The Natural History of Psychosis and Depression in Dementia With Lewy Bodies and Alzheimer's Disease: Persistence and New Cases Over 1 Year of Follow-Up

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Background: Few data are available regarding the natural course of psychiatric symptoms in dementia with Lewy bodies and Alzheimer's disease. To acquire this information is essential to inform differential diagnosis and treatment decisions.

Method: The current study provides prospective data regarding a representative case-register cohort of patients with operationalized clinical diagnoses of dementia with Lewy bodies (N = 82) or Alzheimer's disease (N = 132), with verified accuracy of clinical diagnosis against postmortem examination. Psychosis (Columbia University Scale for Psychopathology in Alzheimer's Disease) and depression (Cornell Scale for Depression in Dementia) were assessed at baseline and annual follow-up.

Results: Visual hallucinations were significantly more likely to be persistent in patients suffering from dementia with Lewy bodies ($\chi^2 = 19.1$, df = 1, $p < .0001$). Although a number of other psychiatric symptoms were also more frequent at baseline in dementia with Lewy body patients, they were not significantly more likely to persist. Delusions and auditory hallucinations did, however, persist in more than 40% of patients across both diagnostic groups. Patients suffering from dementia with Lewy bodies were significantly more likely to develop new auditory hallucinations over the year of follow-up ($\chi^2 = 14.4$, df = 1, $p < .0001$).

Conclusion: These results confirm that, although a number of psychiatric symptoms are common in dementia with Lewy bodies, it is only visual hallucinations that are significantly more persistent, with important treatment implications.

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Dementia with Lewy bodies and Alzheimer's disease (AD) are the 2 most common neurodegenerative dementias, accounting for 10% to 20%[1–3] and 60% of late-onset dementia cases,[4] respectively. International consensus criteria have recently been published for the diagnosis of dementia with Lewy bodies,[5] core features of which include persistent or recurrent visual hallucinations, parkinsonism, and fluctuating confusion associated with disturbances of consciousness. While all studies have found visual hallucinations to occur significantly more frequently in patients with dementia with Lewy bodies than those with AD,[5] a paucity of prospective follow-up information is available. Such data are essential to determine the clinical value of dementia with Lewy bodies as a discrete diagnostic entity, with a stable profile of symptoms. Several small longitudinal studies have suggested that visual hallucinations are significantly more likely to be persistent in dementia with Lewy bodies patients than those with AD.[6–8] Since "persistent" visual hallucinations are described as a core feature of dementia with Lewy bodies, it is important to confirm this observation in a larger prospective study. In addition, it is important to understand the natural course of visual hallucinations to make informed treatment decisions. This issue is of particular clinical relevance in dementia with Lewy bodies, in which severe sensitivity to typical neuroleptic drugs has been described in several large brain bank studies.[9,10] Preliminary reports indicate that these reactions also occur with newer atypical agents.[11–13]

Other psychiatric symptoms such as delusions, delusional misidentification, and depression are also reported as significantly more common in patients with dementia with Lewy bodies than in those with AD, but a similar paucity of data exists regarding their longitudinal course. Preliminary data suggest that differences in the frequency of delusions between dementia with Lewy bodies and AD may diminish over the course of the illness.[8]

The current study examines the persistence of psychiatric symptoms and the frequency of new psychiatric symptoms in a cohort of 132 AD patients and 82 dementia with Lewy bodies patients followed up for 1 year.

METHOD

The cohort is drawn from the Newcastle and Tyneside area dementia case register, which included 244 patients with an operationalized clinical diagnosis of AD[15] or dementia with Lewy bodies[5] from consecutive referrals with mild or moderate dementia, who have an informant in regular contact, seen by psychiatric services within defined geographical catchment areas. After a full explanation, written consent was obtained from the patients with written assent from their nearest relative. The study was approved by the Human Subjects Ethical Committee governing Newcastle and Tyneside. The diagnostic accuracy for the operational clinical diagnosis of both AD and dementia with Lewy bodies against neuropathologic diagnosis had been established for the first 50 patients from the series coming to postmortem, with positive predictive values of 0.92 for dementia with Lewy bodies and 0.80 for probable AD.[15]

The assessment included a standardized psychiatric history (History and Aetiology Schedule[16]), and an assessment of cognitive function using the Cambridge Assessment of Mental Disorders in the Elderly, Section B (CAMCOG),[17] a widely used and validated cognitive assessment instrument scored out of 107. A standardized physical examination was completed, which incorporated the Unified Parkinson's Disease Rating Scale.[18] The assessment of psychosis utilized the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD),[19] and depression was evaluated using the Cornell Scale for Depression in Dementia.[20] Depression was diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) criteria, ignoring the caveat regarding exclusion if there is evidence of organic causation. Definitions regarding the presence and classification of psychotic features were taken from the criteria of Burns et al.[21,22] Delusional misidentification included the Capgras delusion, delusional misidentification of television images, and delusional misidentification of mirror images.

A standardized examination was also completed at 1-year follow-up, incorporating the same measures for the assessment of psychosis and depression.

The persistence of psychiatric symptoms and the frequency of new cases were compared between dementia with Lewy bodies and AD patients using the chi-square test. All statistics were undertaken with the SPSS computerized package, version 9.

RESULTS

Two hundred fourteen patients (88%) with dementia with Lewy bodies (N = 82) or AD (N = 132) completed the 1-year follow-up assessment. The only patients who did not receive a repeat assessment were those who died during the intervening year. These individuals had an overall frequency of psychiatric symptoms similar to that of the entire group, although depression was more common and visual hallucinations less common among dementia with Lewy bodies patients who had died than among the comparable group of AD patients (dementia with Lewy bodies: N = 16; auditory hallucinations, 31% [N = 5]; visual hallucinations, 56% [N = 9]; delusional misidentification, 56% [N = 9]; delusions, 69% [N = 11]; depression, 38% [N = 6]; AD: N = 20; auditory hallucinations, 0%; visual hallucinations, 20% [N = 4]; delusional misidentification, 20% [N = 4]; delusions, 30% [N = 6]; depression, 5% [N = 1]).

In the group in which the 2 assessments were completed, the patients with dementia with Lewy bodies had a mean ± SD CAMCOG score of 44.7 ± 26.8, their mean age was 76.5 ± 7.9 years, and 46 (56%) were female. The AD patients had a mean CAMCOG score of 48.9 ± 23.8, their mean age was 81.1 ± 6.6 years, and 93 (70%) were female. At baseline, visual hallucinations (76% [dementia with Lewy bodies] vs. 17% [AD]; $\chi^2 = 71.5$, df = 1, $p < .00001$), auditory hallucinations (39% vs. 8%; $\chi^2 = 29.1$, df = 1, $p < .00001$), delusions (55% vs. 33%; $\chi^2 = 10.4$, df = 1, $p = .001$), and delusional misidentification (49% vs. 21%; $\chi^2 = 17.7$, df = 1, $p = .00003$) were significantly more frequent in dementia with Lewy bodies patients, and a trend in the same direction was seen for major depression (16% vs. 8%; $\chi^2 = 2.9$, df = 1, $p = .09$). Fourteen of the patients (17%) with dementia with Lewy bodies were taking typical neuroleptics and 11 (13%) were taking atypical agents. Of the AD patients, 29 (22%) were taking typical neuroleptics, and 2 (2%) were taking atypical agents. None of the patients in either group were taking cholinesterase inhibitors.

Details regarding the persistence and frequency of new cases of psychiatric symptoms in dementia with Lewy bodies and AD patients are shown in Table 1. Dementia with Lewy bodies patients were significantly more likely to experience persistent visual hallucinations over the year of follow-up ($\chi^2 = 19.1$, df = 1, $p < .0001$). They were also significantly more likely to develop new auditory hallucinations ($\chi^2 = 14.4$, df = 1, $p < .0001$) and showed a trend toward being more likely to develop new visual hallucinations ($\chi^2 = 3.8$, df = 1, $p = .05$). Only 9 of the dementia with Lewy bodies patients (64%) developing auditory hallucinations had concurrent visual hallucinations. None of the other comparisons were significantly different, although it is notable that both delusions and auditory hallucinations were still present after 1 year in more than 40% of patients with either AD or dementia with Lewy bodies who had these symptoms at the time of the baseline assessment. At the time of the follow-up assessment, 14 dementia with Lewy bodies patients (29%) with visual hallucinations (11 were taking typicals, 3 were taking atypicals) and 7 (50%) of those without (4 were

Table 1. Natural Course of Psychiatric Symptoms in Dementia With Lewy Bodies and Alzheimer's Disease

Symptom	Dementia With Lewy Bodies (N = 82)	Alzheimer's Disease (N = 132)	Statistical Evaluation χ^2	df	p
Persistence of baseline psychotic symptoms[a]					
Visual hallucinations	48/62 (77%)	6/23 (26%)	19.1	1	< .0001*
Delusions	18/45 (40%)	19/43 (44%)	0.03	1	.86
Delusional misidentification	12/40 (30%)	5/28 (18%)	1.3	1	.26
Auditory hallucinations	13/32 (41%)	5/11 (45%)	0.08	1	.78
Depression	5/13 (38%)	4/13 (31%)	0.17	1	.68
New cases of psychiatric symptoms[b]					
Visual hallucinations	6/20 (30%)	14/109 (13%)	3.8	1	.05
Delusions	11/37 (30%)	21/89 (24%)	0.59	1	.47
Delusional misidentification	11/37 (30%)	12/104 (12%)	0.63	1	.43
Auditory hallucinations	14/50 (28%)	8/121 (7%)	14.44	1	< .0001*
Depression	8/69 (12%)	7/119 (6%)	1.94	1	.16

[a]The denominator represents the number of patients with the following symptoms at baseline; the numerator represents the number of cases that persisted at 1-year follow-up.
[b]The denominator represents the number of patients without the following symptoms at baseline; the numerator represents the number of new cases from that group at 1-year follow-up.
*Statistically significant.

taking typicals, 3 were taking atypicals) were taking neuroleptics. This cannot, however, be interpreted in a straightforward way, since a further 20 (32%) had received neuroleptics (14 received typicals, 6 received atypicals) at the time of the baseline assessment or over the course of the follow-up year but had been unable to tolerate treatment.

Compared with the AD patients, the patients with dementia with Lewy bodies were younger and less likely to be women; a logistic regression analysis was hence undertaken to examine the contribution of diagnosis, age, and female gender to the persistence of visual hallucinations. A diagnosis of dementia with Lewy bodies ($\chi^2 = 17.0$, $p = .0002$) was the only variable entered into the equation (age, $\chi^2 = 1.3$, $p = .26$; gender, $\chi^2 = 1.2$, $p = .27$).

DISCUSSION

The current cohort is the largest cohort of patients with dementia with Lewy bodies prospectively followed up over 1 year, and, furthermore, the accuracy of operationalized clinical diagnosis has been established against postmortem examination.

The data strongly support previous preliminary studies[6,7] in suggesting that visual hallucinations are significantly more likely to be persistent in dementia with Lewy bodies patients. In the current cohort, 77% of dementia with Lewy bodies patients and 26% of AD patients with visual hallucinations continued to experience these symptoms after 1 year. Dementia with Lewy bodies patients also showed a trend toward being more likely to develop visual hallucinations during the follow-up year. This confirms that visual hallucinations, particularly if persistent, are a key symptom for the diagnosis of dementia with Lewy bodies. In addition, however, it strongly emphasizes the priority of developing safe and effective treatments, a difficult task given the risk of severe neuroleptic sensitivity reactions in dementia with Lewy bodies patients.[9] Few studies have reported data regarding the tolerability of atypical antipsychotics, which in general have a more favorable side effect profile. In the current report, many patients were unable to tolerate neuroleptic agents, but there was some indication that patients taking these agents at the time of follow-up did appear to be less likely to experience persistent visual hallucinations, although this would need to be evaluated in a placebo-controlled trial. Preliminary reports indicate that severe sensitivity reactions may occur with risperidone[11,12] and olanzapine[13]; no data are available regarding other agents. Particularly since there may be some benefit in preventing persistent visual hallucinations, further trials of these other atypical antipsychotics would be helpful in informing clinical practice, although given the possibility that sensitivity reactions may also be seen with these compounds, any studies would need to incorporate a rigorous monitoring protocol. Retrospective analysis of cholinesterase inhibitor trials in AD suggests that these agents may have antipsychotic properties.[23] This may be particularly relevant to patients with dementia with Lewy bodies given the evidence suggesting an association between visual hallucinations and cholinergic depletion.[24] Trials of cholinesterase inhibitors for the treatment of visual hallucinations in dementia with Lewy bodies are hence strongly indicated, with preliminary data showing some encouraging trends.[25,26]

Although a number of other psychiatric symptoms were significantly more frequent in the dementia with Lewy bodies patients at baseline, they were not significantly more likely to be persistent. The high-frequency psychotic symptoms and other psychiatric features in both dementia with Lewy bodies and AD patients, especially auditory hallucinations and delusions, emphasizes their importance. Additional work is therefore required to progress further in our understanding of optimal management approaches, although treatment decisions need to be informed by an understanding of the natural course of these symptoms, with spontaneous resolution occurring in many patients.

Dementia with Lewy bodies patients were also significantly more likely to develop new auditory hallucinations over the follow-up year, an effect that appears independent of concurrent visual hallucinations. Nevertheless, it

was the persistence of visual hallucinations rather than the other psychotic or psychiatric symptoms that was the unique defining characteristic of the dementia with Lewy bodies group.

CONCLUSION

The current study confirms, in a large prospective cohort of dementia with Lewy bodies patients, that visual hallucinations are significantly more persistent in dementia with Lewy bodies than in AD, confirming their importance as a core diagnostic feature of dementia with Lewy bodies and emphasizing the importance of treatment intervention studies.

Drug names: olanzapine (Zyprexa), risperidone (Risperdal).

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