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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 ($p = 0.003$).

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Authors' roles

(1) the conception and design of the study (A), acquisition of data (B), analysis and interpretation of the data (C).
(2) drafting the article (A), revising it critically (B) for important intellectual content.
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Conclusions: Excessive daytime sleepiness in early DLB is indicative of a more profound loss of basal forebrain cholinergic integrity.

Keywords

Basal forebrain; Hypersomnolence; Fluctuations; Parkinsonism; Epworth sleepiness scale

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 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 ≥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-p.m 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 (form 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 ≥ 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 ≥ 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 distribution of Lewy-related (TLBD vs. DLBD) or in the distribution of AD-related pathology (Braak and Thal stages). The Lewy body disease subtypes (14 TLBD and 26 DLBD) did not differ in nbM counts ($p = 0.90$) or in the presence of any of the four core DLB features. Six DLB patients had exposure to dopamine agonists and/or anticholinergic agents at their baseline assessment, but ESS scores did not significantly differ from those without exposure (medians of 12 vs. 11; $p = 0.51$). Patients with daytime sleepiness did not differ in their use of a cholinesterase inhibitor at baseline ($p = 0.61$), and all but 3 patients were taking a cholinesterase inhibitor by their last evaluation.

The DLB group had severe depletion of nbM neurons compared to the pathologic control group ($p < 0.0001$; Table 1). Neuronal counts of the nbM ranged from 11 to 45/mm2 for the DLB group and from 46 to 114/mm2 for the pathologic controls. There was no correlation between death age and nbM counts for either group (Controls: Spearman's $r = 0.12$, $p = 0.61$; DLB: Spearman's $r = -0.07$, $p = 0.66$).

DLB patients with baseline excessive daytime sleepiness had greater nbM cell loss than their non-sleepy counterparts ($p = 0.0013$: Table 1). In addition, patients with baseline visual hallucinations had lower nbM counts than non-hallucinators ($p = 0.026$). Those with both

excessive daytime sleepiness and visual hallucinations had the lowest nbM neuronal density compared to DLB patients with either sleepiness or visual hallucinations or neither ($p = 0.0008$). There was no difference in nbM density when patients were distinguished on the basis of fluctuations, parkinsonism or probable RBD.

To better understand the relationship between sleepiness, fluctuations and visual hallucinations as it relates to nbM cell loss, multivariate linear regression modeling was carried out. Results showed that daytime sleepiness was predictive of lower nbM density even when adjusted for dementia severity ($p = 0.001$). Sleepiness at baseline also had a stronger predictive value of nbM cell loss over that of the visual hallucinations ($p = 0.009$) or fluctuations ($p = 0.001$:Table 2). This effect was maintained when the model was adjusted simultaneously for dementia severity, visual hallucinations and fluctuations ($p = 0.003$).

4. Discussion

In our DLB cohort, we found significantly greater depletion of nbM cholinergic neurons compared to non-DLB neuropathologic controls. This is consistent with the well-established finding of severe loss of cortical choline acetyltransferase in DLB [8], and with imaging findings of cholinergic deafferentation and basal forebrain atrophy in DLB [9,10].

DLB patients with baseline excessive daytime sleepiness, based on informant-completed ESS scores ≥10, had greater nbM cell loss at autopsy than their non-sleepy counterparts. Excessive daytime sleepiness was present in 58% of our DLB sample and was not attributable to the severity of dementia and parkinsonism, which was predominantly mild. DLB patients with fluctuations or visual hallucinations at their initial clinical evaluation were also more likely to have excessive daytime sleepiness. Despite the overlap between fluctuations and sleepiness, it was the subset of patients who harbored visual hallucinations and sleepiness at baseline who had the greatest nbM cell loss compared to those with one or neither feature. When we modeled the association between nbM integrity with the presence or absence of baseline informant report of sleepiness, visual hallucinations, fluctuations and with dementia severity, the strongest predictor of nbM degeneration was baseline sleepiness. This suggests that excessive daytime sleepiness is an important early indicator of cholinergic denervation in DLB.

RBD is a prodromal feature of the synucleinopathies that may occur years before the onset of parkinsonism or dementia [1]. In our DLB cohort, daytime sleepiness was unrelated to a history of probable RBD. In other words, at their baseline evaluation, DLB patients with RBD were just as likely to be sleepy as those without a history of RBD. Since sleepiness in DLB occurs in the MCI stage and is unrelated to dementia severity [3,4], it is possible that daytime sleepiness is a presymptomatic marker of the early brainstemlimbic pathology in DLB. This argument is supported by evidence that daytime sleepiness based on partner-completed ESS scores ≥8 [14] and scores ≥10 and ≥ 14 [15] predicts the development of parkinsonism or dementia in idiopathic RBD. In contrast, others do not show this predictive relationship in idiopathic RBD [16,17], though this may be related to methodological differences, including the use of patient self-reported sleepiness which tends to

underestimate daytime sleep episodes [12]. This discrepancy may also represent subsets of patients that differ in the severity of the neuronal loss in the ascending reticular activating system sub-serving wakefulness relative to that of the descending reticular formation responsible for RBD. Further investigation is needed to clarify the conditions under which daytime sleepiness is predictive of DLB and to determine whether there are clinical subtypes associated with the presence or absence of daytime sleepiness.

Limitations of this study include the sample size which precluded more comprehensive modeling of the clinical features in relation to nbM neuronal integrity. Also, the unavailability of whether our pathologic controls had excessive daytime sleepiness during life limited the group comparisons. Investigation that includes normal controls and other neurodegenerative conditions would help to verify the relationship between sleepiness and the nbM in DLB compared to those without DLB. Future studies should also assess cholinergic immunoreactivity to confirm that the sampled region of Ch4 cells are indeed cholinergic, and to better detect neurons that may appear shrunken due to neurodegeneration. This study focused on the cholinergic-rich nbM, which is only one component of the ascending reticular activating system. Further investigations should examine other cell clusters of this circuit known to be affected in DLB, including the noradrenergic-rich locus coeruleus, to better understand how damage to each component of the ascending reticular activating system contributes to daytime sleepiness in DLB.

The association between early sleepiness and greater nbM degeneration has implications for treatment. The majority of our patients were taking cholinesterase inhibitors, and these agents are associated with improved alertness and a reduction in neuropsychiatric symptoms in patients with dementia. Very few in our study had exposure to anticholinergic agents, which are well known to trigger drowsiness and delirium-like symptoms in DLB and Parkinson disease dementia. These data highlight the importance of obtaining information from informants regarding the presence of daytime sleepiness in DLB. Our findings suggest that when daytime sleepiness is present in early DLB it may be indicative of a loss of nbM neuronal integrity, and as such, those patients may be particularly sensitive to agents that lower or raise acetylcholine. More studies are needed to evaluate this relationship, and should consider the nbM as a potential target for focused symptomatic treatment in DLB.

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Table 1

Clinical and Pathologic Characteristics of DLB patients and Controls.

Variables	Sleepy ESS ≥10	Non-sleepy ESS <10	Sleepy vs. Non-sleepy DLB p-value	Pathologic Controls	DLB vs. Controls p-value
N	23	17	-	20	-
Males, n (%)	20 (87%)	12 (71%)	0.20	11(55%)	0.006
Death age, yrs	75 (58–92)	76 (60–90)	0.32	78 (49–94)	0.55
Education, yrs	16 (10–20)	16 (10–18)	0.57	-	-
Duration of illness, yrs	8 (3–13)	8 (4–17)	0.36	-	-
Time from baseline to last follow-up evaluation, yrs	3 (0–10)	3 (1–13)	0.75	-	-
Clinical Variables at Baseline Evaluation					
Time from estimated cognitive onset to baseline, yrs	3 (0–7)	3 (0–7)	0.69	-	-
Time from baseline evaluation until death, yrs	4 (1–9)	4 (0–13)	0.80	-	-
Global Deterioration Scale (GLDS)	3 (3–5)	3 (3–5)	0.71	-	-
Mini-Mental State Examination (MMSE)	26 (17–29)	25 (19–29)	0.76	-	-
Visual hallucinations, n (%)	18 (78%)	7 (41%)	0.017	-	-
Parkinsonism, n (%)	15 (65%)	9 (53%)	0.43	-	-
Unified Parkinson's Disease Rating Scale (UPDRS)	12 (0–21)	7 (0–21)	0.18	-	-
Probable REM Sleep Behavior Disorder, n (%)	17 (74%)	14 (82%)	0.53	-	-
REM Sleep without Atonia, n/total with polysomnography (%)	9/11 (81%)	4/4 (100%)	0.36	-	-
Fluctuations, n (%)	14 (61%)	5 (29%)	0.049	-	-
Cholinesterase Inhibitors, n (%)	16 (70%)	12 (71%)	0.94	-	-
Anticholinergic agent or dopamine agonist, n (%)	4 (17%)	2 (12%)	0.62	-	-
Clinical Variables at Last Evaluation					
Time from last evaluation until death, yrs	1 (0–5)	1 (0–3)	0.81	-	-
Global Deterioration Scale Score (GLDS)	6 (4–7)	5 (3–7)	0.52	-	-
Mini-Mental State Examination (MMSE)	17 (3–27)	17 (0–28)	0.98	-	-
Pathology Variables					
Transitional Lewy body disease (TLBD), n (%)	8 (35%)	6 (35%)	0.59	0 (0%)	<0.0001
Diffuse Lewy body diseases (DLBD), n (%)	15 (65%)	11 (65%)	0.43	0 (0%)	<0.0001
Braak neurofibrillary tangle (NFT) stage	3 (0–6)	3 (1–5)	0.44	1 (0–6)	0.0004
Thal Amyloid stage	3 (0–5)	3 (2–5)	0.48	0 (0–5)	0.0005

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Variables	Sleepy ESS ≥10	Non-sleepy ESS <10	Sleepy vs. Non-sleepy DLB p-value	Pathologic Controls	DLB vs. Controls p-value
nbM neuronal count/mm^2	26 (11–44)	33 (16–45)	0.0013	111 (46–144)	<0.0001

Data reflects n (%) or median (minimum-maximum range). Comparisons represent Chi-Square or Mann-Whitney *U* Test.

Table 2

Association between baseline daytime sleepiness and nbM neuronal counts.

Variables	Association with nbM neuronal counts, Regression Coefficient (95% CI)	p-value
Model with baseline dementia severity and sleepiness		
Global Deterioration Scale (GLDS)	−1.66 (−4.62, 1.30)	0.26
Sleepiness	−8.01 (−12.72, −3.30)	0.001
Model with baseline visual hallucinations and sleepiness		
Visual hallucinations	−2.50 (−7.71, 2.71)	0.34
Sleepiness	−6.96 (−12.06, −1.86)	0.009
Model with baseline fluctuations and sleepiness		
Fluctuations	2.77 (−2.12, 7.67)	0.26
Sleepiness	−8.76 (−13.70, −3.81)	0.001
Model with baseline dementia severity, visual hallucinations, fluctuations, and sleepiness		
Global Deterioration Scale (GLDS)	−1.70 (−4.84, 1.43)	0.28
Visual hallucinations	−2.00 (−7.44, 3.44)	0.46
Fluctuations	3.52 (−1.45, 8.50)	0.16
Sleepiness	−8.38 (−13.72, −3.04)	0.003

Associations were evaluated using linear regression models. Regression coefficients represent the change in the mean nbM neuronal count corresponding to a 1-unit increase in GLDS score, presence vs absence of sleepiness (refers to ESS score ≥ 10 vs. ESS <10), presence vs. absence of visual hallucinations, and presence vs. absence of fluctuations.

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