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Dementia severity and Lewy bodies affect circadian rhythms in Alzheimer disease

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Abstract

Sleep disturbance is a symptom shared by all neurodegenerative, dementing illnesses, such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), and its presence frequently precipitates decisions to seek institutional care for patients. Although the sleep disturbances of AD and DLB are qualitatively similar, they appear to be more prominent in patients with DLB. Disturbance of the circadian rhythm has been noted and is a potential factor underlying the nocturnal sleep fragmentation and daytime sleepiness observed in these patients. We studied the circadian variation of core-body temperature and motor activity in a total of 32 institutionalized patients with probable AD by NINCDS-ADRDA criteria, 9 of whom also met pathologic criteria for DLB. Eight, healthy, elderly male controls were studied on a clinical research unit designed to simulate the hospital environment where the dementia patients were studied. Circadian variables generally had greater deviations from normal associated with increasing AD pathology, as measured by postmortem-determined Braak stage, supporting the hypothesis that central changes mediate circadian disturbances in AD and DLB. Patients with a postmortem diagnosis of DLB manifested greater disturbances of locomotor activity circadian rhythms than patients with AD, possibly reflecting the greater sleep disturbances seen in this population, but the differences from normal in the circadian rhythms of the AD and DLB patients were qualitatively similar.
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1. Introduction

Sleep–wake regulation in normal adults can best be characterized as an interaction between two discrete processes. The first, circadian process promotes alertness as a function of time of day. The second, homeostatic process builds need to sleep as a function of the duration of prior wakefulness [5,11]. Aging has been shown to contribute to a deterioration in sleep quality and an increased incidence of reported sleep disturbance [34], including increased wakefulness and decreased time in slow-wave and REM sleep [19,28]. Age-associated changes in sleep appear to be a consequence of changed homeostatic [8] rather than altered circadian function [12].

Sleep disturbance is a frequent symptom in patients clinically diagnosed with age-associated, neurodegenerative dementias such as Alzheimer's disease [21,28], (AD) and Pick's disease [26], and its presence often precipitates decisions by families and others to seek institutional care [27]. Patients diagnosed with probable AD also show direct circadian disturbances including reduced amplitude and phase-delay of circadian variation of core-body temperature and activity [30,35] that could be contributing to the sleep disturbance.

These studies have not addressed the question of whether the circadian abnormalities and sleep–wake disturbances seen in patients with probable AD stem from endogenous or exogenous influences. Dementia patients in nursing homes [1,9], and other institutional environments specializing in the care of patients with neurodegenerative dementia [35] have been found to have lower diurnal and greater nocturnal exposure to light than

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community-dwelling elderly. These changes have been linked to sleep disturbance in residents of these facilities [31], where opportunities for social interaction and other environmental time cues may be reduced and impact the sleep of nursing home patients. These exogenous influences, however, are distinct from the endogenous, neurodegenerative features of dementing illnesses normally thought to cause the emergence of behavioral symptoms, such as sleep and circadian rhythm disturbances. Evidence to date from the limited literature addressing this question, implicates endogenous factors as a prime contributor to circadian disturbances in patients with AD [18]. Patients studied at the same institution, yet with different dementia diagnoses, have demonstrably different circadian abnormalities [18] supporting the hypothesis that the different neurodegenerative patterns of these illnesses had a major influence on the ultimate, observed circadian disturbances.

However, a diagnostic distinction, that has not yet been examined for circadian disturbance, is dementia with Lewy bodies (DLB), a relatively recently defined nosological entity [24]. Lewy bodies are spherical, eosinophilic, neuronal inclusions composed of low molecular-weight neurofilaments and, when seen in the substantia nigra, are the pathological hallmark of Parkinson's disease. In DLB, however, Lewy bodies are seen in cortical as well as in subcortical regions of the brain outside of the substantia nigra. AD and DLB share some neuropathological features such as beta-amyloid plaques, however, patients with DLB often lack the neurofibrillary tangles generally seen in AD [17]. This intricate relationship between DLB and AD makes for great difficulties in accurately distinguishing DLB and AD clinically [15,22].

Patients with DLB have sleep disturbances similar to those with other neurodegenerative dementias, however DLB patients are noted to have greater overall sleep disturbance than patients with AD [16]. Manifestations of their sleep disturbance include some clearly non-circadian phenomena such as a greater incidence of REM sleep behavior disorder, a syndrome characterized by the loss of the ability to maintain muscle atonia during REM sleep [4,13]. The increased daytime sleepiness and nightime arousals seen in DLB compared to AD could have a source in circadian regulation [16].

In the present study, therefore, we further test the hypothesis that endogenous, disease-specific factors are responsible for the circadian disturbances in AD. First, if central, disease-related processes govern the circadian alterations in AD then the more severe the changes, the more profound the circadian disturbances should be. Braak staging of Alzheimer-related changes [6] provides a standardized assessment tool for the evaluation of severity of pathology which correlates well with clinical progression of the illness [3]. Second, if environmental influences are most important, circadian disturbances in DLB should resemble those seen in AD.

2. Methods

2.1. Patients

The subjects were 32 elderly, male, dementia patients hospitalized at the E. N. Rogers Memorial (ENRM) Veterans Hospital in Bedford, MA. Patients were admitted with a diagnosis of probable AD. Following institutional review and informed consent being obtained from the next-of-kin of the subjects, physiological recordings of activity and temperature were obtained every 6 months. Upon the death of the subjects, consent was obtained from the subjects' next-of-kin for autopsy and resultant donation of their brains to the Alzheimer Disease Center at the ENRM VA Hospital. Subjects had a mean age of 70.2 ± 1.0 years, an average age of onset of dementia symptoms of 60.7 ± 1.1 years and a mean duration of neurodegenerative dementia of 11.8 ± 0.7 years measured from the first appearance of symptoms as reported by the next-of-kin. The subjects were all severely impaired and required 24-h nursing care. Except for four subjects with a history of alcohol abuse, yet who still met criteria for probable AD, they had no lifetime history of major affective illness, schizophrenia or substance abuse. All subjects were free from significant intercurrent illnesses and were taking no anti-pyretic medication for at least 24 h prior to the time of physiological recording. Lorazepam and haloperidol were allowed as prns for agitation. Eight, elderly, male comparison subjects were recruited from the community via the Harvard Cooperative Project on Aging and the Massachusetts Institute of Technology's Clinical Research Center. Their mean age was 72.8 ± 2.1 years, they had no evidence of dementia as verified by Mini-Mental State Examination and evaluation by a board-certified psychiatrist. They met all other study inclusion and exclusion criteria.

2.2. Physiological measurements

Locomotor activity and core-body temperature recordings were made using ambulatory monitors during a 72-h, data collection period. Patients were studied in their normal unit environment following usual ward routines. No effort was made to control light, food, nursing care, the patient's sleep schedule or any other masking influences during the recording period. Core-body temperature was measured by a rectal thermistor (YSI, Series 400, Yellow Springs, OH) inserted to 10 cm and connected to a microprocessor-based ambulatory monitor (Mini-Logger, Mini-Mitter Co., Sun River, OR) which sampled temperature every 6 min. Activity was measured by an ankle-worn, piezoelectric, activity monitor sensitive to accelerations of 0.01 g defined as one activity count (AM-16, Ambulatory Monitoring, Inc. Ardsley, NY). We employed the monitor's zero-crossing mode which is more sensitive to intense movements by coding additional activity counts for accelerations much greater than 0.01 g. Activity counts were accumulated over 5-min epochs and the resultant quantity written to memory. Patients were as-

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