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Pathology and temporal onset of visual hallucinations, misperceptions and family misidentification distinguishes dementia with Lewy bodies from Alzheimer's disease

T.J. Ferman [a,*], Z. Arvanitakis [b], H. Fujishiro [a], R. Duara [c], F. Parfitt [a], M. Purdy [d], C. Waters [e], W. Barker [c], N.R. Graff-Radford [a], D.W. Dickson [a]

[a] Mayo Clinic, Jacksonville, FL, USA
[b] Rush University Medical Center, Chicago, IL, USA
[c] Mt. Sinai Medical Center and University of Miami School of Medicine, Miami, FL, USA
[d] Orlando Regional Medical Center, Orlando, FL, USA
[e] Holmes Regional Medical Center, Melbourne, FL, USA

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ABSTRACT

Objective: To determine whether the temporal onset of visual phenomena distinguishes Lewy body disease (LBD) from Alzheimer's disease (AD), and to characterize the extent Lewy bodies and neurofibrillary tangles are associated with these clinical features.
Methods: Consecutive cases of autopsy-confirmed LBD ($n = 41$), AD ($n = 70$), and AD with amygdala-predominant Lewy bodies (AD-ALB) ($n = 14$) with a documented clinical history of dementia were included. We mailed questionnaires to next-of-kin asking about symptoms during life. Lewy pathology and neurofibrillary tangle pathology were assessed.
Results: The occurrence of visual hallucinations, misperceptions and family misidentification did not distinguish LBD from AD or AD-ALB, but the onset was earlier in LBD compared to AD and AD-ALB. When visual hallucinations developed within the first 5 years of dementia, the odds were 4–5 times greater for autopsy-confirmed LBD (or intermediate/high likelihood dementia with Lewy bodies) and not AD or AD-ALB. In LBD, limbic but not cortical Lewy body pathology was related to an earlier onset of visual hallucinations, while limbic and cortical Lewy body pathology were associated with visual misperceptions and misidentification. Cortical neurofibrillary tangle burden was associated with an earlier onset of misidentification and misperceptions in LBD and AD, but only with earlier visual hallucinations in AD/AD-ALB.
Conclusion: When visual hallucinations occur within the first 5 years of the dementia, a diagnosis of LBD was more likely than AD. Visual hallucinations in LBD were associated with limbic Lewy body pathology. Visual misperceptions and misidentification delusions were related to cortical Lewy body and neurofibrillary tangle burden in LBD and AD/AD-ALB.

1. Introduction

Visual hallucinations, misperceptions and family misidentification in the context of dementia represent a major treatment challenge for patients, families and care providers. Although visual hallucinations are a core feature in dementia with Lewy bodies (DLB), and occur in 32%–85% of autopsy-confirmed cases [1–5], this feature also occurs in 11%–38% of those with Alzheimer's disease (AD) without concomitant α-synucleinopathy [1–4]. Distinguishing DLB from AD may be difficult due to the overlap of psychiatric features, and deciding on treatment options can be challenging since some pharmacologic interventions for psychosis are poorly tolerated in DLB. When visual hallucinations occur in AD, they tend to be associated with greater cognitive impairment and a more advanced stage of the dementia [6–10]. The purpose of this study was to determine if an early vs. late temporal onset of visual hallucinations distinguishes autopsy-confirmed DLB from AD, and whether a similar distinction is evident with misperceptions and family misidentification phenomena.

* Corresponding author. Department of Psychiatry & Psychology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA.
E-mail address: ferman.tanis@mayo.edu (T.J. Ferman).

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Psychosis in AD has been associated with greater neocortical neurofibrillary tangle (NFT) density [11,12], while the opposite relationship has been shown in DLB [13]. Visual hallucinations in DLB have been associated with greater Lewy body burden in the temporal lobe, amygdala, transentorhinal region and frontal lobe [5,14]. This suggests that Lewy pathology, and not neurofibrillary tangle pathology may be a vital contributor to psychosis in DLB. A secondary goal of the study was to characterize the contribution of neurofibrillary tangle and Lewy body pathology association with the presentation of visual hallucinations, misperceptions and family visual misidentification in autopsy-confirmed DLB and AD.

2. Methods

The sample included consecutive cases from the State of Florida Alzheimer's Disease Initiative (ADI) Brain Bank [15]. The patients were evaluated during life at Florida ADI memory disorder clinics in Melbourne, Miami Beach, Orlando and Jacksonville, and all had a documented history of dementia using DSM-III-R criteria. The protocols were given ethical approval by the institutional review boards for each institution, and proxies for the subjects provided written informed consent. There was no overlap in patient representation from prior clinicopathologic studies reported from our center [6,16].

Since the samples were initially derived from pathology data, the pathologic designation Lewy body disease (LBD) is used. Autopsy groups included LBD ($n = 41$), AD ($n = 70$), and Alzheimer's disease with amygdala-predominant Lewy bodies (AD-ALB; $n = 14$). The AD group had no concomitant α-synuclein pathology, and the AD-ALB group had Lewy bodies limited to the amygdala [17]. In those with LBD, 16 patients had transitional LBD (TLBD) with Lewy bodies in the brainstem and limbic regions and 25 patients had diffuse LBD (DLBD) with brainstem, limbic and neocortical LB pathology. We compared groups separately, but also did comparisons between the LBD group ($n = 41$) and the AD/AD-ALB combined group ($n = 84$). We also applied the DLB Consortium pathology criteria of no, low, intermediate and high likelihood DLB [18,19]. Specifically, this pathology criteria allocates those with TLBD and a Braak neurofibrillary tangle stage ≥5 into the low likelihood DLB group. With this designation, group membership changed slightly (no/low likelihood DLB group $n = 93$; intermediate/high likelihood DLB $n = 32$).

We mailed questionnaires to the next-of-kin of those who died up to three years earlier. If there was no response after two months of the second mailing, then telephone contact was attempted and if possible, the survey was completed by telephone interview. There was a 71% return rate for the questionnaires. The clinicopathologic analysis is based only on the 71% who responded. Data regarding clinical presentation and onset dates used in the analyses were derived from next-of-kin report.

On the survey, the family member was asked to estimate the age of onset when problems with thinking or forgetfulness began, thereby reflecting the earliest features of the dementia. Estimated dementia duration was calculated by subtracting the death date from the estimated onset of cognitive difficulties. We inquired about visual hallucinations, visual misperceptions and misidentification phenomena (see Fig. 1). Only images of adults, children, tiny people, objects, insects or animals were considered to be a fully formed visual hallucination. Based on next-of-kin report of their recollection of features during the entire disease course, 73% of the LBD had at least 2 of the 4 DLB clinical features (visual hallucinations, parkinsonism, fluctuations, REM sleep behavior disorder), as did 24% of the AD group and 21% of the AD-ALB group.

2.1. Neuropathologic methods

Lewy body density was assessed in limbic (amygdala, cingulate gyrus, parahippocampal gyrus) and cortical (frontal, temporal, parietal, occipital) regions. Given the extent of pathology in the LBD brainstems, a rating scale of Lewy body pathology/neuronal loss in the brainstem regions of substantia nigra, locus ceruleus and medulla was applied using a range from 0 (normal) to 3 (severely impaired). NFT density was determined from the limbic regions (subiculum, CA1, CA2/3, endplate) and cortical (frontal, temporal, parietal, occipital) regions. A Braak NFT stage was assigned to each case using distribution of NFT from thioflavin S fluorescent microscopy, as previously described [20].

3. Results

3.1. Demographics and clinical history

Estimated dementia duration was shortest for the LBD group compared to AD and AD-ALB (see Table 1). Estimated age of cognitive onset did not differ between groups. A clinical diagnosis of parkinsonism that was known to the next-of-kin was made during life for 24% LBD, 7% AD, and 7% AD-ALB. Nonetheless, 85% of the LBD patients had either moderate or severe LB pathology and nigral loss in the substantia nigra, and the remainder had mild pathology. None of the patients had a known history of dopamine

1. Did he or she have trouble recognizing a family member?
   a. If yes, how old was the patient when this first started?
2. Did he or she ever see something and mistake it for something else?
   a. If yes, how old was the patient when this first started?
3. Did he or she see things that others did not see (hallucinations)?
   a. If yes, how old was the patient when this first started?
   b. What things did the patient hallucinate? (check all that apply)

__adults	__animals	__water
__children	__insects	__designs
__family friends	__fire	__objects
__tiny people	__smoke	

   c. How often did the patient have visual hallucinations

__daily	__about once a week
__several times a week	__less than once a week

   d. When did the visual hallucinations seem to occur?

__when he or she was fully awake

__when he or she was waking up or falling asleep

__when he or she was sleepy or drowsy

Fig. 1. Visual hallucination, misperception and misidentification questions.

Table 1
Frequency and onset of demographics and clinical features across groups.

	LBD	AD	AD-ALB	X^2/F	P value
Number	41	70	14	–	–
Males	58%[a]	49%	29%[b]	3.5	0.06
Age at estimated cognitive onset (yrs ± sd)	70.2 ± 8.8	69.1 ± 9.0	68.0 ± 8.7	0.6	0.56
Estimated dementia duration (interval from estimated cognitive onset to death (yrs ± sd)	8.9 ± 4.1[a]	11.2 ± 5.6[b]	14.2 ± 4.3[c]	5.9	0.003
Visual hallucinations (VH)	63%	46%	44%	2.8	0.25
Estimated onset of VH relative to cognitive onset (yrs ± sd)	3.1 ± 1.9[a]	7.3 ± 3.5[b]	7.0 ± 2.2[b]	13.4	0.000
Misperceptions	76%	64%	50%	2.6	0.27
Estimated onset of misperceptions relative to cognitive onset (yrs ± sd)	3.2 ± 2.2[a]	7.1 ± 3.7[b]	5.8 ± 2.9	10.1	0.000
Misidentification of family	66%[a]	70%	93%[b]	3.8	0.05
Estimated onset of family misidentification relative to cognitive onset (yrs ± sd)	4.5 ± 4.1[a]	7.8 ± 4.5[b]	7.4 ± 3.8[b]	4.8	0.01

Separate chi-square or Fisher's least significant differences post-hoc comparisons with different superscript letters indicate significance $p \leq 0.05$.