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Short communication

Daytime sleepiness in dementia with Lewy bodies is associated with neuronal depletion of the nucleus basalis of Meynert

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ABSTRACT

Introduction: Excessive daytime sleepiness is a commonly reported clinical feature of dementia with Lewy bodies (DLB) that can occur early in the disease. Cholinergic depletion is known to be severe in DLB, even when dementia severity is mild. The nucleus basalis of Meynert serves as a primary source of cortical acetylcholine, and has a role in facilitating cortical activation and arousal. We sought to determine whether daytime sleepiness at the initial evaluation of patients with DLB was associated with neuronal loss in the nucleus basalis of Meynert.

Methods: Autopsy-confirmed patients who met clinical criteria for probable DLB at their initial evaluation and who were administered the informant-completed Epworth Sleepiness Scale were included in the study ($n = 40$). Each patient had a dementia at baseline (80% with mild severity) and two or more features of parkinsonism, visual hallucinations, fluctuations, or probable REM sleep behavior disorder. Quantitative digital pathology of the nucleus basalis of Meynert was performed in the DLB group and in 20 non-DLB autopsy controls.

Results: DLB had greater neuronal depletion in the nucleus basalis of Meynert ($p < 0.0001$) than pathologic controls. Sleepiness was present in 58% of the DLB group and those with daytime sleepiness had significantly lower neuron counts in the nucleus basalis of Meynert than their non-sleepy counterparts ($p = 0.001$). Regression modeling revealed that sleepiness was a stronger predictor of neuronal loss in the nucleus basalis of Meynert than visual hallucinations, fluctuations or dementia severity ($p = 0.003$).

Conclusions: Excessive daytime sleepiness in early DLB is indicative of a more profound loss of basal forebrain cholinergic integrity.

1. Introduction

Idiopathic excessive daytime sleepiness is an increasingly recognized problem in dementia with Lewy bodies (DLB), and is a newly added supportive feature of the revised clinical criteria [1]. It often occurs early in the disease [2], and has been documented in patients with Mild Cognitive Impairment (MCI) who subsequently develop DLB [3]. In DLB, informant ratings of daytime sleepiness were objectively confirmed using overnight and daytime polysomnography, and results showed that sleepiness was not secondary to medication-use or to fragmented, non-restorative nighttime sleep [4]. There is overlap between sleepiness and DLB fluctuations, given that the patients experiencing fluctuations often exhibit drowsiness and daytime sleep episodes. Nonetheless, sleepiness can be distinguished from DLB fluctuations because patients may experience one without the other [4,5], a relationship also observed between sleepiness and delirium.

The ascending reticular activating system is comprised of a

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neuronal network that includes the brainstem and basal forebrain. In the basal forebrain, the primary source of afferent cholinergic input to the cortex is the nucleus basalis of Meynert (nbM) which projects diffusely to all areas and layers of each cortical region, and to the reticular nucleus of the thalamus [6]. The nbM serves to mediate attention by enhancing sensory modulation and discriminating signal from noise, and to do this, it is not surprising that this region also facilitates cortical activation and wakefulness [7]. It is well established that cholinergic depletion is far more severe in DLB than in Alzheimer's disease (AD), and is particularly prominent in the earliest stages of DLB [8]. This is based on measurements of cortical choline acetyltransferase and is supported by functional imaging of acetylcholinesterase activity indicative of severe cholinergic cortical deafferentation [9] and by antemortem imaging of basal forebrain atrophy [10]. We hypothesize that when excessive daytime sleepiness is present in the early stages of DLB, this may be a useful indicator of a more profound loss of basal forebrain cholinergic neuronal integrity.

2. Methods

2.1. Clinical assessments

Patients were followed longitudinally as part of the Mayo Alzheimer's Disease Research Center at Mayo Clinic Florida and underwent annual neurologic examination, neurocognitive assessment, and informant questionnaires, as described elsewhere [4,11]. Six patients were excluded because the pathologic diagnosis was not Lewy body disease (two had cerebrovascular disease with Alzheimer's disease, one had Alzheimer's disese, one had Progressive Supranuclear Palsy and Alzheimer's disease, one had Multiple System Atrophy, and one had prion disease). Only patients with autopsy-confirmation of their antemortem clinical diagnosis of probable DLB were included in the analysis ($n = 40$). The clinical diagnosis of DLB was made on the basis of current criteria and required dementia and at least 2 of the following: visual hallucinations, fluctuations, parkinsonism, or rapid eye movement sleep behavior disorder (RBD) [1]. The Epworth Sleepiness Scale (ESS) was completed by informants who were asked to rate the perceived likelihood that the patient would fall asleep in eight everyday situations, yielding a score from 0 to 24 points. An ESS score $\geq$10 was considered to represent excessive daytime sleepiness [12]. Dementia severity was assessed with the Global Deterioration Scale (GLDS) and the Mini-Mental State Examination (MMSE). The presence of fluctuations was based on a score of 3 or 4 on the 4-item Mayo Fluctuations Scale. Parkinsonism was based on neurologic examination, and the Unified Parkinson's Disease Rating Scale part 3 was used to quantify parkinsonism severity. Clinically probable RBD was determined through clinical interview and the Mayo Sleep Questionnaire. Of the 31 patients with RBD, overnight polysomnography confirmed the presence of REM sleep without atonia in 13 patients and verified the absence in two DLB patients without RBD. Use of cholinesterase inhibitors, anticholinergic agents (e.g., diphenhydramine, amitriptyline, ranitidine, paroxetine, olanzepine) and/or dopamine agonists (e.g., pramipexole, ropinirole) at the baseline evaluation was recorded. This study was approved by the Mayo Clinic Institutional Review Board, and informed consent for participation was obtained from every subject and/or an appropriate surrogate.

2.2. Neuropathological assessments

Neuropathologic assessment included a standardized macroscopic and microscopic evaluation. Neocortical samples were taken prior to brain dissection to obtain orthogonal sections of the cortical ribbon and ensure uniformity of sampling. Tissue sections were embedded in paraffin, and 5-μm thick sections were mounted on glass slides for histological examination and immunohistochemistry. Braak neurofibrillary tangle (NFT) stage and Thal amyloid phase were assigned using thioflavin-S fluorescent microscopy based upon the distribution of NFT and senile plaques respectively. For diagnostic and Lewy body classification, immunohistochemistry was performed on all cases with an α-synuclein antibody (NACP, 1:3000 rabbit polyclonal, Mayo Clinic antibody) using a protocol (formic acid pretreatment and DAKO Envision signal detection) that has been shown to be comparable, or better, than other methods. When assigning subtypes of Lewy body disease, the presence, density, semi-quantitative scores and distribution of Lewy-related pathology followed recommendations of the current DLB criteria [1]. Transitional Lewy body disease (TLBD) included individuals with Lewy-related pathology in brainstem and predominantly limbic regions; while, diffuse Lewy body disease (DLBD) included those with Lewy-related pathology in brainstem, limbic, and neocortical regions.

Quantitative digital pathology of the nbM Ch4 region was performed using Aperio ImageScope (Leica Biosystems, Buffalo Grove, Illinois) on sections stained with hematoxylin and eosin as described elsewhere [13]. The nbM was annotated blinded to disease type. Triplicate 600 μm × 600 μm squares were overlaid in areas of highest neuronal density for each case. The output was averaged across the three annotated squares yielding a neuronal count/mm^2. In order to better understand the extent of the neuronal loss in DLB compared to a non-DLB group, we selected a control group of 20 consecutive cases without Lewy-related pathology and without a clinical history of dementia or parkinsonism from the Mayo Clinic brain bank for comparison (5 with end stage liver disease, 5 with cerebrovascular disease, 3 with mild age-associated Alzheimer type pathology, 2 with argyrophilic grain disease, and 5 with no significant pathology).

2.3. Statistical analyses

Continuous variables were summarized using median and range. Correlations between continuous variables were examined using Spearman's test of correlation. Comparisons of clinical and pathologic characteristics between the sleepy (ESS $\geq$10) and non-sleepy (ESS<10) DLB patients, and also between the entire DLB cohort and controls, were made using a Mann-Whitney test or a Chi-square test. In order to evaluate the association between sleepiness and the primary pathologic measure of nbM neuronal counts, we utilized multivariate linear regression models adjusted for GLDS, as a measure of dementia severity, and adjusted for the baseline core features that differed between sleepy and non-sleepy groups ($p<0.05$). P-values of 0.05 or lower were considered to be statistically significant and all statistical tests were two-sided.

3. Results

In our sample of 40 patients who met criteria for probable DLB at their initial evaluation, dementia severity was mild for 80% of the group (GLDS score of 3), and mild-to-moderate or moderate (GLDS score of 4 or 5) for the remaining 20%. The estimated onset of cognitive symptoms was a median of 3 years prior to the baseline evaluation. Time from the last evaluation to death was a median of 11 months. Informant report of excessive daytime sleepiness (ESS $\geq$ 10) was present in 58% of the DLB group at baseline, and these patients were also more likely to have visual hallucinations or fluctuations at their initial evaluation (Table 1). Sleepy DLB patients did not differ from their non-sleepy counterparts in death age, baseline dementia severity, parkinsonism severity, in the

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