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Original article

Association of daytime napping and Parkinsonian signs in Alzheimer's disease

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Abstract

Background and purpose: Excessive daytime sleepiness (EDS) is reported in Alzheimer's disease (AD), with unstable sleep–wake rhythms that worsen with advancing disease stage. EDS is also very common in Parkinson's disease (PD), regardless of disease severity. The purpose of this study was to determine whether more Parkinsonian motor signs exist in AD patients with more reported daytime napping compared to AD patients without daytime napping.
Patients and methods: AD patients ((National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) NINCDS/ADRDA criteria) were prospectively evaluated in a dementia clinic. Parkinsonian motor signs were assessed using a modified motor Unified Parkinson's Disease Rating Scale (mmUPDRS). AD patients were grouped according to daytime napping frequency: (1) minimal napping (AD-Naps), or (2) napping at least once a day (AD + Naps). Wilcoxon rank-sum tests and χ^2-tests computed differences between groups for mmUPDRS, nighttime sleep disturbances, and the Mini Mental State Examination (MMSE). Statistical significance was set at $P < 0.05$.
Results: AD patients were classified as AD-Naps ($n = 155$) or AD + Naps ($n = 180$). Compared with AD-Naps patients, AD + Naps patients had higher total mmUPDRS scores ($P < 0.001$), higher rigidity scores ($P < 0.005$), and more gait impairment ($P < 0.001$).
Conclusion: AD patients with more reported daytime napping had more Parkinsonian motor signs, suggesting that this subgroup may have an increased propensity for sleepiness resembling PD. Longitudinal studies with objective measures are needed to determine whether causal relationships exist between sleepiness and Parkinsonism in AD.

Keywords: Alzheimer's disease; Parkinson's disease; Parkinsonism; Lewy body disease; Excessive daytime sleepiness; Sleep fragmentation

1. Introduction

Neurodegenerative diseases are definitively characterized by pathological processes occurring in specific regions of the brain, which in turn manifest into clinical characteristics that are used by clinicians to diagnose the disease. For example, Alzheimer's disease (AD) is pathologically characterized by accumulation of amyloid plaques and neurofibrillary tangles in the cerebral association cortices and limbic structures, particularly the enterorhinal cortex and other structures in and around the hippocampal formation [1,2]. This neuropathological involvement clinically manifests as progressive memory loss, global cognitive impairment, and functional

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decline. In contrast, Parkinson's disease (PD) is pathologically characterized by progressive cell degeneration of the substantia nigra and other brainstem nuclei, but other pathologic features such as Lewy bodies are also found. Clinically, PD is characterized by the motor manifestations of tremor, bradykinesia, rigidity, and loss of postural reflexes.

Although, AD differs from PD pathologically and clinically, Parkinsonian motor signs are common in AD, affecting 13–36% of AD patients [3]. These motor signs are variable but generally progressive in AD patients [4], and their presence is associated with more rapid cognitive decline, deterioration in physical functioning, and with increased mortality [4–8]. The presence of Parkinsonian signs in AD is often due to AD pathology in the substantia nigra but may also result from nigral Lewy bodies or extranigral pathology [9–15]. However, clinical markers have yet to identify which AD patients will have more motor signs of Parkinsonism.

Sleep abnormalities are common in both AD and PD patients but differ in their presentation. Sleep disturbances in AD include lower daytime activity and higher nocturnal activity, and this near day–night reversal mimics alterations of the circadian rhythm [16–18]. In AD, these sleep disruptions are often initially mild but generally increase in frequency and severity with advancing disease stage [19–23]. It is generally accepted that more severely demented AD patients have more nocturnal sleep fragmentation and worsening sleep–wake rhythms, although research has yet to completely clarify the 24-h pattern in these patients. However, a recent study found that when compared to elderly controls, there is an increased propensity towards daytime sleepiness in the early stages of AD, emphasizing the need to evaluate and perhaps intervene during the mild stages of the disease process [24].

Like AD, sleep disturbances are also frequent in PD patients and include nocturnal sleep disruption and excessive daytime sleepiness (EDS). However, excessive daytime napping in PD patients is present despite higher nocturnal sleep time, indicating that there may be an increased drive towards sleep [25–31]. There is also a suggestion that EDS precedes the motor manifestations in PD, occurring 'earlier' in the PD process than previously suspected [22,32,33].

Because this increased drive towards sleepiness is so prevalent in PD patients, and may pre-date the motor manifestations [32], the pathological processes responsible for the motor signs in PD are also likely responsible for the sleepiness in PD patients. As a result, we hypothesized that the pathology responsible for increased sleepiness in AD patients may also influence the areas in the brain that manifest into the motor signs typically seen in PD. The specific aim of this study was to evaluate whether Parkinsonian motor signs differed in a cross-section of AD patients with and without daytime napping.

2. Methods

2.1. Patients

Consecutive patients were prospectively evaluated from March 1999 to July 2003 in the outpatient offices of the Rush Alzheimer's Disease Center in Chicago, IL. The Institutional Review Board of Rush University Medical Center approved the protocol before data collection, and all patients and caregivers signed informed consent prior to the study. A structured clinical evaluation included a standard assessment of medical history, neurological examination, cognitive testing, and interview with the caregiver present. The details of this clinical evaluation were published previously [19].

Patients were included if they had a diagnosis of probable AD as defined by NINCDS/ADRDA [34,35], a completed modified motor UPDRS (mmUPDRS), and a response to the sleep questions. Patients were excluded from study if there was no informant or if there were features atypical for AD, including evidence of stroke, Lewy body disease, depression or schizoaffective disorder, or alcohol abuse thought to be contributing to cognitive impairment. Patients were included into analysis regardless of whether motor signs of Parkinsonism were present or absent, but were excluded from study if they met clinical diagnostic criteria for Parkinson's disease. Patients were also excluded from analyses if they were treated with sedating medications during the day, including benzodiazepines (e.g. lorazepam, diazepam, alprazolam), tricyclic anti-depressants (e.g. amitryptiline), anxiolytics (e.g. buspirone, clorazepate), selective serotonin reuptake inhibitors (SSRI) anti-depressants (e.g. citalopram), and dopamine agonists (e.g. pramipexole, ropinirole, carbidopa/levodopa) or if they were treated with dopamine receptor antagonists at the time of evaluation (e.g. chlorpromazine, haloperidol, mosaridazine, prochlorperazine, thioridazine, clozapine, quetiapine, and risperidone).

2.2. Assessment of motor items

Patients were examined for Parkinsonian motor signs using the mmUPDRS, which has been used previously in other studies of AD patients and has established reliability across examiners [36]. Briefly, the mmUPDRS consists of the motor portion of the UPDRS with the addition of a turning item from the Consortium to Establish a Registry for Alzheimer's Disease [37]. Further, two motor UPDRS items, speech and facial expression, are not used in analysis based on factor analyses [36] and reliability studies with a similar version of the mmUPDRS [38]. There are four domain scores: (1) bradykinesia, which was assessed in the body, arms and legs; (2) gait disturbance, which assessed overall posture, postural stability, turning, and shuffling gait; (3) rigidity, which was