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

Running title: Patient level 12-year neuropsychiatric profile

Audun Osland Vik-Mo [a,b]*, Lasse Melvaer Giil [a,d], Miguel Germán Borda [b,c], Clive Ballard [d], Dag Aarsland [b,e]

a Department of Clinical Science, University of Bergen, Norway

b Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, Stavanger, Norway

c Faculty of Health Sciences, University of Stavanger, Stavanger, Norway

c Department of Internal Medicine, Haraldsplass Deaconess Hospital, Bergen, Norway

d University of Exeter Medical school, United Kingdom

e Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

*Corresponding author:

Audun Osland Vik-Mo

audun.osland.vik-mo@sus.no

SESAM, Helse Stavanger, PB 8100, N-4068 Stavanger, Norway

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ABSTRACT

Introduction: Understanding the natural course of NPS in dementia is important for planning patient care and trial design, but few studies have described the long-term course of neuropsychiatric symptoms (NPS) in individual patients. We describe the course of NPS in patients with Alzheimer's disease (AD) and Lewy body dementia (LBD) from the time of diagnosis until death.

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

Results: 80% had stable NPI total ≥1, while 50% had stable modest NPI total ≥12 and 25% stable NPI total ≥24 NPI total scores. Very severe NPS (≥48) were mostly single episodes, but 8% of AD patients had stable severe NPS. The AD patients with the highest 20% NPI total scores had 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. 57% of AD and 84% of LBD patients had reoccurring psychotic symptoms.

Conclusion: We observed a highly individual course of NPS, with most NPS presenting as a single episode or relapsing, while 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.

INTRODUCTION

Neuropsychiatric symptoms (NPS) represent a common and important manifestation of the dementia syndrome, with major impact on quality of life, carer burden, and risk of institutionalisation (1, 2). While the non-pharmacological interventions are 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 (3).

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, 4, 5). 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 five-year study, we showed that although most NPS were common already from time of diagnosis, there were individual fluctuations, and thus the group with the symptom present consisted of different individual patients at different time points (6). In one of the longest studies to date, following patients for up to nine years, aggression was found to be persistent, whereas other NPS occurred as single discrete episode (7). Understanding the course of NPS in individual patients is important for precision medicine treatment approach and planning as well as for trial design (8). Here, we present the individual course for up to 12 years from the diagnosis of dementia to death in people with Alzheimer's disease (AD) and Lewy body dementia (LBD).

METHODS

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 outpatient clinics) in the region recruited to the study. To reduce referral bias the GPs in the area were contacted by letter prior to study start and 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), and 223 consented of 325 fulfilling inclusion criteria. 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 ICD 10 (9), defined as Mini Mental Status Examination (MMSE) score of at least 20 or a Clinical Dementia Rating-scale (CDR) global score = 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 which according to the clinician would significantly impact on cognition, function or study participation. The standardised diagnostic assessment is described in detail elsewhere (10). Briefly, physical, neurological, and psychiatric examinations were performed, including a detailed neuropsychological test battery, Montgomery-Aasberg depression rating scale (MADRS) routine blood and CSF analyses and brain MRI. Dopamine transporter SPECT scans were available for most patients with suspected dementia with Lewy bodies. Caregivers completed The Informant Questionnaire on Cognitive Decline in the Elderly (the IQCODE), a questionnaire shown to be a reliable and valid instrument to detect dementia, and the clinician completed the Clinician Dementia Rating scale (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 AD 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 AD and LBD (14). Patients were followed with annual structured assessments. The participating centres followed national guidelines on psychotropic use, offer dementia-carer support groups and practice patient-centred care and provided 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 done based on the best suited informants who had the most day-to-day contact with the patient. These were spouse, children or a at later controls professional caregiver. The 12 items were registered as present or not present during the last 4 weeks, and if present, scored according to their frequency (1-4) and severity (1-3). Here, we report the *frequency* X *severity* score for the individual items. We present data in Table 3 using the established cut-off item score of ≥4 as indicating clinical significance symptom, which includes moderately severe symptoms at frequency rating of ‘often’ or more frequently and ‘mild symptoms’ present ‘very frequent,’ as previously reported (17, 18). In addition, results for NPI item scores present (≥1), severe (≥8) or very severe (=12) are presented in supplements. For NPI total score the cut-offs were set and classified as ≥1 (present), ≥12 (modest severity), ≥24 (significant), and ≥48 (very significant) NPS (Table 2).

The clinical course was coded into four mutually exclusive categories defined in order: *No symptoms*: never having symptom above the relevant cut-off. *Stable*: Symptom being present at all or three consecutive assessments. *Relapsing*: Symptoms present at two or more assessments but with resolution of symptom between. *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 AD and LBD frequencies of symptoms (No/Yes, Table 3) and of clinical course were tested using the chi-squared test as contingency tables. All analysis was done in SPSS (version 13).

Ethics

The study was approved by the regional ethics committee (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 ADs, 84 LBDs (including 16 Parkinson's disease dementia). Ten patients were still alive in January 2018, all of them had completed 12 year follow-up. The mean duration of follow-up was 6.4 (SD 2.9) and 4.3 (SD 1.9) years for AD and LBD, respectively. There were 1080 possible assessments (living patient years), with a mean number of observations of 4.96 (SD 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 AD and LBD patients did not differ regarding age, education, or baseline MMSE score (Table 1), but the AD group included more females and had a shorter duration of symptoms compared to LBD. We have previously reported a shorter survival time and more rapid disease progression in DLB (19, 20). The drug use in the cohort at inclusion was reported previously (Østerhus), and 14% had potentially inappropriate medications and 4 % potentially severe drug–drug interactions, indicating that the prescribing quality was acceptable (Østerhus et al). 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), while 50% had stable modest (NPI total ≥12) and 25% stable significant (NPI total ≥ 24) NPI total scores. Few patient experienced a stable increase in symptoms, only 5 patients (4 with AD) had year-to-next-year increase in the first three follow-ups, and only 11 (all AD) had 4 of 5 year-to-next-year increases. All of these patients had modest NPI total score (<24), and most scores were below 12. A minor group of both AD and LBD patients (5%) experienced few episodes with only mild NPS (Figure 1). Very severe symptoms (NPI Total ≥48) were mostly single episodes, but 8% of AD patients had stable very severe symptoms. LBD patients had mild and moderate NPS more often, but more rarely severe and stable NPS (1%).

Course of individual neuropsychiatric symptoms

The majority of patients had many single episodes or relapsing individual NPS. This is illustrated by the irregular spotted pattern shown on the heat map (Figure 1), best depicted with 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 (Digital supplement). Apathy was the most stable symptom in both AD and LBD with 34% and 27% of patients having stable apathy, respectively. Anxiety and depression had relatively low persistency in both AD and LBD, i.e. 35% of LBD patients (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 AD with 14%, 18%, and 27% having a stable course, respectively (Table 3, chi-squared, $p<0.05$ compared to LBD).

With increasing NPI item scores, the number of patients having stable and relapsing courses significantly decreased, with an increase in single episodes (digital supplement). In AD, the mean risk of having single episode increased from 31% (SD 12%) with NPI score ≥1 of to 62% (SD 14%) with NPI score ≥8 (paired Student's t-test, p≥0,001). This effect was similar in LBD. Of the 496 NPI scores ≥8 in AD as much as only 54% (270 of 496) were single episodes, similarly to LBD 43% (193 of 318, $p=0.081$). There was significant difference in patients scoring a maximum NPI score of 12, with AD 72% (154 of 213) and LBD 83% (98 of 117) having single episodes (chi-squared, $p=0.032$).

Psychotic symptoms

Seventy-nine LBD (94%) and 87 AD (77%) patients experienced at least one psychotic symptom (NPI ≥1 of delusions or hallucinations). In LBD, 83% had reoccurring psychotic symptoms, compared to 57% of AD patients with psychosis. Clinically significant hallucinations (NPI≥4) had a stable course in 24% in LBD and only 4% of AD patients. Hallucinations usually occurred rather early in the course, but some AD patients developed late hallucinations (Figure 1). The percentage of LBD

patients with a stable course of hallucinations decreased with increasing severity from 63% at NPI≥1 to 36% at NPI≥4 (see the digital supplements for more details). Forty-seven (55%) LBD patients had significant delusions, half of which were single episodes, while relapsing course occurred in only 7 LBD patients. Unlike AD, delusions were not associated with severe total NPS in LBD.

The most severe patient's course

The AD patients with the highest NPI total scores (22 patients mean NPI total 38, SD 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 the WADI-symptoms stable or relapsing with high NPI total scores was high with an odds ratio of 55 (SD 12.7-248.7, $p<0.001$). Aberrant motor behaviour reoccurred in all and delusions were present in 21 and reoccurring in 19 of the 22 AD patients with highest total NPI scores. Generally for all patients, severe aggression (item score ≥8) reoccurred in 11 of 32 AD patients with, but only 2 of 18 LBD patients showed severe aggression (item score ≥8, $p=0.001$, digital supplements). Similarly, patients with AD 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 LBD and AD patients for up to 12 years. There were wide variations between patients, diagnoses, and specific NPS. Nearly all patients had clinically significant NPS, and single episodes represented the most common course, followed by a relapsing course, while a stable course was less common. ~~These findings are important for clinicians, since it suggests that psychotropic drugs, with questionable effect and high risk of adverse events, should be limited in this group due to high likelihood of spontaneous remission. In addition, whereas psychosocial strategies have low risk for adverse effects and should always be considered for NPS first, they may also be unnecessary, at least over long term. The administration of antipsychotics or other psychotropic drugs with limited effect and low tolerability might not be necessary, since 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.~~

The finding that single and relapsing courses are common is in line with some earlier studies, but we found less stable symptomatology than most comparable studies (7, 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 (7). 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 to delusions (1, 7, 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 AD 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 symptoms 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 [ref Cummings]. Longitudinal data have challenged the usefulness of such subsyndromes (Haaksma + Connors), including the theoretical background regarding both the assumption of the NPI item scores as continuous and the data inflation of scores equal to 0. In line with their findings, we have also 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 subsydromes of NPS, but rather the importance of full psychiatric assessments in both clinical management 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 one to two years, but no study has reported such a long course or constellation between symptoms. An effort to identify the subgroups of AD patients with persistent and severe NPS may improve both ordinary treatment and trials. ~~Studies have also raised the possibility of biomarkers such as a~~Atrophy of the prefrontal cortex~~, which~~ has been reported to be associated with the stability of NPS over 6 months, while amyloid angiopathy is associated with early and severe psychotic symptoms in diagnosed AD (24, 25).

Few studies have analysed the course of symptoms in LBD compared to AD, but a one-year study found similar differences in hallucinations (26). In current cohort the rate of cognitive decline was associated higher NPI total score and several NPI items, but only the frequency of apathy increased significantly with time, and only for AD (ref). Patients with LBD had higher NPI total score and more hallucinations than AD patients. The differences between AD and LBD in depression and aggression are in line with studies with shorter duration (27, 28). We included PDD in LBD, which could bias our results, but PDD is reported to have an NPS profile more like AD than DLB (29).

Important for dementia carers, the highly individual course of NPS most often presenting as a single episode or relapsing symptoms demonstrate the importance of personalized medicine. A majority of patients also experienced relapsing psychotic symptoms. These findings are important for clinicians, since it suggests that psychotropic drugs, with questionable effect and high risk of adverse events, should be limited in this group due to high likelihood of spontaneous remission. In addition, whereas

psychosocial strategies have low risk for adverse effects and should always be considered for NPS first, they may also be unnecessary, at least over long term. The administration of antipsychotics or other psychotropic drugs with limited effect and low tolerability might not be necessary, since 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 due 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 AD and LBD, with a systematic diagnostic evaluation during the study period and autopsy confirmation of a subgroup.

Limitations include the potential for referral bias since recruitment happened at specialist clinics, but GPs 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 one 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.

AUTHOR CONTRIBUTIONS

AOVM, DA, LMG and MGB performed study and analysed data. AOVM, DA, LMG, MGB and CB drafted and revised the manuscript.

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CONFLICT OF INTEREST

Audun Vik-Mo , Lasse Giil and Miguel G. Borda declare that they have no conflict of interest. Clive Ballard has received grants and personal fees from Acadia and Lundbeck and personal fees from Heptares, Roche, Lilly, Otsuka, Orion, GSK, and Pfizer. Dag Aarsland has received research support

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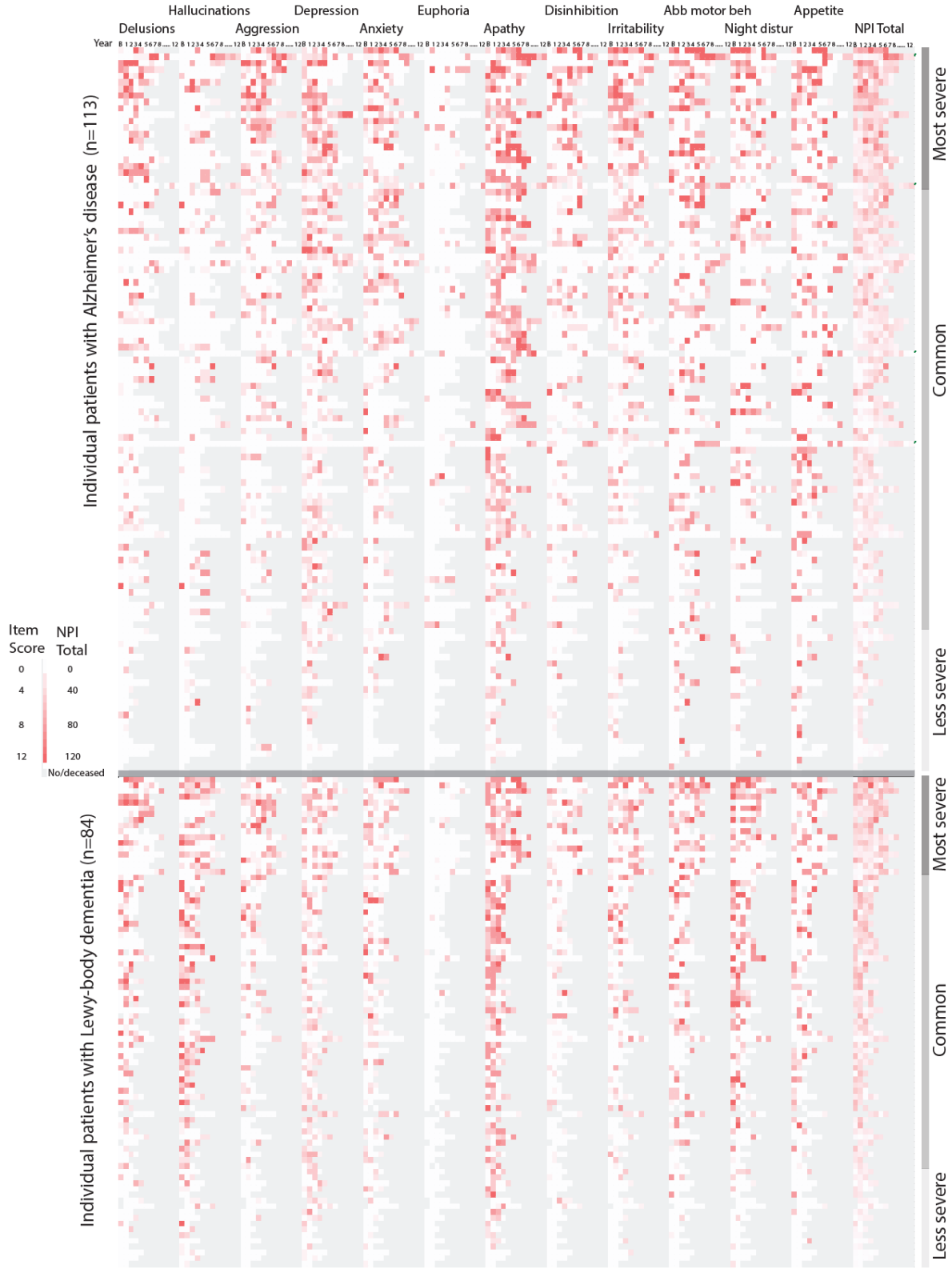
Figure 1: Heatmap of Neuropsychiatric Inventory (NPI) scores at all assessments for Alzheimer's disease and Lewy body dementia sorted by NPI total score



All assessments are shown in Figure 1 as a heatmap graded from 0-12 based in items score. The NPI total score is graded on the full scale 0-144. Patient's death and all missing data is shown as grey. The patients are sorted by diagnosis and highest cumulative NPI total score (Fig 1). To exemplify, the AD patient with the highest NPI total scores (first case) died after 7 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 NPS (NPI total ≥24), while only relapsing very significant NPS (NPI total≥48).

Table 1: *Clinical and demographic variables*

	AD (n=113)		LBD (n=84)		t/z†‡	P
Age (mean, *SD*) †	75.2	*7.7*	75.2	*6.9*	*0.05*	*0.957*
Male/Female ‡	32/81		45/39		*-3.97*	*<0.001*
Years of education (mean, *SD*) †	9.7	*3.0*	9.6	*2.8*	*-0.22*	*0.826*
Years of symptoms (mean, *SD*) †	1.9	*1.8*	2.7	*2.1*	*-2.73*	*0.007*
CIRS (mean, SD) †	5.3	*2.3*	6.6	*2.6*	*-3.3*	*0.001*
CDR-SB (mean, SD) †	4.8	*2.1*	5.8	*2.8*	*2.5*	*0.012*
MMSE score (mean, *SD*) †	23.7	*2.3*	23.8	*3.2*	*-0.28*	*0.774*
Time from inclusion to death†	6.4	*2.9*	4.3	*1.9*	*4.1*	*<0.001*
Nursing home admissions (n) ‡	73		51		*0.31*	*0.576*
Years to Nursing home (mean, SD) †	2.8	*1.5*	1.7	*1.2*	*5.5*	*<0.001*

AD; Alzheimer's disease

LBD; Lewy body dementia

SD; standard deviation

CIRS; Cumulative Illness Rating Scale

CDR-SB; Clinical dementia rating scale sum of boxes

MMSE; Mini Mental State Examination

t/z; Standard score test statistics

† Mann-Witney/ Students t-test showing t-score for AD and LBD

‡ Pearsons chi-square test, showing z-score for AD 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-off (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.