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Research Report

Sleep Fragmentation and Sleep-Wake Cycle Dysregulation Are Associated with Cerebral Tau Burden in Patients with Mild Cognitive Impairment due to Alzheimer's Disease: A Case Series

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Abstract.
Background: Although disturbed sleep is frequent in patients with mild cognitive impairment (MCI) and dementia due to Alzheimer's disease (AD), the association between sleep and tau pathology is unclear.
Objective: This case series focused on measuring the sleep-wake rhythm over 7 days through actigraphy in patients diagnosed with MCI due to AD. Further, the association between sleep-wake cycle and tau deposition measured through positron emission tomography (PET) was explored.
Methods: This case series included 6 MCI due to AD patients (2 women and 4 men, mean age 73.17 ± 5.53 years), who completed neuropsychological testing, 7-day actigraphy, and tau PET imaging with radiolabeled compounds aimed to estimate the density and distribution of aggregated tau neurofibrillary tangles in the brain.
Results: The case series indicated that patients with MCI due to AD who exhibited greater tau deposition in the frontal, parietal, and limbic regions, as well as in the precuneus and olfactory regions, also showed increased sleep fragmentation, as measured through actigraphy.
Conclusion: The findings from this case series suggest a potential link between tau deposition in key brain regions associated with AD and both sleep fragmentation and sleep-wake cycle dysregulation in a small sample of patients with MCI due to AD. These preliminary results warrant further investigation in larger, more comprehensive studies to confirm and expand upon these findings.

Keywords: Alzheimer's disease, mild cognitive impairment, positron emission tomography, sleep, sleep-wake cycle, tau

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INTRODUCTION

Several studies suggest a bidirectional association between sleep-wake cycle impairment and Alzheimer's disease (AD).[1–4] AD pathology can affect sleep by damaging the sleep-wake cycle regulating brain areas, but sleep disturbances and sleep quality reduction can represent a risk factor for AD neurodegeneration.[5] Numerous studies identified the alteration of the sleep-wake cycle in individuals with AD from the early stages of the disease, with some evidence also drawn in studies including individuals with subjective cognitive impairment.[6–10] Subjects presenting biomarkers consistent with AD pathology can show higher sleep fragmentation and poorer sleep efficiency when compared with cognitively normal older adults.[11–13] The prevalence of sleep disturbances in individuals with mild cognitive impairment (MCI) is high,[14] and can increase the risk of transition from MCI to dementia.[15] While past seminal studies have analyzed sleep differences between patients with AD and normal adults showing that AD pathology may cause sleep disruption, a new perspective and field of research have recently emerged suggesting that sleep quality reduction may trigger AD neuropathology. Preclinical studies documented that sleep deprivation or sleep impairment can represent potential risk factors for brain amyloid plaque deposition.[16,17] Moreover, poor sleep quality in cognitively normal humans is associated with the pathological modification of cerebrospinal-fluid (CSF) amyloid-β (Aβ) peptide levels[18] or with cerebral amyloid pathological deposition measured by positron emission tomography (PET) imaging with [^{11}C]-Pittsburgh compound B (PET-PIB).[19] Although the association between sleep impairment and amyloid burden is well-documented, fewer studies have examined the relation between sleep quality and tau burden. Tau-targeted PET tracers, such as flortaucipir (^{18}F-AV-1451, also known as ^{18}F-T807), enabled the investigation of the progression of tau pathology in relation to age, and in predicting the development of cognitive impairment due to AD. Sleep impairment was also associated with tau pathology, and the use of tracers for identifying the deposition of the neurofibrillary tangles of tau pathology in relation to sleep impairment can expand the knowledge about the risk for tau pathology following sleep-wake cycle dysregulation. Recent studies documented an association between sleep deprivation and sleep fragmentation and altered brain dynamics of tau proteins. For instance, mouse model studies have documented an increase in tau levels of approximately 90% during normal wakefulness compared to sleep and around 100% following sleep deprivation in the interstitial-fluid near the hippocampal areas. Moreover, human studies have shown that CSF tau protein levels can increase by more than 50% during sleep deprivation.[20] Although this evidence, the association between objectively measured sleep-wake cycle and tau deposition in subjects with MCI due to AD still needs to be further investigated. In the current case series, sleep and the sleep-wake cycle were assessed using actigraphy, which has the potential for a standard, continuous, long-term monitoring of the sleep quality and the sleep-wake cycle in an ecologic and non-intrusive manner. Actigraphy can be performed instead of the polysomnography for the investigation of the sleep-wake cycle and for obtaining information about sleep quality on consecutive days and in the home setting. Furthermore, actigraphy provides more comprehensive and nuanced information about alterations in circadian sleep-wake cycle profiles.[21–23] Hence, this case series aimed to assess the dysregulation of the sleep-wake cycle, measured through actigraphy, and tau deposition as evaluated by a PET scan in patients with MCI due to AD.

METHODS

Participants

Participants were six subjects with MCI due to AD, diagnosed as current diagnostic criteria suggested by the literature.[24,25]

Those patients were not admitted to perform a lumbar puncture for the quantification of the CSF biomarkers of AD, since they already performed PET examination for investigating both amyloid and tau pathology. During a telephone screening, patients provided demographic information and health history, as well as completed the 15-item Geriatric Depression Scale (GDS).[26,27] In this case series, participants with a prior diagnosis of sleep apnea, a history of clinical stroke or dementia, and use of a sleeping aid, benzodiazepine, or drugs acting on the CNS (such as cholinergic medications) were excluded. In addition, MCI participants were excluded if they had a current psychiatric disorder or a Clinical Dementia Rating (CDR) Scale ≥ 1.[28,29] During an in-person sleep medicine visit, patients completed a series of neuropsychological tests, a medical history form, and the Pittsburgh Sleep Quality Index (PSQI)[30,31] and Epworth Sleepiness Scale (ESS).[32,33]

This case series was declared to the Local Ethical Committee and participants provided written informed consent for allowing the publication of data.

Neuropsychological testing

Participants completed a battery of neuropsychological tests, including the CDR,[28] the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog14)[34] and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[35] These tests were administered by a psychometrist under the supervision of a board-certified neuropsychologist who confirmed the diagnosis of MCI and included the Mini-Mental State Examination.[36]

Actigraphy

Each participant wore an actigraph (MotionWatch 8, CamNTech) for seven consecutive days and nights on their non-dominant wrist. Participants were asked to press an event marker button on the actigraph when going to bed and as soon as they got out of bed in the morning. Moreover, participants were asked to keep a written log of sleep-wake times.

Sleep data was derived from the night following the visit and for six consecutive nights in the patient's home. Epoch length was determined at 30 seconds, using the zero-crossing mode. The following sleep parameters were calculated for every day and night and averaged through the week: time in bed (TIB), total elapsed time between 'Lights Out' and 'Got Up' times; total sleep time (TST), total time spent in sleep according to the epoch-by-epoch wake/sleep categorization excluding sleep latency and wake periods between fell asleep/got up times; sleep efficiency (SE), defined as the ratio between TST and TIB; sleep latency (SL), the time between 'Lights Out' and 'Fell Asleep'; central phase measure (CPM), the midpoint between 'Fell Asleep' and 'Got Up', expressed as the number of minutes past midnight; actual wake time (AWT), defined as the duration expressed in minutes of "wake periods" between 'Fell Asleep' and 'Got Up' times; sleep fragmentation index (FI) defined as the sum of the 'Mobile Time (%)' and the 'Immobile Bouts <=1 min (%)' and is an indicator of the degree of fragmentation of the sleep period.

Sleep and wake characteristics were separately monitored, and non-parametric circadian rhythm activity (NPCRA) was analyzed with CamNTech MotionWare 1.2.26. The following NPCRA parameters were collected: inter-daily stability (IS), quantifying the degree of regularity in the activity-rest pattern, with higher values corresponding to higher synchronization; intra-daily variability (IV), quantifying the degree of fragmentation of activity-rest periods, with higher values representing a very fragmented rest-activity rhythm; least 5 (L5) average activity, providing the average activity level for the sequence of the least five active hours; most 10 (M10) average activity, providing the average activity level for the sequence of the highest ten active hours; relative amplitude (RA), calculated by dividing the L5 to M10 and representing the synchronization with the average 24-h cycle, where higher values represent a better-synchronized rest-activity rhythm.[37,38] These parameters were obtained through the traditional analysis of circadian rhythms that fit physiological indicators to a Cosine waveform shape (Cosinor analysis).[39]

Tau imaging

Brain PET scans using tau imaging agents were obtained from all patients included in this case series. The scans were performed less than three months before the clinical and actigraphic evaluation at our center. Flortaucipir radiotracer was used for all the historical brain PET scan with a GE MI PET/CT scanner. 370 MBq of radiopharmaceutical was used for all the case studies with an interval from injection to acquisition of 80($\pm$5) minutes. Raw Digital Imaging and COmmunications in Medicine (DICOM) files were then converted into the appropriate analysis format using MRIcro software.[40] Spatial reprocessing has been performed using Statistical Parametric Mapping (SPM12)[41] implemented on Matlab r2022b.[42]

For iconography presented in Fig. 1, the Coregister module was used for the estimation and reslicing of PET data. While the analyzed format for each PET was used as a source image, a magnetic resonance imaging (MRI) T1 was used as a reference image. In order to maximize or minimize some objective function, the parameter normalized mutual information was selected. The average distance between sampled points was 4- and 2-mm. Tolerance was set to achieve the ideal accuracy for each parameter with iterations stopping when differences between successive estimates less than the required tolerance were achieved. Gaussian smoothing was applied. Images were then interpolated by using a 4th-degree B-spline. No wrapping or mask was used.

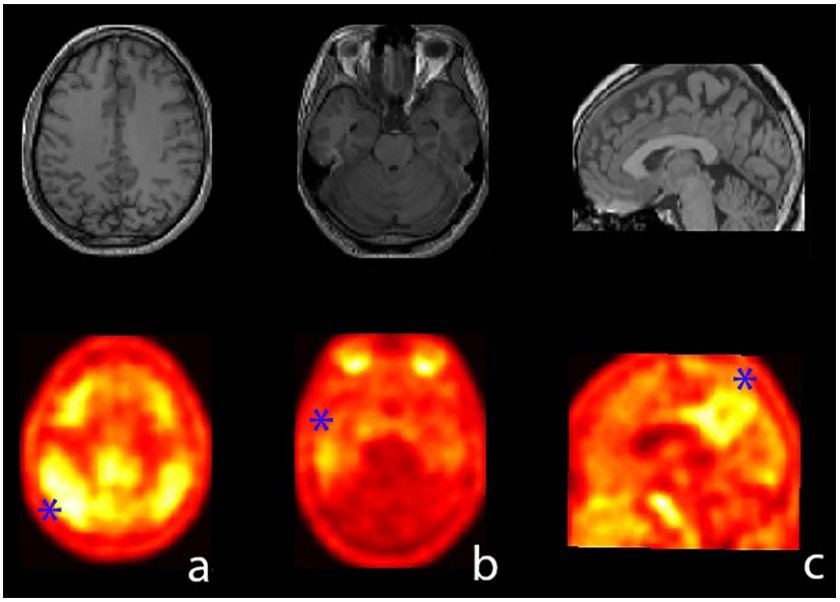

Fig. 1. Exemplification case 2. Co-registered PET imaging (bottom) with a template MRI (top) showing a significant increase of tau burden in the parietal (a, blue asterisk) and temporal (b, blue asterisk) cortex presented in axial view. A detail of the parietal cortex showing the right praecuneus burden is provided in (c, blue asterisk).

Cortical tau burden, as detectable by PET scans, was analyzed following the methodology reported in another similar study from our group in this field.[43] PET scans were analyzed using SPM12, which had been installed in Matlab r2022b.[44] An estimate and write normalization procedure was applied. To reduce biases caused by smooth, spatially variable artefacts that alter the image's intensity and obstruct automated image processing, a bias regularization of 0.0001 was implemented. The FWHM of the Gaussian smoothness of bias was set at a 60-mm cut-off to stop the algorithm from attempting to mimic the intensity variance caused by different tissue types. TPM.nii, the tissue probability map implemented in SPM12, was used. Mutual information affine registration was employed with European brains, the ICBM space template, to approach alignment.[45] The tissue probability maps were registered using mutual information affine registration.[46] The following 1×5 arrays were used to set the warping regularization: 0, 0.001, 0.5, 0.05, and 0.2. The sampling distance, which encodes the approximate distance between sampled points when estimating the model parameters, was set at 3, and smoothness was set at 5 mm to deal with functional anatomical variability that is not compensated by spatial normalization and improves the signal-to-noise ratio. An 8-mm isotropic Gaussian filter was used to reduce the signal-to-noise ratio and blur the individual fluctuations, particularly gyral variations. The following post-processing instruments and parameters were applied before regression analysis: global normalization, which uses proportional scaling to raise images to a global value of 50; masking threshold, which helps find voxels with an acceptable signal and was set to 0.8; statistical parametric maps were transformed into a normal distribution tool; SPM coordinates were corrected to match the Talairach coordinates, a subroutine that was implemented by Matthew Brett (https://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). WFU Pickatlas tool implemented in SPM 12 was used in order to export the cluster of interest using aal atlas.[47] The pons was considered as the reference region for normalizing PET data.

Statistical analysis

Data analysis was performed with the statistical program SPSS for Windows version 25.0.[48] Descriptive statistics were computed to characterize the sample in terms of demographic and clinical, as well as sleep-wake cycle. Data are reported as mean $\pm$ standard deviation. Categorical data are reported as counts and percentages. Correlations between the extrapolated counts in selected areas of PET and actigraphy data were performed using

Kendalls' tau b correlation test. Due to the sample size and the multiple comparisons, the False Discovery Rate (FDR) correction method was employed to adjust for multiple comparisons and control for type I family-wise errors.

RESULTS

Six patients with MCI due to AD, with a mean age of 73.17 (SD = 5.53) y.o., 4 men and 2 women, were included in this case series. The mean years of education of the group were 11.83 (SD = 4.42). The mean MMSE score was 21.50 (SD = 2.59), with a range between 18 and 24, and all patients had a CDR score of 0.5. In Table 1, the description of the patients included in the case series is present.

In the tau imaging PET analysis (Table 2), a significant increase in tau burden was documented in the parietal and temporal cortex, as well as in the precuneus (case 2 study imaging in Fig. 1). Furthermore, a mild burden of tau pathology was shown in the right temporal lobe, as well as a mild uptake in the left temporal lobe (case 6 study imaging in Fig. 2).

The actigraphic sleep-wake rhythm data are presented in Table 3. Actigraphy revealed that participants with MCI presented low sleep efficiency and high sleep fragmentation.

Regarding subjective data (Table 3), the mean score of the ESS was 9.50 (SD = 3.89, range between 6 and 17). Specifically, only one patient (16.7%) reported excessive daytime sleepiness (case 1, ESS > 10), while 3 patients (50%, cases 2, 3, 5) had an ESS score of 9. In terms of sleep quality, the mean score of the PSQI was 4.00 (SD = 1.54), with 1 patient (16.7%, case 1) reporting a PSQI score > 5 and 2 patients (33.3%, cases 3 and 6) with a score equal to 5, which indicates poor sleep quality.

No significant correlations were found between subjective sleep quality, excessive daytime sleepiness, actigraphy and tau imaging, after adjusting for multiple comparisons (Supplementary Table 1).

DISCUSSION

This case series preliminary showed that the sleep-wake cycle dysregulation paired to the cerebral tau deposition, measured through PET, in a small sample of MCI patients. In this group of MCI patients, it was hypothesized that sleep impairment or subjective sleep quality (PSQI-determined), might be associated with tau deposition in critical brain areas for AD pathology, since the tau burden in the olfactory tract, limbic lobe, temporal lobe and entorhinal cortex, parietal lobe, frontal lobe, and the precuneus

Table 1
Patients' demographic and clinical characteristics

	Mean	Standard deviation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex			Female	Female	Male	Male	Male	Male
Age	73.17	5.53	72	76	64	71	80	76
Educational level (y)	11.83	4.42	17	8	8	8	17	13
MMSE	21.50	2.59	24	24	18	21	19	23

Table 2
PET tau binding in crucial areas for Alzheimer's disease

	Mean	Standard deviation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Frontal	0.88	0.45	0.0026	1.2533	1.0774	0.9024	0.9263	1.1202
Parietal	0.89	0.46	0.0030	1.2547	1.0614	0.9065	0.9314	1.2040
Temporal	0.83	0.66	0.0030	1.4374	1.1450	0.0012	1.0346	1.3729
Occipital	0.77	0.60	0.0025	1.2954	1.1652	0.0011	0.9592	1.1786
Precuneus	0.97	0.50	0.0031	1.3133	1.1321	0.9845	1.0354	1.3514
Grey matter	0.91	0.46	0.0026	1.2841	1.1084	0.9642	0.9234	1.1613
Limbic lobe	0.92	0.47	0.0027	1.2002	0.9699	0.9789	1.1198	1.2709
Medulla	1.14	0.42	1.9979	0.9259	0.9718	0.9921	0.9650	0.9789
Midbrain	0.86	0.42	0.0021	1.0750	1.0282	1.0079	1.0350	1.0211
Olfactory left	1.28	0.56	2.4162	1.0615	1.0315	0.9441	1.0909	1.1276
Olfactory right	1.08	0.80	2.4799	0.8507	1.0556	0.0010	0.9821	1.1373
BA 28	0.86	0.69	0.0029	1.2195	1.3870	0.0012	1.0239	1.5531
Hippocampus left	0.69	0.76	0.0027	1.4623	0.0013	0.0011	1.2795	1.3919
Hippocampus right	0.87	0.69	0.0027	1.4654	1.2075	0.0011	1.1278	1.4262

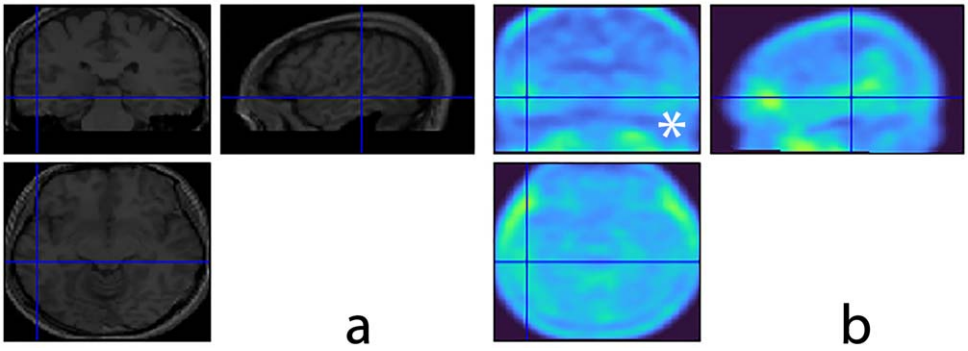

Fig. 2. Exemplification case 6. Template MRI in (a) and co-registered PET tau imaging in (b) show a mild burden of tau protein in the right temporal lobe (blue cross). To note that a very mild uptake, slightly superior to the background, is detectable in the left temporal lobe as well (b, white asterisk).

Table 3
Subjective and objective sleep data

	Mean	Standard deviation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Subjective data								
PSQI	4.00	1.55	6	3	5	2	3	5
ESS	9.50	3.89	17	9	9	7	9	6
Actigraphic data								
Time in bed (min)	468.00	97.34	308	585	452	494	542	427
Total sleep time (min)	360.33	89.36	261	472	359	447	363	260
Actual wake time (min)	86.00	46.57	33	98	78	40	158	109
Sleep efficiency (%)	77.32	11.21	85.0	80.7	79.7	90.6	67.0	60.9
Sleep latency	16.50	18.25	8	6	13	5	14	53
Sleep fragmentation index	45.75	18.82	27.6	54.3	38.8	30.5	44.6	78.7
Central phase measure (min)	193.48	68.17	220.5	135.1	126.6	185	313.4	180.3
L5	2,803.50	1,627.43	5,066	2,234	1,688	679	4,227	2,927
M10	27,697.00	8,243.84	27,571	15,624	36,469	20,312	31,672	34,534
Relative amplitude (RA)	0.82	0.10	0.690	0.750	0.912	0.935	0.765	0.844
Inter-daily stability (IS)	0.46	0.07	0.357	0.439	0.491	0.566	0.405	0.479
Intra-daily variability (IV)	0.50	0.29	0.744	0.827	0.289	0.702	0.343	0.121

PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; L5, Average activity level for the sequence of the least 5-active hours; M10, Average activity level for the sequence of the highest 10-active hours.

was associated not only with sleep fragmentation and sleep efficiency reduction, but also with the lack of regularity of the sleep-wake cycle.[49,50] However, given the small sample of patients included in this preliminary observation, the correlations were not significant after adjusting for multiple comparisons.

All the MCI patients included in this case series underwent a clinical interview to detect subjective sleep complaints and daytime sleepiness, as well as actigraphy to monitor sleep-wake cycle dysregulation. Specifically, MCI patients showed a low sleep efficiency and sleep fragmentation, and sleep-wake rhythm desynchronization. These findings are consistent with the results reported by Guarnieri and colleagues, who compared MCI patients to subjects with normal cognition.[51] Additionally, in the present case series, low IS and high L5 were more evident in patients with tau pathology accumulation in the olfactory tracts, which is an early feature during the AD process.[52]

Although this observation provides new information about sleep impairment and circadian rhythms dysregulation in MCI patients and its potential association with the cerebral burden of tau pathology, the mechanisms at the basis of these findings can be only hypothesized. We are aware that our findings remain yet preliminary, however, it is conceivable that sleep fragmentation and sleep-wake cycle desynchronization may increase tau deposition in the precuneus, limbic lobe, frontal and parietal regions among MCI participants. Night-time hyperarousal and sleep-wake cycle dysregulation may underlie the increased tau deposition in these crucial brain areas, as sleep impairment could contribute to cortical tau accumulation, potentially accelerating the transition from MCI to dementia stage in the AD process.[20] It is impor-

tant to note that this observation is based on a case series analysis, and consequently, it remains unclear whether sleep disturbances may contribute to tau pathology or are a result of it. Considering the previous literature showing that tau neurofibrillary tangles may deposit in the sleep-wake regulating areas of the brainstem, it can be hypothesized that sleep-wake disturbances in tauopathies may depend on tau deposition.[53] Similarly, in the study of Lucey and colleagues that included both cognitively normal and mildly impaired older adults, non-rapid eye movement slow wave activity also decreased when amyloid and tau brain pathology increase.[54] These findings complement past studies documenting that both sleep impairment and sleep-wake cycle dysregulation may represent a risk for developing AD pathology,[8,51] suggesting that sleep impairment, sleep-wake cycle misalignment, and daytime napping[55] may be targeted for reducing the burden of AD pathology from the early stage of the disease.

To our knowledge, there is a paucity of studies examining the relationship between tau pathology and subjective sleep quality.[56,57] Our findings are consistent with this previous evidence linking the subjective sleep disturbances and the reduced sleep efficiency (measured in the present study through the PSQI) to the brain tau deposition,[56,57] particularly in the olfactory tract and entorhinal cortex. The concurrent evidence of tau protein accumulation in the latter area and the sleep-wake cycle dysregulation may further reflect the link between sleep and memory, considering that tau pathology in the entorhinal cortex can lead to synaptic failure in the hippocampus.[58] Finally, this case series documented that MCI patients with low TIB present a more evident tau accumulation in the olfactory tract. Although this finding is challenging to discuss, it may suggest that tau pathology can potentially disrupt the sleep-wake cycle by increasing arousal, thus lowering the TIB and possibly increasing nocturnal behavioral problems.

The present case series has several limitations that need to be addressed. Given that this case series included only six subjects, the statistical power was insufficient to perform a robust analysis, and the correlations identified lost the significance when adjusted for multiple comparisons. More comprehensive analyses with a larger sample size would be necessary to increase statistical power and allow for adjustment for potential confounding factors, such as age. Despite the preliminary nature of the analyses and the inclusion of few MCI due to AD patients, the need for further investigation in larger studies emerged since MCI patients showing a more severe sleep-wake cycle dysregulation seem to be those showing a greater tau deposition in several brain areas.

Considering this case series and previous prospective studies demonstrating that, among individuals with normal cognition at baseline, sleep and circadian rhythm measures were associated with an increased likelihood of progression to MCI or AD dementia,[59–61] one may hypothesize that future therapeutic strategies targeting sleep-wake cycle dysregulation could reduce the patient's and caregiver's burden, and perhaps slow the progression of the disease. Moreover, although daytime napping was not analyzed in this study due to limited occurrence, future research should consider this factor as it can significantly impact circadian rhythm. Given the nature of a case series, in the present observation a normal cognitive group compared to MCI patients was not included. Nonetheless, normative actigraphy data[62] suggest that the median sleep duration for individuals aged 60 years and older is approximately 6.5 to 6.8 h, which is higher than the duration observed in the patients evaluated in our study. Nonetheless, this preliminary observation suggests the inclusion of actigraphy, a gold standard method for investigating the sleep-wake cycle, in future studies on patients with cognitive impairment to explore the impact of sleep-wake cycle dysregulation on the burden of AD pathology.

In conclusion, the present results reinforce the hypothesized association between tau pathology and sleep-wake cycle desynchronization in the early stages of AD. These findings should be prompt followed by prospective studies with larger samples to confirm these exploratory and preliminary observation.

AUTHOR CONTRIBUTIONS

Mariana Fernandes (Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing); Agostino Chiaravalloti (Data curation; Formal analysis; Investigation; Methodology; Writing – review & editing); Emanuele Cassetta (Investigation); Fabio Placidi (Supervision; Writing – review & editing); Nicola Biagio Mercuri (Supervision; Writing – review & editing); Claudio Liguori (Conceptualization; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing).

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/ADR-230187.

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