Visual Hallucinations in Dementia: A Prospective Community-Based Study With Autopsy

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Objective: *Several studies have demonstrated that specific neuropathologic features may be associated with the presence of visual hallucinations in dementia patients, but the clinical usefulness of these studies has been limited because their subjects were selected on the basis of neuropathologic findings rather than clinical presentations. This study seeks to investigate the demographic, clinical, and neuropathologic features of community-based dementia subjects with and without visual hallucations.* **Design:** *A prospective examination of the clinical and neuropathologic correlates of visual hallucinations in community-based dementia subjects.* **Participants:** *One hundred forty-eight subjects with sufficient clinical and neuropathologic data from a community-based incident dementia autopsy case series.* **Results:** *Subjects were classified according to the presence or absence of visual hallucinations and subjects with visual hallucinations (N = 27) were younger at intake and more likely to exhibit agitation, delusions, and apathy than subjects without visual hallucinations (N = 121). Subjects with visual hallucinations were also more likely than subjects without visual hallucinations to have Lewy-related pathology (LRP) (78% versus 45%). In addition, a higher frequency of visual hallucinations was observed in subjects with neocortical LRP than subjects with limbic-, amygdala-, or brainstem-predominant LRP. Although Alzheimer disease with concomitant LRP was the most common neuropathologic subtype in the visual hallucinations-positive group (59%), the frequency of subjects with Alzheimer disease pathology did not differ significantly between those with and without visual hallucinations (74% versus 62%).* **Conclusions:** *Subjects with visual hallucinations were more likely to have concomitant postural and gait disturbance, additional neuropsychiatric symptoms, and neocortical LRP than subjects without visual hallucinations. Visual hallucinations accompanying dementia have distinct clinical and neuropathologic characteristics that are important for prognosis and clinical management.* (Am J Geriatr Psychiatry 2009; 17:317–323)

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Visual hallucinations (VHs) are a common and problematic behavior in dementia.[1,2] In the short term, VHs pose treatment challenges for clinicians because of the risks of prescribing neuroleptics to dementia patients,[3] but more globally, these symptoms are also associated with rapid cognitive decline, early institutionalization, and high mortality.[1,4–6]

Several clinicopathological studies have addressed the neuropathologic (NP) features underlying VHs in dementia. These studies have consistently reported a higher frequency and earlier onset of VHs in dementia subjects with Lewy-related pathology (LRP)[7–9] (i.e., subjects with dementia with Lewy bodies [DLB] or Parkinson's disease dementia) than in dementia subjects with Alzheimer disease (AD). In fact, most prospective studies have reported VH frequencies greater than 50% in subjects with confirmed LRP (i.e., Lewy bodies and Lewy neurites).[10,11] Some studies have suggested that concomitant AD pathology obscures the clinical presentation of VHs in subjects with LRP,[12–16] whereas others suggest that VH frequencies vary according to the location and severity of LRP[17] and that VH frequencies are especially associated with the density of LRP in the medial temporal lobe.

Unfortunately, most clinicopathological studies have enrolled autopsied subjects according to their clinical diagnoses (e.g., probable or possible DLB) or, alternatively, their NP findings (e.g., neocortical LRP). Although these studies are critical to our understanding of the underlying neurobiology of VHs in dementia, they are limited by their bias toward specific clinical or NP diagnoses. To address this limitation, our study selected subjects with a clinical history of dementia as determined by a comprehensive assessment of both clinical and NP information rather than a narrow focus on specific clinical or NP diagnostic categories. Using this more general approach to case selection, we examined the demographic, clinical, and NP differences between subjects with and without VHs who underwent autopsy from this community-based sample of individuals with dementia.

METHODS

Participants

The University of Washington Alzheimer's Disease Patient Registry (ADPR) enrolled patients from the Group Health Cooperative, a well-established consumer-owned HMO in the Puget Sound area. The purpose of the ADPR was to identify and enroll incident cases with dementia who came to medical attention in the central Seattle, WA, region of the Group Health Cooperative HMO. We determined the eligibility of HMO patients with symptoms that were potentially consistent with previously undiagnosed dementia by reviewing specialty and primary care clinic logs, hospital records, head CT scan requests, and referrals from primary care practitioners and neurologists. The majority of referred cases, 48.8%, were from primary care physicians.[18] In addition, 19.8% of the referrals were based on CT scan requisitions that suggested dementia, and 10% of the referrals were derived from hospital admission records. Other sources for subjects included emergency room logs and referrals from mental health specialists. Persons with symptoms of memory loss that were suggestive of dementia were enrolled in the ADPR, where they were given a full dementia workup and a differential diagnosis. Persons who had been previously diagnosed with dementia for more than 1 year (prevalent cases) were excluded from the study. Approximately 34% of the persons who were initially identified as having cognitive impairment declined to participate in the ADPR.[19] The ADPR sample closely resembles the demographics of the general elderly population in the Puget Sound region.[18,20–22] In this study, we constructed a sample that consisted of all of the ADPR subjects with adequate clinical and NP information.

Assessment of Clinical Features

At the time of enrollment, subjects participated in detailed clinical and neurological examinations by physicians and cognitive assessments by neuropsychologists. The systematic neurological examinations included assessments for asymmetrical resting tremor, rigidity, bradykinesia, and gait disturbances. We applied the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM–III–R*)[23] and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for dementia.[24] Subjects were followed-up annually with either an in-person examination or a telephone interview, using abbreviated neuropsychological evaluations (Mini-

Mental State Examination and Mattis-Coblentz) and assessments of behavioral symptoms (BEHAVE-AD[25]). Clinical and neuropsychological examinations were repeated if new signs and symptoms emerged, and diagnoses were changed only by consensus.

Using these prospectively collected clinical data, we evaluated all records for the presence of behavioral and parkinsonian signs and symptoms. Our evaluation of behavioral symptoms included an assessment of the presence of paranoid and delusional ideation, auditory and visual hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxiety and phobias. Our evaluation of parkinsonian signs and symptoms included an assessment of tremor, bradykinesia, stooped posture, cogwheeling, and rigidity.

NP Evaluation

We performed a standard NP workup, including gross and microscopic examinations, on all autopsied subjects. Histological evaluations included hematoxylin-eosin, modified Bielschowsky, and thioflavine S staining. In addition, we performed alpha-synuclein immunostaining (antibody LB509, dilution, 1:400; generous gift from John Q. Trojanowski)[26] to fully characterize LRP in each subject.[27] We also reviewed the medulla, substantia nigra, hippocampus, entorhinal cortex/parahippocampal gyrus, amygdala, cingulate gyrus, and frontal cortex for the presence of LRP.[27–29] LRP includes both classic Lewy bodies (as seen with hematoxylin-eosin histological stain) and abnormal alpha-synuclein (SNCA) deposition in Lewy inclusions and neurites. Subjects were divided into two subgroups based on NP findings: 1) LRP-negative = no LRP in any region; 2) LRP-positive = alpha-synuclein immuno-positive inclusions and/or neurites in any sampled region. Furthermore, using a modification of the consensus neuropathological criteria for DLB,[9,27] each LRP-positive subject was assigned a region of LRP predominance (i.e., brainstem-, amygdala-, limbic-, or neocortical-predominance). Braak stage for neurofibrillary tangle pathology[30] and CERAD plaque scores were determined for each case.[31] Cases with a Braak stage greater than IV and a CERAD plaque score of B or C were considered to have met neuropathological criteria for AD.[32]

Statistical Analysis

We evaluated demographic and clinical characteristics for associations with the presence of VHs by using t tests for continuous variables assuming unequal variances and using Satterthwaite's approximate df[33] and Fisher's exact test (based on hypergeometric probabilities) for categorical variables. We defined statistical significance as $p < 0.01$. We did not perform formal adjustments for multiple comparisons. The statistical package STATA Version 8.2 was used for all analyses.[34]

RESULTS

Nine hundred eighty-seven individuals were initially enrolled in the ADPR between 1987 and 1996. Seven hundred twenty-eight individuals are now deceased. Of the 285 subjects who subsequently underwent autopsy, 260 were diagnosed with dementia during the study, but 72 were excluded due to insufficient clinical information, and 31 were excluded due to insufficient tissue for a complete NP evaluation. Seven additional subjects were excluded due to a previous diagnosis of dementia secondary to Parkinson disease, as were two subjects whose parkinsonian signs and symptoms were thought to be related to antipsychotic medication use. One hundred forty-eight ADPR subjects with sufficient clinical information available and a complete NP workup were included in this analysis. Only subjects with a clearly documented presence of VHs unrelated to dopaminergic-agent use were classified as VH-positive in the study.

Table 1 summarizes the demographic characteristics of the sample, and it is stratified by the presence and absence of VHs. Subjects who experienced VHs were younger at intake ($t_{[41]} = 2.13$, $p = 0.04$), but in other respects, the two groups were similar. There was little difference in *APOE**4 allele frequencies between VH-positive and VH-negative groups (36% versus 31%, data not shown).

Table 2 summarizes the clinical signs and symptoms of the sample, and it is stratified by the presence or absence of VHs. VH-positive subjects were generally more likely to exhibit clinical parkinsonism than VH-negative subjects, but at the 1% level there

TABLE 1. Comparison of Clinical Characteristics in Subjects With and Without Visual Hallucinations[a]

Clinical Characteristics	Mean (SD) VH-Negative (N = 121)	Mean (SD) VH-Positive (N = 27)	p	Approx *df*
Continuous				
Age at onset	76.9 (7.2)	74.2 (6.4)	0.06	42.0
Age at intake	79.8 (7.1)	76.8 (6.5)	0.04	41.1
Age at death	84.4 (6.7)	82.1 (5.5)	0.07	45.0
MMSE score at baseline	20.7 (4.7)	20.3 (5.4)	0.72	35.3
MMSE score at final visit[b]	13.5 (7.6)	11.3 (7.5)	0.18	39.4
Average change in MMSE per year[c]	−3.9 (3.4)	−3.6 (2.2)	0.58	59.0
ADL score at final visit	10.9 (4.6)	12.2 (3.8)	0.13	44.7
Categorical	n (%)			
Female	67 (55.4)	14 (51.9)	0.83	
Final DSM-III-R diagnosis of AD	83 (68.6)	21 (77.8)	0.49	

Notes: VH: visual hallucination; *df*: degrees of freedom; MMSE: Mini-Mental State Examination; ADL: activities of daily living; DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders*, *Third Edition, Revised*; AD: Alzheimer's disease.
[a]t tests for continuous variables assuming unequal variances and using Satterthwaite's approximate degrees of freedom.
[b]MMSE data available for n = 116 VH-negative, n = 27 VH-positive.
[c]MMSE change data available for n = 103 VH-negative, n = 26 VH-positive.

TABLE 2. Comparison of Clinical Signs and Symptoms in Subjects With and Without Visual Hallucinations

Individual Symptoms	N (%) VH-Negative (N = 121)	N (%) VH-Positive (N = 27)	p
Parkinsonism			
Asymmetrical tremor	11 (9.1)	6 (22.0)	0.09
Rigidity	11 (9.1)	6 (22.0)	0.09
Bradykinesia	16 (13.2)	4 (14.8)	0.76
Postural or gait disturbance	24 (19.8)	11 (40.7)	0.04
Masked facies	8 (6.6)	4 (14.8)	0.23
Shuffling gait	13 (10.7)	6 (22.2)	0.12
Multiple falls	25 (20.7)	10 (37.0)	0.08
Neuropsychiatric			
Delusions	48 (39.7)	19 (70.4)	**0.005**
Agitation or aggression	68 (56.2)	22 (81.5)	0.02
Depression or dysphoria	73 (60.3)	19 (70.4)	0.39
Anxiety	71 (58.7)	19 (70.4)	0.29
Elation or euphoria	0 (0.0)	0 (0.0)	—
Apathy or indifference	70 (57.9)	23 (85.2)	**0.008**
Disinhibition	14 (11.6)	6 (22.2)	0.21
Irritability	61 (50.4)	12 (44.4)	0.67
Lability	43 (35.5)	10 (37.0)	1.000
Aberrant motor behavior	65 (53.7)	18 (66.7)	0.29
Pacing	31 (25.6)	12 (44.4)	0.06

Notes: All p <0.01 are in bold, tests based on Fisher's exact method for 2 × 2 tables.
VH: visual hallucination.

were no significant differences between the two groups. Behaviorally, VH-positive subjects were more likely than VH-negative subjects to have exhibited delusions (p = 0.005; Fisher's exact test), agitation and aggression (p = 0.02; Fisher's exact test), and apathy (p = 0.008; Fisher's exact test).

The frequency of AD and LRP in the sample differed according to VH status (Table 3), although these differences were not significant at the 1% level (p = 0.02, Fisher's exact test). For instance, 78% (21 of 27) of VH-positive subjects had LRP, whereas only 45% of VH-negative subjects had LRP. The frequency of neuropathologic AD was similar in VH-positive (74%) and VH-negative subjects (62%, p = 0.27; Fisher's exact test). The frequency of VHs in LRP-positive subjects with and without concomitant AD was similar (30% and 24%, respectively, p = 0.78; Fisher's exact test).

TABLE 3. Comparison[a] of Neuropathologic Changes in Subjects With and Without Visual Hallucinations[b]

NP Diagnosis	N (%) VH-Negative (N = 121)	N (%) VH-Positive (N = 27)
AD without LRP	37 (30.6)	4 (14.8)
AD with LRP	38 (31.4)	16 (59.3)
LRP without AD	16 (13.2)	5 (18.5)
No AD or LRP	30 (24.8)	2 (7.4)

Notes: VH: visual hallucination; NP: neuropathologic; AD: Alzheimer disease (Braak Stage > IV and CERAD plaque score B or C); LRP: Lewy-related pathology (classic Lewy bodies or abnormal Lewy inclusions or neurites).

[a]Fisher's exact test for r × c tables, p = 0.02.

[b]Percentage of VH-positive subjects by neuropathologic category: AD without LRP (10% VH-positive), AD with LRP (30%), LRP without AD (24%), no AD or LRP (6%).

TABLE 4. Distribution of Lewy-Related Pathology[a] in Subjects With and Without Visual Hallucinations[b]

LRP Distribution	N (%) VH-Negative (N = 54)	N (%) VH-Positive (N = 21)
Amygdala	11 (20.4)	1 (4.8)
Brainstem	12 (22.2)	4 (19.0)
Limbic	11 (20.4)	2 (9.5)
Neocortical[c]	18 (33.3)	13 (61.9)
Mixed	2 (3.7)	1 (4.8)

Notes: VH: visual hallucination; LRP: Lewy-related pathology.

[a]According to the modified International Consensus Diagnostic criteria for dementia with Lewy bodies[27]; 44 148 cases (29.8%) met the 2005 neuropathological criteria for dementia with Lewy bodies.[9]

[b]Fisher's exact test for r × c tables, p = 0.16.

[c]Comparison of neocortical frequency with and without VHs: Fisher's exact test, p = 0.02.

The distribution of LRP for the 75 subjects with any LRP is shown by VH status in Table 4. The majority of VH-positive subjects had neocortical LRP (13 of 21, 62%), whereas neocortical LRP was less common in the VH-negative subjects (18 of 56, 32%, p = 0.02; Fisher's exact test). For subjects with neocortical LRP, individuals with coexistent AD had a similar frequency of VHs (9 of 23, 39%) to individuals without coexistent AD (4 of 8, 50%, p = 0.69; Fisher's exact test).

CONCLUSIONS

Although previous studies of VHs in dementia have focused on specific clinical or NP diagnostic groups,[10,17] our study examined a community-based sample of incident dementia subjects without imposing such a selection, albeit the study focused only on subjects who underwent autopsy. An important difference between our study, which considers the clinical symptoms of all autopsied subjects, and studies that have selected subjects based on autopsy findings is that although the latter studies may illuminate correlates within NP diagnosis categories, they have less value from a clinician's perspective. Findings based on NP exclusion criteria are more difficult to generalize to clinical settings, where autopsy findings are unknown. Our decision to include all autopsied subjects therefore resulted in an investigation of the pathologic correlates of VHs in dementia from a clinical vantage point.

In our study, 18% of dementia subjects were VH-positive. Previous studies of VHs in dementia have reported widely variant VH frequencies, ranging from 25% to 83%.[2,10,17] Some of these differences are likely due to subject selection, including factors such as referral bias and the age of subjects enrolled.[20,35] Studies that include subjects from geriatric psychiatry inpatient services are likely to have a higher frequency of VHs than studies that include subjects from outpatient medical clinics. Furthermore, studies differ in the instruments that they use to assess psychiatric symptoms and in whether the data are collected retrospectively or prospectively.

After prospectively collecting clinical data from a community-based sample with an average age at death in the early 1980s, we found that VH-positive subjects were younger at intake than VH-negative subjects, but there were no other demographic differences between the two groups. We speculate that VHs are associated with a more aggressive clinical course and an earlier age of onset.[36] However, some studies have reported no differences in age at onset between DLB subjects with and without VHs.[6,37] Thus, because of the highly selective nature of the previous studies, the association between age and VH status in neurodegenerative dementia remains inconclusive and requires further investigation by studies that directly address the effect of selection bias on age.

The clustering of neuropsychiatric and parkinsonian signs and symptoms in DLB subjects has been reported previously.[38,39] We extended these findings

in that we found that VH-positive subjects were more likely to exhibit delusions and apathy compared with VH-negative subjects. Galvin et al.[40] also reported an association between personality change, including apathy, and VHs in individuals with autopsy-confirmed DLB. In contrast, Borroni et al.[37] reported that VH-negative DLB subjects had higher delusion, agitation, and anxiety scores than VH-positive DLB subjects, but the subjects were recruited from specialty clinics (movement disorder and neurodegenerative disorder clinics) and lacked clinical diagnoses confirmed by neuropathology.

Consistent with previous studies of VHs and dementia, we found an association between VHs and LRP, especially neocortical predominant LRP. Harding et al.[17] have reported that the high density of amygdala and parahippocampal cortex LRP is associated with VHs, that the high density of temporal-lobe LRP is associated with an earlier onset of these symptoms, and that the density of frontal cortical LRP has no relationship with VHs. Because our LRP assessments in specific brain regions were semiquantitative, we cannot directly compare our findings with their work; moreover, there are also important sample differences between our studies, such as age and sample selection (their sample included some subjects with parkinsonism and no dementia). Nonetheless, both our study and that of Harding et al.'s support a relationship between the presence of LRP and VHs. Further quantitative study of limbic and neocortical subjects with and without VHs would be helpful to determine whether density of LRP in the limbic region or density of LRP in the neocortical region underlies VHs.

Some investigators have reported that the clinical presentation of DLB is less clear in subjects with LRP and coexistent AD than in subjects with LRP alone[41] and that severe AD neuropathologic changes suppress the manifestation of VHs.[38] We observed no significant differences in VH frequency between cortical LRP subjects with or without AD. However, given our small sample size in these categories, this result should be interpreted with caution.

Unfortunately, because the majority of our subjects were evaluated before the publication of the consensus diagnostic criteria for DLB, a clinical diagnosis of DLB was generally not considered. The clinical criteria of cognitive fluctuation and rapid eye movement sleep behavior disorder were also not systematically assessed. Other limitations of this study include our small sample size and the possibility of selection bias because not all of our deceased subjects underwent autopsy. However, this sample closely resembles the demographic characteristics of the general elderly population in the region,[20] and only moderate differences exist between the autopsied and nonautopsied subjects.[22] Because we conducted multiple statistical comparisons in this study, we regard our findings as primarily descriptive and hypothesis-generating. Finally, although autopsy studies are not representative of the entire study sample, our earlier report demonstrated that the effect of selection bias is modest for the NP diagnosis of LRP in the ADPR sample.[20]

Multiple other studies with a variety of study designs have found associations between VHs and LRP, and the presence of VHs is thought to be highly predictive for the presence of LRP at autopsy in subjects with dementia or parkinsonism.[36,38] In fact, this clinicopathological association is sufficiently strong that some researchers have advocated the inclusion of VHs as a supportive criterion for the clinical diagnosis of Parkinson's disease.[36] This study confirms the association between VHs and LRP, and although the absence of VHs in dementia patients were not predictive of LRP at autopsy, the association was particularly strong in subjects with neocortical LRP, regardless of the presence of coexistent AD pathology.[36,38] Further studies are needed to improve the clinician's ability to predict which dementia patients will have LRP, especially in patients without VH.

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