Disturbed sleep in Alzheimer's disease (AD) is a major clinical problem.1-7 There is accumulating evidence that greater disease severity is associated with greater sleep disturbance.8,9 Ultimately, with advancing disease severity, both the ability to maintain sleep and the ability to maintain wakefulness deteriorate.10 Not only is patients’ nocturnal sleep disruption reported as a major source of caregiver burden,6,11,12 it is often related to the decision to institutionalize.13,14

Although the apolipoprotein ε4 (APOE ε4) allele is an established risk factor for AD,15 there have been few studies of sleep per se in relation to APOE status, and the findings are somewhat fragmentary. In a retrospective case-control study, Asada et al16 found that limited napping for up to 60 minutes had an apparently protective effect against the development of AD, especially for carriers of the APOE ε4 allele, although napping for more than 60 minutes was associated with greater risk of development of AD in APOE ε4 carriers. Cacabelos and associates,17 studying the relations between APOE carrier status and behavioral symptoms in patients with dementia, found that sleep disorders appeared more frequently in APOE ε3/ε4 carriers than in APOE ε4/ε4 carriers. To date, there have been no studies of the effects of APOE carrier status on...
changes in sleep parameters and circadian rest/activity rhythm in AD patients during the course of their illness.

Our National Institute on Aging AD Center has been conducting longitudinal actigraphic assessment of AD patients. Actigraphy allows noninvasive and convenient determination of sleep/wake parameters via a small wrist-worn device containing a motion sensor. In prior reports, we found a moderate positive association between nocturnal sleep disturbance and behavioral disturbance in a cross-sectional analysis of actigraphic data for 41 AD patients,18 a significant deterioration of nocturnal sleep in data for 61 AD patients followed for a minimum of 1.5 years,19 and evidence for a significant trait component in sleep/wake characteristics over the trajectory of the illness.20 The purpose of this article is to determine if sleep parameters in AD patients change over time as a function of APOE carrier status.

METHODS

Subjects
Center inclusion criteria at the time of entry were (1) diagnosis of probable AD by NINCDS-ADRDA criteria21 and (2) a score of 15 or higher at entry on the Mini-Mental State Exam (MMSE).22 Patients are excluded if they have active major medical problems (eg, congestive heart failure or recent life-threatening cancer) that would make participation in an intensive longitudinal study difficult. To determine the clinical diagnosis, each patient has a medical, psychiatric, neurological, and neuropsychological assessment. Based on these evaluations, an interdisciplinary team including 1 to 3 physicians and at least 2 other experienced clinicians reaches a consensus diagnosis for each patient. To be included in the current analysis, the patient must have been assessed during at least 2 stages of cognitive impairment, defined as a decline from one stage of AD to another. The staging scheme we used (described below) is based on scores on the MMSE22 and is similar to staging based on the Global Deterioration Scale.

Forty-four subjects met the criteria for inclusion in the current analysis. The study was approved by the local Institutional Review Board, and written informed consent was obtained from all subjects or their caregivers. Twenty-five subjects are APOE ε4 carriers and 19 are non-ε4 carriers. The sample as a whole is highly educated (50% college graduates), predominantly nonminority (84% Caucasian), and contains equal numbers of men and women. The average age at entry into this study was 71.8 years (SD = 7.9) and was similar for ε4 carriers (71.6 years, SD = 8.3) and non-ε4 carriers (72.1 years, SD = 7.6). All subjects were initially living at home or in board-and-care homes; that is, none were in skilled nursing facilities at entry. We calculated the amplitude of the 44 subjects’ rest/activity circadian rhythms and nocturnal sleep/wake parameters from the 209 actigraphic recordings they completed.

Measures

MMSE. The MMSE, a 30-point scale, was administered every 6 months and was used to describe the subject’s stage of cognitive impairment at each occasion activity data were collected. Kraemer and associates23 proposed the following MMSE staging system: MMSE stage 1 = 24-30, stage 2 = 15-23, stage 3 = 8-14, stage 4 = 4-7, stage 5 = 0-3.

Actigraph recordings. Rest/activity, sleep/wake data were collected at 6-month intervals by means of an actigraph, a wrist-worn, watch-size ambulatory motion-detecting and recording device, the Basic Mini-Motionlogger (Ambulatory Monitoring Systems, Inc, Ardsley, NY 10502). The actigraph was set to record motion in 30-second epochs. These activity data were used to measure circadian rhythmicity of rest and activity and, when there was a caregiver able to complete daily sleep logs, to estimate nocturnal amounts of sleep and wake. Patients were asked to wear the actigraph 24 hours a day on their nondominant wrists for 5 consecutive days and were instructed to remove the device only for bathing or swimming. Caregivers completed a sleep log each day noting the patient’s in- and out-of-bed times.

We computed measures of circadian rest/activity by using a least-squares method to fit the actigraph data to a cosine curve. The amplitude of the fitted curve was our primary measure of circadian rhythmicity; larger amplitudes suggest a more robust circadian rhythm. Measures of nighttime sleep/wake behavior, for example, sleep efficiency (SE), or the ratio of total nocturnal sleep time to total time in bed, were obtained by computer scoring (ACTION software version 1.3). The algorithm, supplied by the manufacturer of the actigraph, scores the actigraph recordings following entry of subjects’ evening bed times and final morning out-of-bed times recorded in caregiver-completed sleep logs and generates information on the following parameters: time in bed (TIB) = the amount of time (minutes) spent in bed between into-bed and final out-of-bed times of nocturnal sleep period; sleep latency (SL) = time elapsed (minutes) between into-bed time and initial sleep onset; total sleep time (TST) = the sum (minutes) of all sleep bouts from initial sleep onset until out-of-bed time; wake after sleep onset (WASO) = the sum (minutes) of wake bouts between sleep onset and final wake time. SE = TST/TIB. The scores for each individual used in the data analyses were averaged over the days of the recording period. Not all data were usable due to occasional technical failures of the device. The amount of actigraph data collected varied across subjects depending on their compliance, but 80% of the subjects had at least 4 days of data per recording period. The 209 actigraphic recordings for the 44 subjects spanned a total of 1015 days. Of the 209 recordings,
genotypes were determined as previously described. APOE status. Genomic DNA was extracted from EDTA-treated whole blood by using the Puregene DNA extraction kit (Gentra Systems, Minneapolis, MN). APOE genotypes were determined as previously described.24 Electrophoretic gel images were assessed independently for APOE genotype by 2 observers blinded to clinical data. If there was disagreement, the assay was repeated until the result was unequivocal.

Procedure
Patients were asked to begin the actigraph recordings immediately following a clinic visit. The MMSE and other cognitive measures were administered to all center patients at each 6-month visit. When patients became institutionalized or could no longer come to the clinic, an outreach nurse administered the MMSE at the patient’s residence. Follow-up assessments ceased when patients scored a zero on the MMSE at 2 successive visits. At some visits, the MMSE was incomplete or the actigraph recording was delayed by the family; in these cases, we matched the actigraphy scores to the MMSE score that was closest in time (maximum of 90 days separation). Subjects’ average length of follow-up was 2.6 years (SD = 1.6) during which the median MMSE stage decline is 1 stage for both carriers and noncarriers.

RESULTS
For the APOE ε4 carriers, 17 subjects spanned 2 MMSE stages, 5 subjects 3 MMSE stages, 1 subject 4 stages, and 2 subjects all 5 stages. For the 19 noncarriers, the number of subjects was 12, 1, 5, and 1, respectively; therefore, the median MMSE stage decline is 1 stage for both carriers and noncarriers. The mean slopes were then calculated for APOE ε4 carriers and noncarriers separately. The Wilcoxon signed rank test was used for testing the hypothesis that the mean slope was zero for each genotype group, and the Mann-Whitney-Wilcoxon test was used to compare the mean slopes of the ε4 carriers versus noncarriers. The analysis was repeated for each sleep parameter.

Table 1. Longitudinal Alzheimer’s Disease Follow-up Over at Least 2 MMSE Stages of Disease (n = 44)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Baseline</th>
<th>Mean Change/Stage</th>
<th>SD</th>
<th>Slope = 0 Significance Levela</th>
<th>Mean Baseline</th>
<th>Mean Change/Stage</th>
<th>SD</th>
<th>Slope = 0 Significance Levela</th>
<th>Slope Difference Significance Levelb</th>
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</thead>
<tbody>
<tr>
<td>TIB (minutes)</td>
<td>554.7</td>
<td>9.3</td>
<td>41.2</td>
<td>523.6</td>
<td>23.7</td>
<td>70.9</td>
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<td></td>
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<tr>
<td>TST (minutes)</td>
<td>435.8</td>
<td>–3.2</td>
<td>50.4</td>
<td>427.0</td>
<td>–33.2</td>
<td>73.1</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE (%)</td>
<td>78.9</td>
<td>–1.7</td>
<td>7.6</td>
<td>81.7</td>
<td>–8.6</td>
<td>10.8</td>
<td>**</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>SL (minutes)</td>
<td>20.0</td>
<td>–2.5</td>
<td>8.5</td>
<td>18.5</td>
<td>3.2</td>
<td>16.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WASO (minutes)</td>
<td>82.2</td>
<td>16.7</td>
<td>43.5</td>
<td>*</td>
<td>64.0</td>
<td>50.9</td>
<td>61.6</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>62.8</td>
<td>–3.0</td>
<td>10.3</td>
<td>61.6</td>
<td>0.2</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>47.0</td>
<td>–3.1</td>
<td>9.1</td>
<td>46.5</td>
<td>–5.9</td>
<td>10.4</td>
<td>*</td>
<td></td>
<td></td>
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<tr>
<td>Tmax</td>
<td>15.6</td>
<td>0.01</td>
<td>0.52</td>
<td>15.1</td>
<td>–0.06</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: TIB = time in bed; TST = total sleep time; SE = sleep efficiency; SL = sleep latency; WASO = wake after sleep onset.

a. Tests the hypothesis that the mean slope is zero, using the Wilcoxon signed rank test.
b. Tests the hypothesis that the mean slopes of the ε4 and non-ε4 carriers are the same, using the Mann-Whitney-Wilcoxon test.

35 were for 7 days, 36 for 6 days, 61 for 5 days, 36 for 4 days, 16 for 3 days, 19 for 2 days, and 6 for 1 day.

For these analyses, we first averaged for each subject the sleep/wake scores to the MMSE score that was closest in time MMSE scores fell an average of 9.0 points (SD = 6.2) from a mean of 19.7 (SD = 5.2) to a mean of 10.7 (SD = 6.7) at US DEPT OF VETERAN AFFAIRS on October 20, 2016jgp.sagepub.comDownloaded from
significant (Mann-Whitney-Wilcoxon test: $Z = 2.37, P < .05$). We note that the means for this variable (SL) improved by a small amount in the ε4 patients and deteriorated by a small amount in the non-ε4 patients.

Decreases in SE over time were strongly associated with an increase in WASO (overall Spearman correlation between change in SE and change in WASO = −0.93; $P < .0001$; for ε4’s: $r = −0.92, P < .0001$; for non-ε4’s: $r = −0.90, P < .0001$). In addition, the deterioration in SE parallels deterioration in circadian rhythm (overall $r$ with change in amplitude = 0.68, $P < .0001$; for ε4’s: $r = 0.58, P < .005$; for non-ε4’s: $r = 0.71, P < .001$).

**DISCUSSION**

In these data, APOE status was associated with the progression of sleep/wake disturbances in AD. Overall, greater deterioration on several sleep parameters, including SE and WASO, was observed in AD patients who were negative for the ε4 allele than in AD patients carrying an ε4 allele. A strong relation between WASO and SE is expected since an increase in WASO would lead to a decrease in SE. Such findings are consistent with evidence for the increasing fragmentation of sleep in severe AD patients. The decline found in the amplitude of the rest/activity rhythm (overall $r$ with change in amplitude = 0.68, $P < .0001$; for ε4’s: $r = 0.58, P < .005$; for non-ε4’s: $r = 0.71, P < .001$).

It is unclear why there should be less deterioration over time in the sleep of AD patients who are ε4 carriers. Several studies have examined APOE ε4 allele status in relation to development of sleep apnea. The findings of studies attempting to relate APOE status and development of sleep apnea in general populations are inconsistent, and the mechanisms associating ε4 and sleep apnea have yet to be explicated (see Bliwise for a review). Nonetheless, although we did not screen for sleep apnea in our subjects, we considered the possibility that our findings of a lower rate of decline with APOE ε4 allele status could be due to a higher prevalence of a sleep disorder such as sleep apnea in that group resulting in lower SE at baseline and consequently less opportunity for decline over time. However, mean baseline SE in Figure 1 does not suggest that the patients with APOE ε4 allele status started at lower baseline SE than did noncarriers.

It is possible that rates of deterioration of relevant neuroendocrine functions or neuroanatomical structures differ according to APOE ε4 allele status. For example, it is possible that changes in melatonin levels in relation to APOE status could affect the sleep/wake cycle. Liu and associates determined melatonin levels in the ventricular cerebrospinal fluid (CSF) of 85 patients with AD and in 82 age-matched controls. Although they found that CSF melatonin levels in AD patients were only one fifth that of control subjects, and melatonin levels within the AD patients expressing APOE ε3/ε4 was significantly higher than that
of patients expressing APOE ε4/ε4, melatonin levels in APOE ε3/ε4 carriers appeared higher than that of APOE ε3/ε3 carriers. Given the large number of patients studied by Liu and associates and the mixed findings regarding melatonin levels in relation to APOE carrier status, it appears unlikely that melatonin levels alone could account for the differences we observed in rate of change in sleep/wake parameters.

It is also possible that rates of deterioration of the suprachiasmatic nucleus (SCN) might differ by APOE status. There are, however, currently no neuropsychological studies that directly address this issue, despite the fact that it has been shown that deterioration of the SCN is significantly worse in AD patients than in age-matched controls. In a recent review of the issue, Skene and Swaab remarked that the details of such relationships are yet unproven. Currently, we plan to follow all patients in this study to autopsy when a detailed examination of relevant SCN neuropathology can occur. It is very likely that only through such follow-up will we be able to unravel the details of the neurological basis for the deterioration of the sleep/wake cycle in AD patients.

References