M. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 34:939–944; 1984.
25. Mant, A.; Saunders, N. A.; Eyland, A. E.; Pond, C. D.; Chancellor, A. H.; Webster, I. W. Sleep-related respiratory disturbance and dementia in elderly females. J. Gerontol.: Med. Sci. 43:M140–M144; 1988.
26. Moldofsky, H.; Goldstein, R.; McNicholas, W. T.; Lue, F.; Zamel, N.; Phillipson, E. A. Disordered breathing during sleep and overnight intellectual deterioration in patients with pathological aging. In: Guilleminault, C.; Lugaresi, E., eds. Sleep/wake disorders: Natural history epidemiology, and long-term evolution. New York: Raven Press; 1983:143–150.
27. Norton, P. G.; Dunn, E. V. Snoring as a risk factor for disease: an epidemiological survey. Br. Med. J. 291:630–632; 1985.
28. Partinen, M.; Palomaki, H. Snoring and cerebral infarction. Lancet ii:1325–1326; 1985.
29. Pickering, T. G.; Harshfield, G. A.; Kleinert, H. D.; Blank, S.; Laragh, J. H. Blood pressure during normal daily activities, sleep and exercise. JAMA 247:992–996; 1982.
30. Rechtschaffen, A.; Kales, A., eds. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: BIS/BRI, UCLA; 1968.
31. Reynolds, C. F., III; Kupfer, D. J.; Taska, L. S.; Hoch, C. C.; Sewitch, D. E.; Restifo, K.; Spiker, D. G.; Zimmer, B.; Marin, R. S.; Nelson, J.; Martin, D.; Morycz, R. Sleep apnea in Alzheimer's dementia: Correlation with mental deterioration. J. Clin. Psychiatry 46:257–261; 1985.
32. Richardson, D. W.; Honour, A. J.; Fenton, G. W.; Stott, F. H.; Pickering, G. W. Variation in arterial pressure throughout the day and night. Clin. Sci. 26:445–460; 1964.
33. Roehrs, T.; Zorick, F.; Sicklesteel, J.; Wittig, R.; Roth, T. Age-related sleep-wake disorders at a sleep disorders center. J. Am. Geriatr. Soc. 31:364–370; 1983.
34. Rosen, W. G.; Terry, R. D.; Fuld, P. A.; Katzman, R.; Peck, A. Pathological verification of ischemia score in differentiation of dementias. Ann. Neurol. 7:486–488; 1980.
35. Smallwood, R. G.; Vitiello, M. V.; Giblin, E. C.; Prinz, P. N. Sleep apnea: Relationship to age, sex, and Alzheimer's dementia. Sleep 6:16–22; 1983.
36. Smirne, S.; Franceschi, M.; Bareggi, S. R.; Comi, G.; Mariani, E.; Mastrangelo, M. Sleep apneas in Alzheimer's disease. Sleep 1980. 5th Eur. Congr. Sleep Res. Amsterdam; 1980:442–444.
37. Vitiello, M. V.; Prinz, P. N.; Personius, J. P.; Nuccio, M. A.; Ries, R. K.; Koerker, R. M. History of chronic alcohol abuse is associated with increased nighttime hypoxemia in older men. Alcoholism (NY) 11:368–371; 1987.
38. Vitiello, M. V.; Prinz, P. N.; Williams, D. E.; Frommlet, M.; Ries, R. K. Sleep related respiratory dysfunction in normal healthy aged individuals, Alzheimer's disease and major depressive disorder patients. Sleep Res. 16:453; 1987.