The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study

Audun Osland Vik-Mo, Lasse Melvaer Giil, Miguel Germán Borda, Clive Ballard and Dag Aarsland

Introduction

Understanding the natural course of neuropsychiatric symptoms (NPS) in dementia is important for planning patient care and trial design, but few studies have described the long-term course of NPS in individuals.

Method

Primary inclusion of 223 patients with suspected mild dementia from general practice were followed by annual assessment, including the Neuropsychiatric Inventory (NPI), for up to 12 years. Total and item NPI scores were classified as stable, relapsing, single episodic or not present based on 4.96 (s.d. 2.3) observations (98% completeness of longitudinal data) for 113 patients with Alzheimer's disease and 84 patients with LBD (68 dementia with Lewy bodies and 16 Parkinson's disease dementia).

Results

We found that 80% had stable NPI total ≥1, 50% had stable modest NPI total ≥12 and 25% had stable NPI total ≥24 scores. Very severe NPS (≥48) were mostly single episodes, but 8% of patients with Alzheimer's disease had stable severe NPS. Patients with Alzheimer's disease and the highest 20% NPI total scores had a more stable or relapsing course of four key symptoms: aberrant motor behaviour, aggression/agitation, delusions and irritability (odds ratio 55, $P < 0.001$). This was not seen in LBD.

Finally, 57% of patients with Alzheimer's disease and 84% of patients with LBD had reoccurring psychotic symptoms.

Conclusions

We observed a highly individual course of NPS, with most presenting as a single episode or relapsing; a stable course was less common, especially in LBD. These findings demonstrate the importance of an individualised approach (i.e. personalised medicine) in dementia care.

Neuropsychiatric symptoms (NPS) represent a common and important manifestation of the dementia syndrome, with major effects on quality of life, carer burden and risk of institutionalisation.[1] Although non-pharmacological interventions are a good first-line option, there are few treatment options for the more severe and persistent symptoms, and clinical trials are hampered by a large placebo effect, which could be due to natural fluctuations of symptoms.[2] The longitudinal course of NPS is only partly known. Longitudinal studies have often been based on small sample sizes of mixed dementia groups, and with a short duration of follow-up. Studies usually report summary data, i.e. the proportion of patients with NPS at each time point.[1,3,4] However, the different symptoms may vary in each patient, from single occurrence over a short period, via a fluctuating course with remission and relapse, to a persistent course, and thus the proportion with a symptom at each time point does not inform about the course of NPS in individual patients. For example, in our recent 5-year study, we showed that although most NPS were common already from the time of diagnosis, there were individual fluctuations, and thus the group with the symptom present consisted of different individual patients at different time points.[5] In one of the longest studies to date, following patients for up to 9 years, aggression was found to be persistent, whereas other NPS occurred as single discrete episode.[6] Understanding the course of NPS in individual patients is important for precision medicine treatment approach and planning, as well as for trial design. Here, we present the individual course for up to 12 years from diagnosis of dementia to death in people with Alzheimer's disease and Lewy body dementia (LBD).

Method

Study design

The Dementia Study of Western Norway (Demvest) is a longitudinal cohort study of patients referred to dementia clinics in Hordaland and Rogaland counties. There is little private healthcare for these patients and all dementia units (i.e. geriatric, neurology and geriatric psychiatry out-patient clinics) in the region were recruited to the study. To reduce referral bias, the general practitioners in the area were contacted by letter before study start and were invited to refer all patients with suspect dementia. Residents are covered by the same National Insurance Scheme with restricted co-payments, allowing the representation of a general dementia population. All patients referred with suspected mild dementia were screened ($n = 657$), 325 fulfilled the inclusion criteria and 223 consented to the study. After the main inclusion period between 2005 and 2007, we continued to selectively recruit patients with LBD (i.e. dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)) to enhance the number of patients in this group.

Procedure

Criterion for inclusion was mild dementia according to the ICD-10,[7] defined as a Mini-Mental State Examination (MMSE)[8] score of at least 20 or a Clinical Dementia Rating (CDR) global score of 1, were included. Exclusion criteria were moderate or

severe dementia, acute delirium, previous bipolar disorder or psychotic disorder, terminal illness or recently diagnosed major somatic illness that, according to the clinician, would significantly affect cognition, function or study participation. The standardised diagnostic assessment is described in detail elsewhere.[9] Briefly, physical, neurological and psychiatric examinations were performed, including a detailed neuropsychological test battery, Montgomery–Aasberg Depression Rating scale,[10] routine blood and cerebrospinal fluid analyses and brain magnetic resonance imaging. Dopamine transporter single-photon emission computed tomography scans were available for most patients with suspected DLB. Caregivers completed The Informant Questionnaire on Cognitive Decline in the Elderly, a questionnaire shown to be a reliable and valid instrument to detect dementia, and the clinician completed the CDR and the Hachinski Ischemia Scale.[11–13]

The clinical diagnoses were reviewed by a consensus group at regular intervals, taking into account all available information, including the electronic medical records. The final clinical diagnosis was made according to the consensus criteria for dementia with LBD, PDD and Alzheimer's disease after a consensus meeting with three specialists, including both geriatric psychiatry and geriatric medicine. A pathological diagnosis was available for 56 patients, showing diagnostic accuracy above 80% for both Alzheimer's disease and LBD.[14] Patients were followed with annual structured assessments. The participating centres follow national guidelines on psychotropic use, offer dementia-carer support groups, practice patient-centred care and provide ambulatory services to nursing homes.

Assessment and classification of NPS

The validated Norwegian Neuropsychiatric Inventory (NPI) was used to interview to family or caregivers, and the nursing home version NPI-Nursing Home was used after participants moved to nursing homes.[15,16] All assessments were completed by the best-suited informants who had the most day-to-day contact with the patient. Informants were the spouse, children or, at later assessments, a professional caregiver. The 12 items were registered as present or not present during the past 4 weeks, and if present, scored according to their frequency (1–4) and severity (1–3). Here, we report the frequency × severity score for the individual items. We present data in Table 3, using the established cut-off item score of ≥4 to indicate a clinically significant symptom, which includes moderately severe symptoms present at a frequency rating of 'often' or more frequently, and mild symptoms present 'very frequently,' as previously reported.[1,17] In addition, results for NPI item scores present (≥1), severe (≥8) and very severe (12) are presented in Supplementary Table 1 available at https://doi. org/10.1192/bjp.2019.195. For NPI total score, the cut-offs were set and classified as NPS ≥1 (present), ≥12 (modest severity), ≥24 (significant) and ≥48 (very significant) (Table 2).

The clinical course was coded into four mutually exclusive categories defined as follows: no symptoms, never having symptom above the relevant cut-off; stable, symptom present at all or three consecutive assessments; relapsing, symptom present at two or more assessments but with resolution of symptom between assessments; single episode, symptom only present at one assessment during follow-up.

Statistics

Clinical and demographic variables are shown as mean or proportions and statistical differences are tested with Mann–Whitney and Student's t-test (in Table 1). Differences between Alzheimer's disease and LBD frequency of symptoms (no/yes, Table 3) and clinical course were tested with the χ^2 test, as contingency tables. All analysis was done in SPSS (version 13 for Windows).

Ethics

The study was approved by the regional ethics committee (approval no. 2010/633). All participants signed informed consent at study start when they had mild dementia and capacity to consent. Next-of-kin provided signed informed consent as well. We received financial support only from the regional health authorities of western Norway, Helse-Vest and non-profit organisation Norwegian Health Association. All data were handled and kept in accordance with national health and data privacy protocol.

Results

Clinical and demographic variables

The cohort consisted of 113 patients with Alzheimer's disease and 84 patients with LBD (including 16 patients with PDD). Ten patients were still alive in January 2018, all of whom had completed the 12-year follow-up. The mean duration of follow-up was 6.4 (s.d. 2.9) and 4.3 (s.d. 1.9) years for Alzheimer's disease and LBD, respectively. There were 1080 possible assessments (living patient-years), with a mean number of observations of 4.96 (s.d. 2.3) and total of 1063 completed observations. The attrition and missing rates for reasons other than death were very low; only 19 patients missed one single follow-up assessment and two missed two assessments, leading to 98% total completeness of the longitudinal data. The characteristics of patients with Alzheimer's disease and LBD did not differ regarding age, education or baseline MMSE score (Table 1), but the Alzheimer's disease group included more

Table 1 Clinical and demographic variables						
	Alzheimer's disease (n = 113)		LBD (n = 84)		t/z[a,b]	P-value
Age (mean, s.d.)[a]	75.2	7.7	75.2	6.9	0.05	0.957
Male/Female[b]	32/81		45/39		−3.97	<0.001
Years of education (mean, s.d.)[a]	9.7	3.0	9.6	2.8	−0.22	0.826
Years of symptoms (mean, s.d.)[a]	1.9	1.8	2.7	2.1	−2.73	0.007
CIRS (mean, s.d.)[a]	5.3	2.3	6.6	2.6	−3.3	0.001
CDR-SB (mean, s.d.)[a]	4.8	2.1	5.8	2.8	2.5	0.012
MMSE score (mean, s.d.)[a]	23.7	2.3	23.8	3.2	−0.28	0.774
Years from inclusion to death[a]	6.4	2.9	4.3	1.9	4.1	<0.001
Nursing home admissions (n)[b]	73		51		0.31	0.576
Years to nursing home (mean, s.d.)[a]	2.8	1.5	1.7	1.2	5.5	<0.001

LBD, Lewy body dementia; t/z, Standard score test statistics; CIRS, Cumulative Illness Rating Scale; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination.
a. Mann–Whitney/ Student's t-test showing t-score for Alzheimer's disease and LBD.
b. Pearson's χ^2 test, showing z-score for Alzheimer's disease and LBD.

Table 2 The clinical course of Neuropsychiatric Inventory (NPI) total score in Alzheimer's disease and Lewy body dementia at different severity levels

NPI total scores	No	Stable	Relapsing	Single
Alzheimer's disease (*n* = 113)				
Present (≥1)	1%	78%	17%	4%
Modest severity (≥12)	4%	46%	40%	10%
Significant (≥24)	23%	26%	30%	21%
Very significant (≥48)	71%	8%	4%	18%
Lewy body dementia (*n* = 84)				
Present (≥1)	0%	83%	15%	1%
Modest severity (≥12)	8%	49%	35%	8%
Significant (≥24)	24%	31%	23%	23%
Very significant (≥48)	70%	1%	4%	25%

The clinical course was coded into four different categories defined at different cut-offs (NPI total ≥1, ≥12, ≥24 and ≥48): no symptom, never having symptom; stable, symptom being present at all or three consecutive assessments; single episode, symptom only present at one assessment during follow-up; relapsing, symptoms present at two or more assessments but with resolution of symptom between assessments.

women and had a shorter duration of symptoms compared with the LBD group. We have previously reported a shorter survival time and more rapid disease progression in DLB.[18,19] The drug use in the cohort at inclusion was reported previously, and 14% had 'potentially inappropriate' and potentially severe drug–drug interactions.[20] These relatively low proportions indicate that the prescribing practice was acceptable.[20] At the first follow-up, 61% used antidementia drugs, 9% used antipsychotics and 40% used antidepressants.

NPI total course

Only one patient was without NPS, but the longitudinal course of the NPI total score varied considerably among patients. The proportion of patients having no, stable, relapsing or single episode courses of the different NPI total score categories are shown in Table 2. Most patients (80%) had stable NPS total (≥1), whereas 50% had stable modest (NPI total ≥12) and 25% stable significant (NPI total ≥24) NPI total scores. Only five patients (four with Alzheimer's disease) had year-to-next-year increase in the first three follow-up assessments, and only eleven (all with Alzheimer's disease) had four of five year-to-next-year increases. All of these patients had modest NPI total score (<24), and most scores were <12. A minor group of both patients with Alzheimer's disease and LBD (5%) experienced few episodes, and with only mild NPS (Fig. 1). Very severe symptoms (NPI total ≥48) were mostly single episodes, but 8% of patients with Alzheimer's disease had stable, very severe symptoms. Patients with LBD had mild and moderate NPS more often, but more rarely had severe and stable NPS (1%).

Course of individual NPS

The majority of patients had many single episodes or relapsing individual NPS. This is illustrated by the irregular spotted pattern shown on the heatmap (Fig. 1), best depicted by depression and anxiety. Some patients had complete symptom resolution late in the course, even in patients with severe symptoms. Relapsing or single episode patterns were more pronounced among the higher item scores (Supplementary Table 1). Apathy was the most stable symptom in both Alzheimer's disease and LBD groups, with 34 and 27% of patients having stable apathy, respectively. Anxiety and depression had relatively low persistency in both patients with Alzheimer's disease and LBD, i.e. 35% of patients with LBD (60% of symptomatic patients) had only a single episode of depression symptoms. Anxiety, irritability and aberrant motor behaviour were more common and relatively more stable in the Alzheimer's disease group, with 14, 18 and 27% having a stable course, respectively ((Table 3; χ^2 $P < 0.05$ compared with LBD).

With increasing NPI item scores, the number of patients having stable and relapsing courses significantly decreased, with an increase in single episodes (Supplementary Table 1). In Alzheimer's disease, the mean risk of having single episode increased from 31% (s.d. 12%) with NPI score ≥1 to 62% (s.d. 14%) with NPI score ≥8 (paired Student's *t*-test, $P \geq 0.001$). This effect was similar in LBD. In Alzheimer's disease, of the 496 NPI scores ≥8, 54% (270 of 496) were single episodes, similar to LBD at 43% (193 of 318, $P = 0.081$). There was a significant difference between groups in the course of patients scoring a maximum NPI item score of 12, with 72% (154 of 213) of patients with Alzheimer's disease having

Table 3 Clinical course of neuropsychiatric symptoms in Alzheimer's disease and Lewy body dementia

NPI item	Alzheimer's disease (*n* = 113)					Lewy body dementia (*n* = 84)				
	No *n*, (%)	Yes *n*, (%)	Stable	Relapsing	Single	No *n*, (%)	Yes *n*, (%)	Stable	Relapsing	Single
Delusions	59 (52)	54 (48)	11%	14%	23%	37 (44)	47 (56)	17%	9%	28%
Hallucinations	72 (64)	41 (36)	13%	4%	19%	26 (31)	58 (69)**	24%	14%	29%
Aggression	57 (51)	56 (49)	10%	17%	23%	49 (58)	35 (42)	12%	8%	21%
Depression	36 (32)	77 (68)	18%	24%	27%	33 (39)	51 (61)	10%	14%	35%
Anxiety	45 (40)	68 (60)	15%	18%	27%	50 (60)	34 (40)**	8%	8%	23%
Euphoria	94 (83)	19 (17)	2%	4%	11%	79 (94)	5 (6)	0%	0%	6%
Apathy	18 (16)	95 (84)	29%	39%	16%	13 (15)	71 (85)	34%	27%	22%
Disinhibition	50 (44)	63 (56)	18%	18%	20%	43 (51)	41 (49)	12%	16%	20%
Irritability	61 (54)	52 (46)	14%	10%	22%	65 (77)	19 (23)**	3%	8%	10%
Aberrant motor symptoms	31 (27)	82 (73)	27%	19%	27%	35 (42)	49 (58)*	15%	13%	29%
Appetite	53 (47)	60 (53)	17%	16%	20%	31 (37)	53 (63)	16%	17%	28%
Sleep	30 (27)	83 (73)	19%	23%	32%	34 (40)	50 (60)	8%	19%	31%

Symptoms assessed annually with the Neuropsychiatric Inventory (NPI). The clinical course was coded into four different categories defined in order: no symptom, never having symptom above set cut-off of ≥4; stable, symptom being present at all or three consecutive assessments; single episode, symptom only present at one assessment during follow-up; intermediary, symptoms present at two or more assessments but with resolution of symptom between.
Statistical test Alzheimer's disease versus Lewy body dementia: *$P < 0.05$ χ^2 test no/yes symptoms present, **$P < 0.001$ χ^2 test no/yes symptoms present.
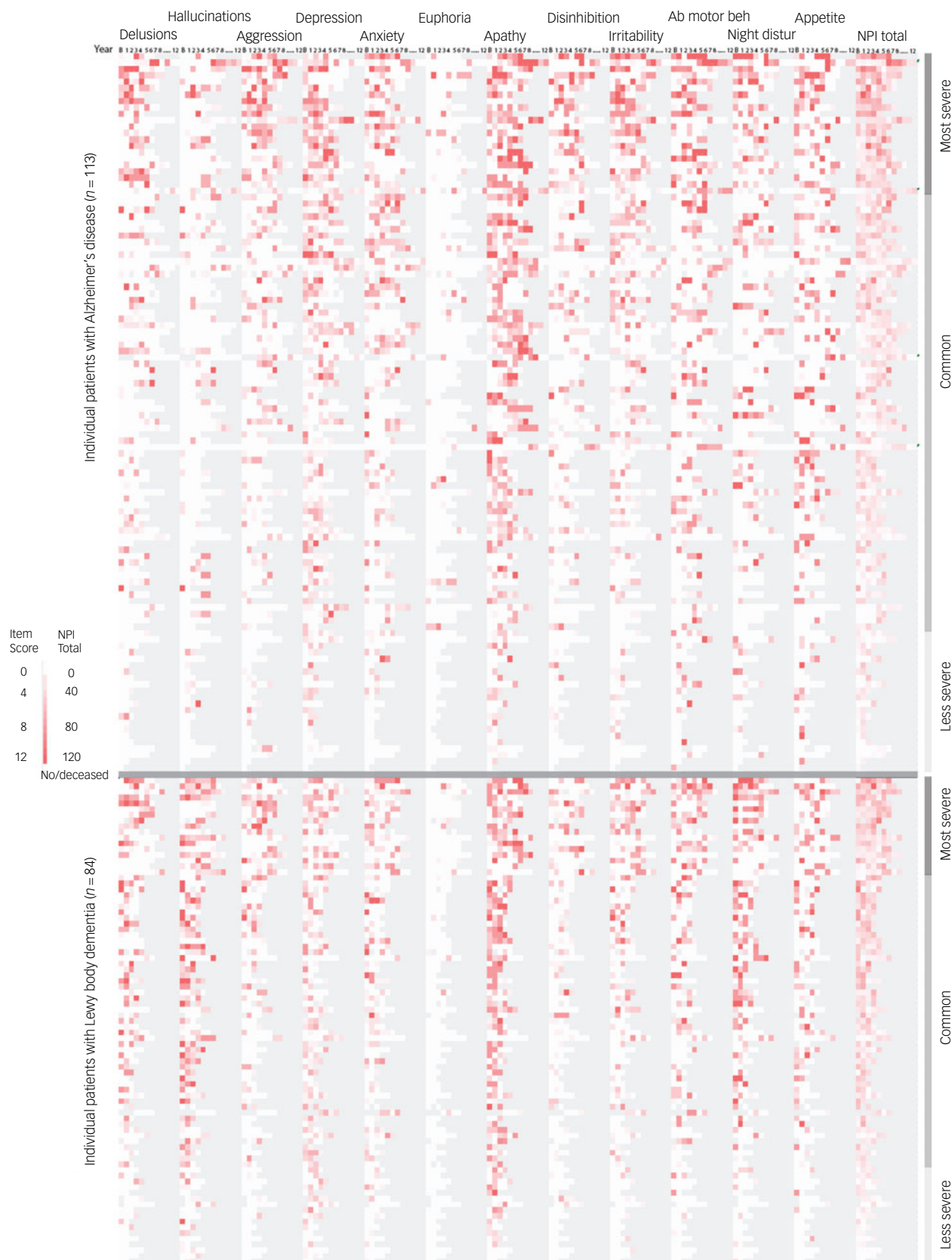
Fig. 1 Heatmap of Neuropsychiatric Inventory (NPI) scores at all assessments for Alzheimer's disease and Lewy body dementia sorted by NPI total score. All assessments are shown as a heatmap graded from 0 to 12 based on items score. The NPI total score is graded on the full scale, 0–144. Patient death and all missing data is shown in grey. The patients are sorted by diagnosis and highest cumulative NPI total score. To exemplify, the patient with Alzheimer's disease with the highest NPI total score (first case) died after seven follow-up assessments. He had mild delusions at baseline and more severe at years four and five (relapsing course), hallucination only at year five (single episode) and aggression from year three to seven (stable course). He also had a stable course of significant neuropsychiatric symptoms (NPI total score ≥24), but only relapsing very significant neuropsychiatric symptoms (NPI total score ≥48).

Ab motor beh, Aberrant motor behaviour; Night distur, Night time disturbances/sleep.

these as single episodes, compared to 83% (98 of 117) of patients with LBD (χ^2 $P = 0.032$).

Psychotic symptoms

Seventy-nine patients with LBD (94%) and 87 patients with Alzheimer's disease (77%) experienced at least one psychotic symptom (NPI ≥1 of delusions or hallucinations). In LBD, 83% had reoccurring psychotic symptoms, compared with 57% with psychosis in Alzheimer's disease. Clinically significant hallucinations (NPI ≥4) had a stable course in 24% in LBD but only 4% in Alzheimer's disease. Hallucinations usually occurred rather early in the course, but some patients with Alzheimer's disease developed late hallucinations (Fig. 1). The percentage of patients with LBD with a stable course of hallucinations decreased with increasing severity from 63% at NPI ≥1 to 36% at NPI ≥4 (see Supplementary Table 1 for more details). Forty-seven (55%) patients with LBD had significant delusions, half of which were single episodes, whereas relapsing course occurred in only seven. Unlike Alzheimer's disease, delusions were not associated with severe total NPS in LBD.

The most severe patient's course

Patients with Alzheimer's disease with the highest NPI total scores (22 patients, mean NPI total 38, s.d. 12, 163 observations) had more stable (55%) and relapsing (43%) course of four key symptoms: aberrant motor behaviour (wandering), aggression/agitation, delusions and irritability (abbreviated WADI). This was not seen in LBD to the same degree. The association between having all WADI symptoms stable or relapsing with high NPI total scores was high, with an odds ratio of 55 (s.d. 12.7–248.7, $P < 0.001$). Aberrant motor behaviour reoccurred in all 22 patients; delusions were present in 21 and reoccurring in 19. Generally for all patients, severe aggression (item score ≥8) reoccurred in 11 of 32 patients with Alzheimer's disease and severe aggression, but only two of 18 patients with LBD showed reoccurring severe aggression (item score ≥8, $P = 0.001$, Supplementary Table 1). Similarly, patients with Alzheimer's disease were more likely to have a stable course of irritability (Table 3, $P = 0.003$).

Discussion

We studied the individual course of NPS in a cohort of patients with LBD and Alzheimer's disease for up to 12 years. There were wide variations between patients, diagnoses and specific NPS. Nearly all patients had clinically significant NPS; single episodes represented the most common course, followed by a relapsing course, whereas a stable course was less common.

The finding that single and relapsing courses are common is in line with some earlier studies, but we found less stable symptoms than most comparable studies.[6,21] Methodological differences such as selection criteria, psychometric instruments, frequency of assessments and the duration of study make comparisons between studies difficult, but a more relapsing pattern of affective symptoms (not including apathy) is similar.[6] Few studies have assessed the long-term course of psychotic symptoms, but they are reported as either persistent or single episodes;[22] studies also report greater stability for hallucinations compared with delusions.[1,6,21] The lower stability of hallucinations seen in our cohort may be due to a longer follow-up and longer intervals between assessments. Differences between delusions and hallucinations in Alzheimer's disease are in line with genetic findings of delusions but not hallucinations being associated with schizophrenia risk genes.[23] Several studies show that cross-sectional NPI assessments can be statistically reduced to subsyndromes such as psychosis, hyperactivity and affective symptoms,

using principal component analysis or factor analysis. The NPI was not originally designed for this.[16] Longitudinal data have challenged the usefulness of such subsyndromes[4,24] because of the assumption that the NPI item scores are continuous and the data inflation of scores equal to 0. In line with this, we have shown a high degree of instability of symptoms when assessed longitudinally. The instability and the differences between assumed associated symptoms, like hallucination and delusions in recent studies, argue against clearly defined subsyndromes of NPS, and underline the importance of full psychiatric assessments in clinical practice and trials.

Interestingly, the reported association between WADI symptoms and high NPI total score included delusions but not hallucinations; we did not find a similar pattern for LBD. Other single symptoms studies report of wandering or aggressive resistance persistent over 1–2 years, but no study has reported such a long course or association between WADI symptoms and severe NPS. An effort to identify the subgroups of patients with Alzheimer's disease with persistent and severe NPS may improve both ordinary treatment and trials. Atrophy of the prefrontal cortex has been reported to be associated with the stability of NPS over 6 months, whereas amyloid angiopathy is associated with early and severe psychotic symptoms in diagnosed Alzheimer's disease.[25,26]

Few studies have analysed the course of symptoms in LBD compared with Alzheimer's disease, but a 1-year study found similar differences in hallucinations.[27] The differences between Alzheimer's disease and LBD in depression and aggression are in line with studies with shorter duration.[28] We included PDD in LBD, which could bias our results, but PDD is reported to have an NPS profile more like Alzheimer's disease than DLB.[29] We have previously shown that DLB is only associated with more frequent hallucination, delusions and apathy when controlling for the rate of cognitive decline and time.[5] Current data show that only hallucinations have more stable course in DLB, whereas anxiety, irritability and aberrant motor behaviour are less stable in DLB compared with Alzheimer's disease, but this may also be biased by shorter survival in the DLB group, which also had a slightly longer reported duration of symptoms before inclusion.

Important for dementia carers are the highly individual course of NPS, demonstrating the importance of personalised medicine. A majority of patients also experienced relapsing psychotic symptoms. These findings are important for clinicians because they suggest that although psychosocial strategies with low risk for adverse effects should always be considered for NPS first, they may also be unnecessary, particularly for more costly interventions of longer duration. The administration of antipsychotics or other psychotropic drugs with limited effect and low tolerability might not be necessary because NPS often tend to remit spontaneously. These findings are also important for the planning of trials for NPS, showing that spontaneous resolution is common and thus reducing the chances of finding significant drug effects.

Strengths and limitations

The strengths of the study include the long follow-up time and the very high completeness of data, except for attrition owing to death, which is a unique feature of this study. Patients were included at the time of diagnosis and most of them were followed until death. Unlike most previous studies, we report separately for Alzheimer's disease and LBD, with a systematic diagnostic evaluation during the study period and autopsy confirmation of a subgroup.

Limitations include the potential for referral bias because recruitment happened at specialist clinics, but general practitioners were invited to refer any patients with suspected dementia, and patients were included from psychiatric, neurologic and geriatric

clinics. We did not have full clinical description of the excluded and non-consenting patients. The interval between assessments was 1 year, and thus we do not know what happened between assessments. The informant to NPI (carer or family) changed over follow-up for most patients. Finally, we did not standardise drug and psychosocial management, which might have influenced the course. The restrictive use of psychotropics in the Demvest study is consistent with the most recent guidelines.

Audun Osland Vik-Mo (ID), PhD, MD, Senior Consultant, Centre for Age-Related Medicine (SESAM), Stavanger University Hospital; and Researcher, Department of Clinical Science, University of Bergen, Norway; **Lasse Melvaer Giil**, PhD, MD, Researcher, Department of Clinical Science, University of Bergen; and Resident, Department of Internal Medicine, Haraldsplass Deaconess Hospital, Norway; **Miguel Germán Borda**, MD, PhD student, Centre for Age-Related Medicine (SESAM); PhD student, Stavanger University Hospital; and Faculty of Health Sciences, University of Stavanger, Norway; **Clive Ballard**, PhD, MD, Professor, Pro-Vice Chancellor and Executive Dean, Institute for Health Research, University of Exeter Medical School, UK; **Dag Aarsland**, PhD, MD, Head of Research, Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, Norway; and Professor, Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

Correspondence: Audun Osland Vik-Mo, Centre for Age-Related Medicine (SESAM), Helse Stavanger, PB 8100, N-4068 Stavanger, Norway. Email: audun.osland.vik-mo@sus.no

First received 18 Mar 2019, final revision 29 May 2019, accepted 20 Jul 2019

Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2019.195.

Funding

Acknowledgements

References

1 van der Linde RM, Dening T, Stephan BC, Prina AM, Evans E, Brayne C. Longitudinal course of behavioural and psychological symptoms of dementia: systematic review. Br J Psychiatry 2016; 209(5): 366–77.

2 Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S, Patel N, et al. Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. Br J Psychiatry 2014; 205(6): 436–42.

3 Selbaek G, Engedal K, Bergh S. The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. J Am Med Dir Assoc 2013; 14(3): 161–9.

4 Haaksma ML, Leoutsakos JS, Bremer JAE, Aalten P, Ramakers I, Verhey FRJ, et al. The clinical course and interrelations of dementia related symptoms. Int Psychogeriatr 2018; 30(6): 859–66.

5 Vik-Mo AO, Giil LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. Int J Geriatr Psychiatry 2018; 33(10): 1361–9.

6 Hope T, Keene J, Fairburn CG, Jacoby R, McShane R. Natural history of behavioural changes and psychiatric symptoms in Alzheimer's disease. A longitudinal study. Br J Psychiatry 1999; 174: 39–44.

7 World Health Organization (WHO). ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision 2nd ed. WHO, 2004.

8 Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12(3): 189–98.

9 Aarsland D, Rongve A, Nore SP, Skogseth R, Skulstad S, Ehrt U, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. Dement Geriatr Cogn Disord 2008; 26(5): 445–52.

10 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134: 382–9.

11 Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, et al. Cerebral blood flow in dementia. Arch Neurol 1975; 32(9): 632–7.

12 Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989; 19(4): 1015–22.

13 Morris JC. Clinical Dementia Rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997; 9(Suppl 1): 173–6; discussion 7–8.

14 Skogseth RE, Hortobagyi T, Soennesyn H, Chwiszczuk L, Ffytche D, Rongve A, et al. Accuracy of clinical diagnosis of dementia with Lewy bodies versus neuropathology. J Alzheimers Dis 2017; 59(4): 1139–52.

15 Selbaek G, Kirkevold O, Sommer OH, Engedal K. The reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, nursing home version (NPI-NH). Int Psychogeriatr 2008; 20(2): 375–82.

16 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44(12): 2308–14.

17 Brodaty H, Connors MH, Xu J, Woodward M, Ames D. The course of neuropsychiatric symptoms in dementia: a 3-year longitudinal study. J Am Med Dir Assoc 2015; 16(5): 380–7.

18 Rongve A, Soennesyn H, Skogseth R, Oesterhus R, Hortobagyi T, Ballard C, et al. Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. BMJ Open 2016; 6(2): e010357.

19 Oesterhus R, Soennesyn H, Rongve A, Ballard C, Aarsland D, Vossius C. Long-term mortality in a cohort of home-dwelling elderly with mild Alzheimer's disease and Lewy body dementia. Dement Geriatr Cogn Disord 2014; 38(3–4): 161–9.

20 Oesterhus R, Aarsland D, Soennesyn H, Rongve A, Selbaek G, Kjosavik SR. Potentially inappropriate medications and drug-drug interactions in home-dwelling people with mild dementia. Int J Geriatr Psychiatry 2017; 32(2): 183–92.

21 Ballard CG, O'Brien JT, Swann AG, Thompson P, Neill D, McKeith IG. 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. J Clin Psychiatry 2001; 62(1): 46–9.

22 Ballard CG, Margallo-Lana M, Fossey J, Reichelt K, Myint P, Potkins D, et al. A 1-year follow-up study of behavioral and psychological symptoms in dementia among people in care environments. J Clin Psychiatry 2001; 62(8): 631–6.

23 Creese B, Vassos E, Bergh S, Athanasiu L, Johar I, Rongve A, et al. Association between schizophrenia polygenic score and psychotic symptoms in Alzheimer disease: meta-analysis of 11 cohort studies. bioRxiv 2019: 528802.

24 Connors MH, Seeher KM, Crawford J, Ames D, Woodward M, Brodaty H. The stability of neuropsychiatric subsyndromes in Alzheimer's disease. Alzheimers Dement 2018; 14(7): 880–8.

25 Poulin SP, Bergeron D, Dickerson BC. Risk factors, neuroanatomical correlates, and outcome of neuropsychiatric symptoms in Alzheimer's disease. J Alzheimers Dis 2017; 60(2): 483–93.

26 Vik-Mo AO, Bencze J, Ballard C, Hortobagyi T, Aarsland D. Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2019; 90: 728–30.

27 Ballard C, Bannister C, Graham C, Oyebode F, Wilcock G. Associations of psychotic symptoms in dementia sufferers. Br J Psychiatry 1995; 167(4): 537–40.

28 Kazui H, Yoshiyama K, Kanemoto H, Suzuki Y, Sato S, Hashimoto M, et al. Differences of behavioral and psychological symptoms of dementia in disease severity in four major dementias. PloS One 2016; 11(8): e0161092.

29 Chiu PY, Tsai CT, Chen PK, Chen WJ, Lai TJ. Neuropsychiatric symptoms in Parkinson's disease dementia are more similar to Alzheimer's disease than dementia with Lewy bodies: a case-control study. PloS One 2016; 11(4): e0153989.

EXTRA CONTENT ONLINE