

Dementia with Lewy Bodies

Identification, frequency and sleep- disturbances

A cross-sectional clinical dementia cohort study

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Scientific environment

This thesis was conducted during the years 2007 to 2010 at the Section for Old Age Psychiatry and the Section for Mental Health Research, Department of Psychiatry, Haugesund Hospital, Helse-Fonna HF, Haugesund, Norway under supervision from Stavanger Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway. Abroad experiences were sought and found at the Clinical Aging Research Unit and Wolfson Research Centre, Institute for Aging and Health, Campus for Aging and Vitality, Newcastle University, Newcastle upon Tyne, UK.

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Abbreviations

AChEI	Acetylcholine esterase inhibitor
α S	Alpha-synuclein
AD	Alzheimer's disease
CDR	Clinical dementia rating scale
CI	Confidence interval
CIT-SPECT	^{123}I -2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I -FP-CIT) Single photon emission computed tomography
CVLT-2	California verbal learning test-2
DaTSCAN	Dopamine transporter scan
DemVest-study	The Dementia Study of Western Norway
DLB	Dementia with Lewy Bodies
DSM-IV	Diagnostic and statistical manual, 4 th edition
EDS	Excessive daytime sleepiness
EPS	Extra pyramidal symptoms
ESS	Epworth sleepiness scale
FTD	Frontotemporal dementia
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
MADRS	Montgomery-Asberg Depression Rating Scale
MMSE	Mini mental status examination
MSQ	Mayo Sleep Questionnaire
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Diseases and Stroke-Association Internasjonale pour la Recherche et L'Enseignement en Neurosciences

NPI	Neuropsychiatric Inventory
OSA	Obstructive Sleep Apnea
LBD	Lewy Body Disease
MRI	Magnetic Resonance Imaging
PLMS	Periodic leg movements during sleep
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PSG	Polysomnography
RBD	REM sleep behaviour disorder
RCT	Randomized Controlled Trial
RBDQ-HK	13 item self reported RBD questionnaire
RDRS-2	Rapid Disability Rating Scale-2
RLS	Restless legs syndrome
SD	Standard deviation
SPECT	Single photon emission computed tomography
SRLC	Sleep related leg cramps
STMS	Kokmen Short Test of Mental Status
SNCA	α -synuclein gene
SPSS	Statistical package for the social sciences
SW	Sleep walking
UPDRS	Unified Parkinson's disease Rating Scale
VaD	Vascular dementia
VOSP	Visual Object and Space Perception Battery

Abstract

Background

Dementia with Lewy Bodies (DLB) has existed as a formal consensus diagnosis since 1996 and is defined by dementia and the core features parkinsonism, visual hallucinations and cognitive fluctuations. The original consensus criteria had low sensitivity (20-60%) although the specificity was satisfying. (80-100%) From 2005 the additional suggestive features rapid eye movement (REM) sleep behaviour disorder (RBD), low uptake on Dopamine Transporter Scan (DaTSCAN) and neuroleptic sensitivity have been included to improve sensitivity of the clinical diagnosis. The nosological status of DLB is still discussed, and the frequencies of DLB, and of RBD and other sleep disturbances in DLB, are not known.

Objectives

In our first paper we sought to find the frequency of DLB in the Dementia Study of Western Norway, (The DemVest-Study) applying the revised clinical diagnostic DLB-criteria. We compared the frequency of DLB in our cohort applying both the new revised and the original consensus criteria for diagnosing DLB to find if the new criteria are more sensitive.

In the second paper we compared the frequency of sleep disturbances in Lewy Body Dementia (LBD) as compared to Alzheimer's Dementia (AD) and healthy controls.

In the third paper we examined how the core and suggestive features of DLB were distributed among all individuals with mild dementia to find empirical support for diagnosing DLB as an own diagnostic entity and to find cut- off values for core and suggestive features designating DLB.

Methods

All referrals to 5 specialists out patient clinics doing dementia work up in Western Norway were screened during a 2 year inclusion period. Particular care was taken to screen all included patients for the core and suggestive features of DLB. We offered inclusion to everybody presenting with a first time diagnosis of mild dementia with a MMSE score ≥ 20 . Exclusion criteria were normal cognition or mild cognitive impairment, severe dementia, organic or functional psychosis and a diagnosis of severe or terminal physical illness.

For the first paper dementia was diagnosed according to DSM-IV criteria and DLB according to both the 1996 and 2005 criteria. For the second paper we applied the Mayo Sleep Questionnaire (MSQ) and the Neuropsychiatric Inventory (NPI) to screen for sleep disturbances. Healthy elderly subjects from the Mayo Clinic Study of Aging were available for comparison.

In the third paper we used a two step cluster analysis to classify persons with mild dementia according to continuous scores on scales for the DLB symptoms; hallucinations, fluctuations, parkinsonism and RBD.

Results

196 subjects were included in the first paper and of these 20 % had DLB according to the revised consensus criteria. We compared the 1996 criteria to the 2005 criteria and found a 25% increase in patients fulfilling the probable DLB category with the new criteria. The proportion with DLB did not differ according to age bands and dementia severity. (CDR)

In the second paper 155 patients with mild dementia who had a caregiver who was also their bed-partner and 420 age matched controls without dementia were included. Participants with Lewy Body Dementia, i.e. DLB and PDD combined, had significantly more sleep disturbances than those with AD (89% vs. 64%, $p=0.008$)

particularly regarding RBD. (39% vs. 9%, $p < 0.0005$) Having any sleep disturbance correlated with both anxiety ($p = 0.02$) and depression. ($p = 0.03$)

In the third paper we included 139 persons with mild dementia who had a complete data set for hallucinations, parkinsonism, fluctuations and RBD. Four clusters were identified, one containing persons with high scores on scales for hallucinations, fluctuations and motor parkinsonism (the “LBD-cluster”). A distinct cognitive profile was found for this cluster, with more marked visuospatial deficits. The three other clusters included subjects with very mild or no DLB symptoms (“non LBD-cluster”) and two cluster with pronounced RBD or Visual hallucinations. (VH) Cut-off scores on scales for the DLB symptoms were suggested based on the scores in the four clusters.

Conclusions

DLB is the second most frequent primary dementia in specialist out patients’ clinics in Western Norway and accounts for 20% of the mild dementia population in this setting. The revised clinical diagnostic criteria have increased sensitivity as compared to the original criteria. LBD patients have significantly more sleep disturbances as compared to AD supporting the incorporation of RBD in the clinical diagnostic criteria for DLB. Sleep disturbances in mild dementia is related to anxiety and depression underlining their clinical importance. The core and suggestive features of DLB cluster in our sample of persons with mild dementia, thereby supporting the validity of DLB as a distinct diagnostic entity. The differentiation of DLB from other types of mild dementias can be made according to suggested cut-off values on scales for the core and suggestive DLB features

List of publications

1. Aarsland D, Rongve A, Nore SP, Skogseth R, Skulstad S, Ehrt U, Hoprekstad D, Ballard C: Frequency and case identification of dementia with lewy bodies using the revised consensus criteria. *Dement Geriatr Cogn Disord* 2008;26:445-452.
2. Rongve A, Boeve BF, Aarsland D: Frequency and correlates of caregiver-reported sleep disturbances in a sample of persons with early dementia. *J Am Geriatr Soc* 2010;58:480-486.
3. Rongve A, Bronnick K, Ballard C, Aarsland D: Core and suggestive symptoms of dementia with lewy bodies cluster in persons with mild dementia. *Dement Geriatr Cogn Disord* 2010;29:317-324.

List of other publications

1. Rongve A, Aarsland D, Ballard C. Current perspectives in dementia with Lewy bodies. *Aging Health* 2006;Vol. 2:461-472. Review.
2. Rongve A, Aarsland D: Management of Parkinson's disease dementia: Practical considerations. *Drugs & Aging*. 2006;23(10):807-22. Review.
3. Skogseth R, Mulugeta E, Ballard C, Rongve A, Nore S, Alves G and Aarsland D. Neuropsychiatric correlates of CSF biomarkers in Alzheimer's disease; *Dement Geriatr Cogn Disord* 2008;25:559-563
4. Biringer E, Rongve A and Lund A: A Review of Modern Antidepressants' Effects on Neurocognitive Function; *Current Psychiatry Reviews* 2009;5:164-174
5. Sonnesyn H, Nilsen DW, Rongve A, Nore S, Ballard C, Tysnes OB, Aarsland D: High prevalence of orthostatic hypotension in mild dementia. *Dement Geriatr Cogn Disord* 2009;28:307-313.

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General introduction

This thesis is based on the baseline data from the Dementia Study of Western Norway, (the Dem-Vest study) a clinical dementia cohort study, and consists of 3 published papers and this summary. The focus has been on Dementia with Lewy bodies (DLB). The literature review constituting the first part of the summary is based on publications registered in the PubMed database. For the chapter on the frequency of DLB we tried to include all publications available, otherwise we choose the most recent or relevant citations.

Background

The aging of the population is reaching the shores of the world as we speak and has become a major concern for politicians worldwide due to the dramatic increases in costs for the care of the elderly. In the western developed world the elderly population is growing fast and the oldest age group (85+) is the fastest growing.(WHO, 2010) Statistics Norway has estimated that this effect will kick in at full speed during the next decades as today 617000 persons 67 years or older are living in our country and in 2060 the number will have increased to 1.5millions. The most common causes of dementia are AD, DLB and Vascular Dementia.(VaD) In Norway it is estimated that at present about 60000 - 70000 people have dementia and the number is expected to rise to 94000 in 2030 and to 142000 in 2050.(Hjort & Waaler, 2010) As still no cure is available the expenses due to dementia in the society will increase dramatically. Dementia is already regarded more expensive to society than all cancer and heart disease together.(Reuters, 2010) Societal expenses in dementia are mainly due to long term admissions to nursing homes. The Western societies are now facing the start of

these challenges concerning increasing costs and lack of manpower to care for persons with dementia.

The most frequent neurodegenerative conditions are Alzheimer's Disease (AD), Dementia with Lewy bodies (DLB) and Parkinson's Disease. (PD) These three diagnoses can both clinically and pathologically be viewed as existing on a continuum or alternatively as overlapping categories. Dementia with Lewy Bodies (DLB) is part of a group of neurodegenerative disorders termed the α -synucleinopathies. (table 1) These are characterized neuropathologically by eosinophilic intraneuronal Lewy bodies composed of mainly α -synuclein and ubiquitin located in affected areas of the central and peripheral nervous system. They include disorders like Parkinson's disease and Multiple System Atrophy. (Galvin, Lee, & Trojanowski, 2001) Recently published studies from Swedish colleagues found that persons with DLB have more impaired quality of life and use more resources as compared to persons with AD, thus underlining the clinical importance of the condition. (Bostrom, Jonsson, Minthon, & Londos, 2006, 2007)

Table 1 The α -synucleinopathies

Name	Characteristic features
Lewy Body Dementia	Parkinsonism, visual hallucinations, fluctuations and RBD
Parkinson's Disease	Tremor, rigidity, akinesia and gait disturbance
Parkinson's Disease Dementia	Dementia developed after more than 1 year of motor symptoms
Multiple System Atrophy	Autonomic dysfunction, parkinsonism and ataxia
Idiopathic REM sleep behaviour Disorder	Acting out dream content during REM sleep
Pure autonomic failure	Orthostatic hypotension, constipation, sweating and impotence

Historical background

Fritz Heinrich Lewy (1885-1950) discovered what was later named “Lewy bodies” during his research on parkinsonism in 1912. The designation Lewy body was suggested by Tretiakoff in his thesis from 1919. In 1923 Lewy published his monograph concerning 43 patients with parkinsonism of which 21 were demented. (Alafuzoff, et al., 2009; Rodrigues, et al. 2010) The recognition of Dementia with Lewy Bodies (DLB) as an independent neurodegenerative entity grew after Okazaki described two clinical cases with dementia, disorientation, hallucinations and profound motor symptoms with rapid progression. The autopsy confirmed the presence of cortical Lewy bodies which morphologically were indistinguishable from those seen in the brains of PD patients. Lewy bodies were distributed widely in the cortical areas. Senile plaques and tangles were not observed and as such distinguished these cases from AD. (Okazaki, Lipkin, & Aronson, 1961) These results were first presented in 1958 and linked cortical Lewy bodies and dementia. In 1976-1980 several series of clinical case studies were published from Japanese groups and in 1984 Kosaka et al. proposed the name diffuse Lewy Body disease. (Kosaka, Yoshimura, Ikeda, & Budka, 1984)

The triad of dementia and parkinsonism and psychosis was from the start considered the core syndrome. Later fluctuating confusion, frequent falls, neuroleptic sensitivity and syncope were added. Cognitive deficits that differed from AD were described i.e. relatively more pronounced impairment of attention and executive and visuospatial functions compared to less severe memory impairment. The significance of the underlying pathology was controversial regarding the relative contribution from Lewy body pathology and AD pathology with plaques and tangles and this was reflected in the diverse nomenclature applied for this condition before the consensus criteria were first published in 1996. In 1998 Spillantini et al. published their paper stating that alpha-synuclein (α S) is the main constituent of Lewy bodies, designating a new group of neurodegenerative disorders named the α -synucleinopathies. (Spillantini, Crowther, Jakes, Hasegawa, & Goedert, 1998)

Nomenclature and clinical diagnostic criteria for DLB

Uncertainty regarding the contribution of underlying pathology to the clinical picture resulted in different groups publishing different names for the same disorder. Some groups regarded the cortical Lewy Bodies as the major contributor to the clinical picture and designed names like Diffuse Lewy Body Disease,(Kosaka, et al., 1984) Dementia with cerebral Lewy bodies(Eggertson & Sima, 1986) or Senile dementia of Lewy body type.(Perry, Irving, Blessed, Fairbairn, & Perry, 1990) The importance of AD pathology was stressed by other groups suggesting names like Alzheimer's disease with Parkinson's disease changes,(Ditter & Mirra, 1987) Alzheimer disease with incidental Lewy bodies(Joachim, Morris, & Selkoe, 1988) and Lewy Body variant of Alzheimer's disease.(Hansen, et al., 1990)

In 1991 The Nottingham group first proposed their clinical diagnostic criteria for what later became DLB (Byrne, Lennox, Godwin-Austen, Lowe, & Mayer, 1991) and later the Newcastle group published their criteria in 1992.(I. G. McKeith, Perry, Fairbairn, Jabeen, & Perry, 1992) In 1995 the DLB consortium developed the first consensus criteria for a clinical diagnosis of DLB(I. G. McKeith, et al., 1996) characterized by dementia accompanied by the "core" features fluctuating cognition and consciousness, spontaneous features of parkinsonism and visual hallucinations, with additional "supporting" features like frequent falls, syncope, transient loss of consciousness, systematized delusions and severe sensitivity to treatment with antipsychotic drugs. The criteria have been validated and later updated, and in the revised version of the international consensus criteria from 2005 "suggestive" features like RBD and a positive CIT-SPECT or PET scan and neuroleptic sensitivity were added, see appendix for criteria.(I. G. McKeith, et al., 2005)

Clinical differential diagnosis

Being the two most common forms of primary degenerative dementia DLB and AD can clinically sometimes be hard to reliably differentiate. The clinical diagnosis of DLB is based on the clinical interview with the person with dementia and the caregiver plus a clinical examination and a set of cognitive tests. Supplemental tests include Magnetic Resonance Imaging (MRI) to exclude other intracranial pathology and DaTSCAN to confirm the diagnosis. To make a reliable DLB diagnosis the clinician will have to screen for both core, suggestive and supportive features of the disease. A cognitive profile with executive and visuospatial impairment and preserved memory and language can aid in the differential diagnosis between DLB and AD as can results from the CSF analysis, MRI scan and in particular DaTSCAN as described in the proposed new and updated diagnostic research criteria for AD (Dubois, et al., 2007) and the revised DLB criteria. (I. G. McKeith, et al., 2005)

DLB can be differentiated from Parkinsons Disease Dementia (PDD) based on the 1 year rule, i.e. in DLB motor symptoms can start before, i.e. up to one year before dementia. If motor parkinsonian symptoms started more than 1 year before dementia the condition will be diagnosed as PDD. Clinicians will often find it difficult to determine the exact starting time of the different cognitive and neuropsychiatric symptoms as compared to motor symptoms.

Vascular Dementia (VaD) and Frontotemporal Dementia (FTD) can in most cases be differentiated from DLB based on the clinical interview and examination and supplemental tests like MRI and a SPECT-scan. Vascular parkinsonism due to vascular damage in the basal ganglia can be difficult to differentiate from parkinsonism in PD, PDD and DLB, although a MRI scan can contribute. When diagnosing DLB clinically the clinician needs to have other less frequent conditions like the Parkinson plus syndromes in mind:

Progressive Supranuclear Palsy (PSP) is a tauopathy, characterized by axial parkinsonism, early tendency to fall backwards and impaired vertical eye movements. PSP can be complicated by subcortical dementia and is sometimes hard to differentiate

from another tauopathy, namely frontotemporal dementia (FTD). Corticobasal degeneration (CBD) is a rare tauopathy characterized by more severe motor impairment with apraxia and agnosia with poor response to L-DOPA. Multiple system atrophy (MSA), another α -synucleinopathy, is characterized clinically by the early development of ataxia, autonomic failure and symmetrical parkinsonism with rigidity and bradykinesia without tremor. Patients have poor response to L-dopa treatment and poor prognosis. MRI can in many cases inform the clinical diagnosis. In frail elderly people symptoms like parkinsonism and impaired cognition can be caused by neuroleptic medication and thus a drug history must be taken in the diagnostic process.

Epidemiology

Dementia with Lewy bodies (DLB) was first considered to be a rare condition. Now most authors agree that DLB is the second most common form of neurodegenerative dementia comprising 15-20% of the primary degenerative dementias. The revised clinical diagnostic criteria from 2005 have not yet been applied in any population based or clinical epidemiological study.

In previous clinical and population based dementia-cohort studies applying the original criteria from 1996 the reported proportion with DLB ranges from 0% to 30.5%. (Rongve, Aarsland, & Ballard, 2006; Zaccari, McCracken, & Brayne, 2005; Aarsland, et al., 2008) (See table 1&2 in the Appendix for a complete overview of studies) Few population based epidemiological findings have been published and only two studies present follow up data with pathological verification of the diagnosis. (Matsui, et al., 2009; Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS, 2001) More recently a community based survey from Japan, the Hisayama Study, was presented finding DLB in 10.6 % of cases in neuropathologically confirmed cases and pure DLB neuropathologically in 4.4% of the dementia cases, and thus

confirming previous findings that DLB might be less and VaD more prevalent in Asian countries as compared to Western countries. The frequency of pure VaD in this study was 29.5%.(Matsui, et al., 2009)

The Islington Community Study of Dementia from North London UK found a high prevalence of dementia of 9.86% in the age group of 65 years and older with 9.7% of this dementia cohort having probable DLB and 30.5% possible or probable DLB combined.(Stevens, et al., 2002) Diagnosis was based on a validated screening instrument of dementia and an unstructured interview of a caregiver. A diagnosis of DLB was made only if the patient had progressive dementia with prominent visual hallucinations and either fluctuating cognition or spontaneous features of parkinsonism and thus patients with DLB without hallucinations were not included. On the other hand they did not limit the duration of parkinsonism before onset of dementia to a maximum of one year and therefore might have included also patients with Parkinson Disease Dementia (PDD).(Stevens, et al., 2002) A health survey in the Kupio area in Finland of people 75 years and older found a dementia prevalence of 22% in their screened population. The proportion of DLB was 21.9% in this dementia cohort. This study used a structured clinical interview and examination. They collected information from carers but did not use a structured interview for this purpose and did not use instruments to detect and measure parkinsonism, fluctuating cognition, visual hallucinations and RBD.(Rahkonen, et al., 2003)

These two studies, the Islington and Kuopio studies, provide the best estimate of the prevalence of DLB in the general population published this far and suggest that DLB accounts for about 10-22% of the dementias in the 65+ age group thus indicating that about 1% of the population over 65 years suffer from DLB. Other population based studies performed with less stringent methods have found lower prevalence of DLB, see table 1 & 2 in Appendix.(de Silva, Gunatilake, & Smith, 2003; Herrera, Caramelli, Silveira, & Nitrini, 2002; Haan, et al., 2003; Yamada, Hattori, Miura, Tanabe, & Yamori, 2001; Yamada, et al., 2002; Zaccai, et al., 2005)

Only four incidence studies exist and report the incidence of DLB to lie between 0.7-1.4 new cases for every 1000 persons per year. (de Lau, et al., 2004; Matsui, et al., 2009) (Table 3 Appendix) In summary, only two community based epidemiological studies have specifically focused on the prevalence of DLB. None have applied the revised clinical criteria and applied specific instruments to detect core and suggestive features. Therefore the prevalence of DLB according to the latest criteria is not known.

Molecular pathology

The Lewy body diseases share aggregation of alpha-Synuclein (α S) and formation of Lewy bodies as their common hallmarks of pathology. The normal structure and function of α S is not well known although it is believed to be involved in synaptic plasticity. Norwegian researchers have recently shed some light on possible pathogenic mechanisms finding in a mouse model that increased expression of α S will inhibit synaptic reclustering after neurotransmitter release and thus inhibit neurotransmitter release in the synaptic cleft. (Nemani, et al. 2010) Pathological phosphorylation and aggregation into toxic oligomers and pathological spread of oligomers from one neuron to adjacent neurons has been suggested as a possible mechanism for spreading the α S-pathology within the CNS. (Danzer, Krebs, Wolff, Birk, & Hengerer, 2009) It has been shown that α S produced intracellularly can be excreted in the extracellular space in a calcium dependent way and that extracellular α S can decrease cell viability and amplify and propagate the Lewy related pathology. (Emmanouilidou, et al. 2010)

Lewy bodies are intraneuronal cytoplasmic, eosinophilic and spherical inclusion bodies composed of α S and ubiquitin. They form the altered neurofilaments which accumulate after abnormal cleavage and phosphorylation of the α S protein. (Cummings, 2004) Two morphologically distinct subtypes i.e. the brainstem and cortical Lewy body types have been described. Lewy bodies were thought originally to cause cell damage in the same way as the beta- amyloid plaques in AD

but are now hypothesised to represent the result of a well performed cell defence system to protect against more toxic species like the alpha-synuclein oligomers.(Tanaka, et al., 2004)

Neuropathology

Lewy bodies and Lewy neuritis in brainstem, midbrain and cortical areas have been extensively studied and correlated to specific clinical features.(CG Ballard, Mohan, Patel, & Bannister, 1993) 3 out of every 4 patients with DLB in addition have Alzheimer pathology, although usually with fewer tangles than in AD.(Del Ser, Hachinski, Merskey, & Munoz, 2001; Merdes, et al., 2003) Different pathological staging-systems have been proposed by different authors regarding the staging of DLB, PDD and PD. First Kosaka in 1980 proposed to differentiate 3 subtypes of DLB pathologically; brainstem, transitional and cortical.(Kosaka, et al., 1984) The revised pathological consensus criteria now implement severity and distribution of both Alzheimer and Lewy pathology in the CNS according to these three subtypes.(Fujishiro, et al., 2008; I. G. McKeith, et al., 2005)

Braak more recently have proposed criteria for staging the Lewybody pathology in Parkinsons Disease (PD) and others have proposed such models for DLB.(Leverenz, et al., 2008; Muller, et al., 2005) In Australia three distinctive groups have been described neuropathologically in dopa-responsive PD patients recruited and followed until death; One with younger onset PD and long duration of the disease with neuropathology corresponding to the Braak stages. The second with early malignant dementia dominant syndrome and severe neocortical disease as described in DLB. The third group with older onset, shorter survival and a more complex disease with additional pathologies and higher Lewybody loads in the brain.(Halliday, Hely, Reid, & Morris, 2008) (See table 4 and 5 in the Appendix)

According to Kurt Jellinger: “The neuropathology of PDD and DLB is similar without significant differences between cortical and subcortical Lewy bodies and the pattern of

synuclein pathology in the brainstem. There are topographic differences in nigral lesions, more frequent affection of the hippocampal CA 2/3 subareas and more severe diffuse amyloid plaque load in the striatum of DLB".(Jellinger, 2009)

Genetics

The genetic underpinnings of PD have been studied extensively during the last decade based on studies in families with autosomal dominant parkinsonism. Several gene mutations and their misfolded proteins have been recognized and labelled PARK 1-16 of which many have been given additional names. Both motor parkinsonism and dementia have been found to occur in the same families. Most DLB cases occur sporadically although families have been described having many affected members with gene alterations in different locations of which some overlap with PD. The gene encoding α S, the α -synuclein gene (SNCA) have been named PARK1 / PARK4 in PD.(Kurz, Schlitter, Larsen, Ballard, & Aarsland, 2006) Three different mutations have been published in addition to duplication and triplication of the SNCA-gene and and two mutations in the gene encoding β -synuclein have been described. (Table 6 in Appendix) In summary, more studies are needed to identify the genetic contributions to DLB.

Biomarkers

CIT-SPECT or DaTSCAN, the visualisation of the striatal dopamine transporter, a measure of the dopaminergic pre-synaptic nigro-striatal system, now has become established as a biomarker in DLB(O'Brien, et al., 2009) In Japan myocardial scintigraphy has been shown to reliably identify DLB even in mild cases.(Suzuki, et al., 2005) Earlier studies found reduced perfusion in occipital cortical areas in DLB as compared to AD on perfusion SPECT-images but this finding is not useful clinically

due to low sensitivity and specificity.(Lobotesis, et al., 2001) Promising findings have been reported also using quantitative EEG.(Bonanni, et al., 2008) In AD the concentration pattern of cerebrospinal fluid (CSF) proteins like beta-amyloid species such as $a\beta_{42}$, total tau and p-tau and the rate and degree of atrophy in hippocampal structures on MRI have been established as a biomarker of the disease and included in the latest diagnostic research criteria.(Dubois, et al., 2007) However, the specificity against DLB is not high and thus CSF cannot presently be used to distinguish between AD and DLB.(Mollenhauer, et al., 2006) In DLB the concentration of αS in CSF has not convincingly been shown to differentiate DLB from AD or normal controls,(Noguchi-Shinohara, et al., 2009; Spies, Melis, Sjogren, Rikkert, & Verbeek, 2009) although the concentration of αS oligomers in plasma have been suggested as a potential biomarker in DLB.(El-Agnaf, et al., 2006) Low CSF concentrations of $a\beta_{42}$ in PD have been found to correlate with poor cognition in cross-sectional studies, particularly regarding memory.(Alves, et al. 2010) Recently this finding was confirmed in a longitudinal study showing that low CSF levels of $a\beta_{42}$ predicted significant cognitive decline during the next two years.(Siderowf, et al. 2010) MRI was found to differentiate between DLB and AD and vascular cognitive impairment in a prospective study with pathological verification of the clinical diagnosis.(Burton, et al., 2009) To conclude, only DaTSCAN are readily available as a reliable clinical biomarker of DLB today.

The clinical profile of DLB

Cognitive profile

In DLB most studies describe an initial impairment in visuospatial and executive cognitive domains as opposed to in AD where memory function and specifically encoding and storage of episodic memory is lost first. In a review from 2003 the authors concluded that DLB is a visual-perceptual and attentional-executive dementia.(Collerton, Burn, McKeith, & O'Brien, 2003)

Neuropsychiatric symptom profile

Few studies have directly compared the neuropsychiatric symptom profile in DLB, AD and normal controls. Visual hallucinations are an intrinsic part of the DLB diagnosis and most authors agree that hallucinations, delusions including Capgras or misidentification syndrome, depression and anxiety are more frequent in DLB than in AD.(Ricci, et al., 2009) In PD impulse control disorders like pathological gambling, hyper-sexuality and compulsive buying have been described and found to be associated with dopamine-agonist treatment,(Weintraub, et al. 2010) but these symptoms have rarely been explored in DLB. Recently somatoform disorder, defined as medically unexplained symptoms, was found occurring in 7% of patients with PD and 12 % of DLB patients preceding the DLB diagnosis for 6 months to 10 years in all cases.(Onofrij, Bonanni, Manzoli, & Thomas 2010) Personality traits like diminished emotional response may distinguish DLB from AD.(Galvin, Malcom, Johnson, & Morris, 2007)

Sleep disturbances in dementia

In DLB sleep and sleep disturbances have not been described in any detail, although RBD was recently included as a suggestive feature of the disease. Normal sleep changes as persons age and above 60 years of age normal persons sleep on average 6.5 hours every night. Older people tend to fall asleep earlier and as a consequence also wake up early i.e. the so called phase advance.(Wolkove, Elkholy, Baltzan, & Palayew, 2007) In addition old people have more sleep disturbances like insomnia and obstructive sleep apnea (OSA) and reduced amount of slow wave sleep and REM sleep.(Wolkove, et al., 2007)

In DLB Farina et al. reported finding an overall 44.1% frequency of sleep disturbances,(Farina, et al., 2009) but the frequencies of specific sleep disturbances except RBD have not been reported. In one study DLB patients were found to have more overall sleep disturbances as compared to AD.(Grace, Walker, & McKeith, 2000)

In AD changes in sleep are more pronounced than in normal aging and differ substantially from normal control subjects at least in moderate and severe stages of the

disease. Sleep changes in AD are not diagnostically useful in mild forms of the disease.(Vitiello, Prinz, Williams, Frommlet, & Ries, 1990) Typical changes include phase advance, reduced amount of time asleep, disrupted sleep and reduced amount of slow wave sleep, altogether reducing sleep efficiency in these persons. Night time behaviours often induce excessive sleepiness during daytime. The frequency of sleep disturbances increase with dementia severity and are related to sundowning and agitation. Increased caregiver distress and early institutionalization and are reported to occur in 25-40% of patients with AD due to sleep disturbances.(Carpenter, Strauss, & Patterson, 1995; Dauvilliers, 2007)

RBD with lack of relaxation of muscles during REM sleep phases and acting out of dream content has been reported to occur in about 10% of AD patients.(Sinforiani, et al., 2007) Other sleep disturbances like insomnia, restless legs syndrome (RLS), OSA, sleep related leg cramps (SRLC) and sleep walking (SW) have not been extensively studied in AD or other dementias.

In PD, a wide range of different sleep disturbances have been described including insomnia, excessive daytime sleepiness (EDS), sleep attacks or unintended sleep episodes, REM sleep behaviour disorder (RBD), restless legs syndrome (RLS), sleep related leg cramps (SRLC), periodic leg movements during sleep (PLMS), obstructive sleep apnoea and sleep walking/ somnambulism.(Jauregui-Barrutia, Tijero-Merino, Gomez-Esteban, & Zarranz 2010; Mondragon-Rezola, Arratibel-Echarren, Ruiz-Martinez, & Marti-Masso 2010)

Sleep disturbances in dementia have been thought to relate to pathology in specific brain areas such as the suprachiasmatic nucleus, the hypothalamus and brainstem and pons area. Neurochemical changes including melatonin and acetylcholine and thus tend to differ in different types of dementia related to the specific brain pathology of the type of dementia involved.

In summary, specific sleep disturbances like RBD have been found to occur in the α -synucleinopathies, RBD may start several decades before cognitive and motor

symptoms,(Claassen, et al. 2010) but the frequency of RBD and other sleep disturbances have not been described in DLB.

Motor symptoms in dementia

In DLB the dementia syndrome develops within the first year of parkinsonian symptoms whereas in PDD dementia develops on the background of established PD. In DLB these symptoms do not typically start with unilateral tremor as in PD, but instead postural instability and gait disorder (PIGD) and rigidity.(Burn, et al., 2006) In VaD motor symptoms will depend on the specific location of vascular lesions and therefore parkinsonian symptoms in addition to paresis, paralysis and spasticity may occur.(Demirkiran, Bozdemir, & Sarica, 2001; Staekenborg, et al., 2008) Ballistic or chorea-like movements have also been described in relation to cerebral haemorrhages and infarctions.(Vidakovi , Dragasevi , & Kosti 1994) In pure AD motor symptoms will normally not occur initially but as the disorder progresses parkinsonian symptoms like gait disorder and rigidity will increase in later stages.(Wilson, et al., 2000). In heritable forms of FTD like frontotemporal dementia with parkinsonism linked to chromosome 17, parkinsonian motor symptoms are part of the clinical picture. Neuroleptic medication can cause or severely worsen parkinsonism and other motor disability in dementia, particularly in DLB and PDD.(Aarsland, et al., 2005)

Autonomic failure in dementia

The α -synucleinopathies have been found not only to affect the CNS. Autonomic failure can be an early and prominent feature of the disease as a consequence of affection of the ganglia and peripheral nervous system and can be visualized with heart scintigraphy. Symptoms of autonomic failure are more common in DLB than in AD and include orthostatic hypotension, cardiac arrhythmias, syncope, constipation, impotence, urinary retention and excessive sweating.(Sonnesyn, et al., 2009)

Pain in dementia

Pain have not been studied in DLB, specifically not in mild dementia. In AD pain has been found to be frequent in advanced stages, and specific instruments have been designed to detect pain in dementia.(Husebo, 2009; Husebo, Strand, Moe-Nilssen, Husebo, & Ljunggren, 2009)

Mild cognitive impairment

Recently a case series of MCI in DLB was presented; Of eight patients identified 6 were male, 7 developed DLB and 1 continued to have MCI. 7 had RBD, 8 parkinsonism, 6 fluctuations and 6 had visual hallucinations.(Molano, et al. 2010)

Table 2 Clinical symptoms in mild DLB and AD

Symptom	DLB	AD
Cognition	Visuospatial and executive Fluctuating	Memory Stable
Neuropsychiatric	Depression Delusions Hallucinations	Depression
Sleep	REM sleep behaviour disorder Excessive daytime sleepiness	Insomnia
Motor	Parkinsonism	No motor symptoms in mild stages
Autonomic	Orthostatic hypotension	No autonomic symptoms in mild stages

Pharmacological treatment

In DLB very few RCTs with cognitive enhancers exist although rivastigmine was studied and found to improve both cognition and psychotic symptoms.(I. McKeith, et al., 2000; I. G. McKeith, Wesnes, Perry, & Ferrara, 2004) Rivastigmine is therefore often preferred by the prescribing clinician if the patient can tolerate its side effects. Recent studies have suggested that memantine is a safe and a potentially effective treatment for DLB regarding both cognition and BPSD(Emre, et al., 2010; Aarsland, et al., 2009)

AChEI's are established as symptomatic treatment in mild AD and the same holds true for memantine in more advanced stages of the disease. Combinations of the two classes of anti-dementia drugs have been shown to be more effective in the symptomatic treatment of AD in some studies.(Farlow, Alva, Meng, & Olin, 2010) Levodopa has been shown to improve parkinsonian symptoms in DLB in open-label studies.(Molloy, McKeith, O'Brien, & Burn, 2005) There are no placebo-controlled

trials of antipsychotic drugs in DLB but several open-label reports suggest that atypical antipsychotics such as quetiapine and clozapine may be useful.(Kurlan, Cummings, Raman, & Thal, 2007; Poewe, 2005) However adverse effects are common and are sometimes severe including cerebrovascular incidents and increased mortality.(Sacchetti, Turrina, & Valsecchi, 2010) Autonomic failure can be treated symptomatically i.e. orthostatic hypotension can be improved by reducing anti-hypertensive drugs and secure intake of sufficient amounts of liquids. Polyethylene glycol can be used to treat constipation, anticholinergic agents are used to treat bladder dysfunction but should be used with caution particularly in elderly patients who have cognitive decline. Phosphodiesterase inhibitors can be used to treat sexual dysfunction.(Zesiewicz, et al. 2010) RBD can be successfully treated using clonazepam, melatonin or pramipexole. RBD with concomitant synucleinopathy may be treated with AChEI.(Aurora, et al. 2010) Pharmacological treatment of DLB is however particular challenging as improving one aspect of the disease might worsen other aspects, for example will treating the motor symptoms with dopaminergic medication in some persons release or increase psychosis and delirium and symptoms of autonomic failure like orthostatic hypotension. Treating psychosis with antipsychotic medication will frequently increase parkinsonian motor symptoms and in many patients result in severe worsening of both cognitive and motor symptoms and even sometimes lead to death, a syndrome termed “neuroleptic hypersensitivity syndrome.” Since there is a balance between cholinergic and dopaminergic activities treating cognitive impairment with AChEI’s may worsen motor symptoms and tremor.

Table 3 Pharmacological treatment in DLB

Treatment target	Prevalence*	Screening	Intervention	Evidence Class I-IV**
Impaired cognition	100%	MMSE 20-30	rivastigmine	I
			memantine	I
			donepezil	IV
Hallucinations/ delusions	50%/ 40%	NPI \geq 1	galantamin	IV
			rivastigmine	I
			memantine	I
			donepezil	IV
			galantamin	IV
			clozapine	IV
			quetiapine	IV
Depression	50%	MADRS \geq 10	risperidon***	II
			citalopram***	II
RBD	31%	MSQ	SSRI	---
			bupropion	---
Insomnia	44%	NPI	clonazepam	IV
			melatonin	--
			pramipexole	--
			AChEI	--
			melatonin	--
EDS	41%	MSQ/ ESS	modafinil	--
Parkinsonism	49%	UPDRS	levodopa	IV

* from the DemVest-study ** See Appendix for definition of evidence class I-IV.

***not recommended

Non-pharmacological treatment

To our knowledge no systematic studies have yet been reported regarding the nonpharmacological treatment of DLB, but general principles regarding nonpharmacological interventions in dementia apply. It is important to inform patients and caregivers regarding the characteristic features of DLB including the potentially harmful effects of RBD and neuroleptics. Most authors recommend identifying one or only a few target symptoms to deal with first. Online support groups for carers and information for carers, patients and professionals are available on the internet, see at <http://lbda.org/> or <http://www.lewybody.org/>

AIMS OF THE STUDY

The primary objectives of this study were 1) to find the frequency of DLB in a referral sample of people with mild dementia, 2) to find the frequency and pattern of sleep disturbances in DLB and 3) to examine whether the core and suggestive symptoms of DLB cluster together in individual patients with mild dementia.

The specific study aims were as follows

1. To find the frequency of DLB in the DemVest-study applying the revised consensus criteria as compared to the original consensus criteria. (Paper 1)
2. To find the frequency of DLB in different age groups and across different dementia severity groups. (Paper 1)
3. To find the frequency of sleep disturbances in DLB and AD as compared to age matched control subjects. (Paper 2)
4. Identify clinical significant correlates of sleep disturbances in mild dementia. (Paper 2)
5. To explore whether the core and suggestive features of DLB cluster in persons with mild dementia. (Paper 3)
6. To explore whether specific clusters based on the continuous measures of parkinsonism, visual hallucinations, cognitive fluctuations and RBD are associated with a specific pattern of cognitive failure in mild dementia. (Paper 3)
7. To identify cut-off values on scales for continuous measures of parkinsonism, hallucinations, cognitive fluctuations and RBD regarding the designation of what constitutes DLB. (Paper 3)

METHODS

Design

The DemVest-study is a prospective study of dementia in Western Norway aiming at exploring various aspects of the dementia subtypes at baseline and on 12 months intervals thereafter. All 5 centres in old age psychiatry and geriatric medicine established at time of inclusion in Western Norway have participated in the inclusion and the 3 neurology departments agreed to refer all cases of suspected mild dementia to one of the study centres during the inclusion period. Data for this PhD-thesis are based on the baseline examination in the DemVest-study.

Inclusion criterion

The inclusion criterion was any type of mild dementia. Mild was defined here as a MMSE score ≥ 20 . Dementia should be diagnosed for the first time between 2005 and 2007 in Rogaland and Hordaland counties. An age matched control group was recruited from the Mayo study of Aging, Mn. USA.(Roberts, et al., 2008)

Exclusion criteria

The exclusion criteria were; normal cognition, mild cognitive impairment, moderately and severe dementia with MMSE<20, schizophrenia or other functional psychosis, bipolar disorder, other organic dementia, severe medical illness or terminal diseases were causes for exclusion in the DemVest-study.

Dementia diagnosis

The diagnosis of dementia was made according to the Diagnostic and Statistical Manual for Mental Disorders 4th edition. The diagnosis for Alzheimer's disease dementia was made according to The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). (McKhann, et al., 1984) Vascular dementia (VaD) was diagnosed according to the National Institute of Neurological Diseases and Stroke-Association Internationale pour la Recherche et L'Enseignement en Neurosciences (NINDS-AIREN) criteria. (Roman, et al., 1993) DLB was diagnosed according to the revised consensus criteria. (I. G. McKeith, et al., 2005) A diagnosis of Parkinson's disease dementia (PDD) was made according to the Task Force organized by the Movement Disorder study. (Emre, et al., 2007) Since clinical symptoms and brain changes are similar both Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD) were grouped as Lewy-body dementia (LBD) in the sleep study. The clinician completed the Clinician Dementia Rating scale (CDR) range 0 – 3. 0 meaning no cognitive impairment, 0.5 mild cognitive impairment or very mild dementia, 1 mild dementia, 2 moderately severe dementia and 3 severe dementia. (Morris, 1997) Activities of daily living were assessed using the Rapid Disability Rating Scale-2. (Linn & Linn, 1982) The clinical diagnosis was made by two of the researchers taking into account all available information and the diagnosis was revised annually. The research group including study nurses had several meetings before study start and also bi-annually after study start to ensure adequate reliability and consensus and harmonisation of the conduct of the study program.

Clinical examination

A detailed and comprehensive battery of assessment instruments was employed. We emphasized instruments that have been standardized and validated to diagnose people with early dementia including DLB. The history and clinical examination was

performed by the study clinician who was a psychiatrist experienced in old age psychiatry or a geriatrician. A trained study nurse performed a structured interview and tests of the caregiver and the cognitive battery with the participant with dementia.

Neuropsychiatric assessment

The psychiatric assessment focused on key symptoms such as visual hallucinations and depression and was based on the Neuropsychiatric Inventory (NPI). The NPI was specifically designed to assess psychiatric symptoms in subjects with dementia based on a structured interview of a caregiver. The NPI screens for 12 different neuropsychiatric symptoms; delusions, hallucinations, agitation, depression, anxiety, euphoria/mania, apathy, lack of normal conduct, irritability, aberrant motor behaviour, sleep and appetite/eating behaviour. Each item is scored on a frequency scale 0-4 and on a severity scale 0-3 and a total score of frequency times severity 0-12 is calculated, i.e. with a total NPI score of 0-144. Included is a caregiver distress score 0-5 for each item with a total score 0-60.(Cummings, et al., 1994) A Norwegian version of the NPI have been validated, and was found to be reliable and valid in assessing neuropsychiatric symptoms in dementia.(Selbaek, Kirkevold, Sommer, & Engedal, 2008) In addition patients and caregivers were asked whether *visual hallucinations* had ever occurred. The presence of recurrent and formed visual hallucinations was based on the NPI visual hallucinations item, the clinical interview and any comments in the medical record. *Depression* was rated using the Montgomery and Asberg Depression Rating Scale (MADRS) which is a clinical interview with 10 items scored 0-6 and a total scoring range 0-60. Depression was defined as a score above 10.(Montgomery & Asberg, 1979) A history of clinically relevant depression was asked for in the interview. *Parkinsonism* was rated using the UPDRS motor subscale which has a scoring range from 0 to 108. The score is given based on an examination of the motor system performed by a trained physician.(Fahn, R.L., & Committee., 1987) A diagnosis of parkinsonism required two or more of the four cardinal symptoms: tremor, rigidity, bradykinesia and gait disturbance/postural instability. *Marked*

neuroleptic sensitivity required evidence of both motor and cognitive worsening after treatment with an antipsychotic agent.(Aarsland, et al., 2005) *Fluctuating cognition* was rated using the Clinician Assessment of Cognitive Fluctuations(Walker, et al., 2000) or the Mayo Fluctuation Questionnaire(Ferman, et al., 2004) using the recommended cut-off scores i.e. one example given from the last month from question a) or b) and a total score of 5 or more from the Clinician Fluctuation Scale or 3 or 4 features from the Mayo Fluctuation Questionnaire.(AASM, 2005)

Neuropsychological examination

A comprehensive battery of neuropsychological tests was administered by a trained study nurse to corroborate a history and/or clinical signs of cognitive impairment. Validated and published norms were used.

Verbal Memory

The California Verbal Learning Test II (Delis, Kramer, Kaplan, & Ober, 1987) consists of a list of 16 words read 5 times and a distractor list, providing sub scores of immediate and delayed recall, free recall, recognition and discrimination.

Language

The Boston Naming Test is a highly sensitive tool to identify naming deficits and impaired word-retrieval capacities in a variety of neurodegenerative disorders. We used a 15-item version of the test.(Graves, Bezeau, Fogarty, & Blair, 2004)

Visuospatial abilities

Two subtests from the Visual Object and Space Perception Battery (VOSP)(Warrington & James, 1991) were used: the Cube and Silhouette tests.

Executive functions

We assessed three different aspects of executive functioning: *Verbal fluency* (categorical) was tested by asking the patients to generate as many names of animals as possible within 1 minute.(B. A. Steinberg, Bieliauskas, Smith, Ivnik, & Malec, 2005) *The Trail Making Test A and B* is as a measure of attention shift and psychomotor speed.(B. A. Steinberg, Bieliauskas, Smith, & Ivnik, 2005) *The Stroop Color-Word Test* is a test of selective attention, disinbition and interference.(Golden, 1978)

Sleep assessment

Insomnia

The Neuropsychiatric Inventory (NPI)(Cummings, et al., 1994) sleep item was used to diagnose and rate severity and frequency of insomnia. The score was based on the bed-partners response to 4 items. The normal controls completed the NPI-Q(Kaufer, et al., 2000) which is a simplified questionnaire. A composite score above 0 was defined as insomnia in accordance with the instructions for the scale.(Cummings, et al., 1994)

Excessive daytime sleepiness

The Epworth Sleepiness Scale(M. W. Johns, 1993) was administered to the caregivers for the persons with dementia and the normal control persons. This scale scores the likelihood of dozing in 8 different situations: while reading, while watching TV, while in the theatre or attending a meeting, as passenger in the car, during a rest and while talking to someone and after eating lunch. Each item is scored on a scale from 0 meaning never falls asleep in this situation to 3 meaning high probability of falling asleep. The sum score is from 0 to 24 and a sum total score > 10 was defined as excessive daytime sleepiness.(M. Johns & Hocking, 1997)

The Mayo Sleep Questionnaire

Parasomnias and sleep related movement and breathing disorders in dementia cases and normal controls were assessed using the Mayo Sleep Questionnaire (MSQ) which is a structured and validated instrument designed to screen for the presence of a wide range of sleep disturbances. The MSQ consists of a 16 items measure and is completed by a bedpartner who regularly sleeps with the subject

(<http://www.mayoclinic.org/sleep-disorders/research.html>). Originally both a patient version and a bedpartner version were used. The initial validation data involving patients (and their bedpartners) being evaluated in a Sleep Disorders Center (Boeve, Silber, Ferman, Smith, & Petersen, 2002) and a separate analysis involving patients (and their bedpartners) being evaluated in a Behavioral Neurology Clinic (Boeve, Ferman, Silber, & Smith, 2002) demonstrated the high sensitivity and moderate to high specificity for most items. (Boeve, personal communication) The sensitivity and specificity were superior for the bedpartner version and therefore only the bedpartner version has been used since 2002. New data from the normative group of elderly without dementia or other cognitive disorders are available. (Roberts, et al., 2008) Completion of this measure typically requires 5 minutes.

Parasomnias

REM sleep behaviour disorder is characterized by recurrent dream enactment behaviour during REM sleep. (Schenck, Bundlie, Patterson, & Mahowald, 1987) Probable REM sleep behaviour disorder was diagnosed if there was a history of recurrent, i.e. 3 times or more, nocturnal dream enactment behaviours recorded by the MSQ. REM sleep behaviour disorder was explored by means of questions to the bed partner regarding duration of symptoms, injuries to patient or bed partner, dream content and whether the dream content mirrored the movements of the patient during sleep. (AASM, 2005) *Sleepwalking* was assessed by means of a screening question to the bed partner: Did the patient ever go sleepwalking in the bedroom or house? Probable sleepwalking was diagnosed if this had happened 3 times or more. *Sleep related leg cramps* were explored by a screening question to the bed partner: Does the patient have cramps in the legs in the evening/night? Probable sleep related leg cramps were noted if this had occurred on at least 3 occasions.

Sleep related movement disorders

Probable periodic leg movements during sleep was diagnosed if the bed partner confirmed 3 or more episodes of recurrent periodic leg movements during sleep and not just while falling asleep.

Restless legs symptoms was noted if the bed-partner could confirm that the patient complained about a restless, pins and needles or creepy-crawly sensation in the lower extremities on at least 3 occasions. (Allen, et al., 2003)

Sleep related breathing disorder

Obstructive sleep apnea was explored by means of a screening questions to the bed partner: Did the patient ever snore or did he get a feeling of suffocation while awake? Did the patient ever stop breathing while asleep? If yes: Does the patient get treatment for this condition like a continuous positive airway pressure machine? Probable obstructive sleep apnea was diagnosed if the bed partner reported that there had been at least 3 episodes of arrested respiration during sleep or answered “yes” to the question involving continuous positive airway pressure use since this indicates that patient had obstructive sleep apnea confirmed by polysomnography and is being treated as such.

Diagnosing core and suggestive symptoms of DLB

The *hallucinations* item from the Neuropsychiatric Inventory (NPI)(Cummings, et al., 1994) was used for assessing hallucinations with a scoring range of 0 – 12. This score is rated by a caregiver and includes all types of hallucinations: visual, auditory, olfactory, tactile and gustatory. Normally a combined score (intensity X frequency) ≥ 4 is regarded as clinical significant. The combined score of frequency times intensity for all modalities of hallucinations was used as a continuous measure for hallucinations, i.e. including both visual, auditive, tactile and gustatory hallucinations. *Parkinsonism* was identified using the UPDRS motor subscale with a scoring range of 0-108 with no cut-off defined.(Fahn, et al., 1987) *Fluctuating cognition* was identified using the Clinician Assessment of Cognitive Fluctuations (n=120) scored 0-16, no cut-

off defined.(Walker, et al., 2000) For a subgroup (n=39) the Mayo Fluctuation Questionnaire was applied, (Ferman, et al., 2004) cut-off defined as ≥ 3 . Scores from the Mayo Fluctuation Questionnaire (0-4) were multiplied by 4 and thus it was possible to combine the two fluctuation scales. *RBD* was identified using the *Mayo Sleep Questionnaire (MSQ)*.(Boeve, Ferman, et al., 2002) A RBD score from 0-4 was calculated, no cut-off defined 1 point was given if the bed-partner reported dream enactment behaviour on 3 or more occasion An additional 1 point each was given if the patient was ever hurt, the bed-partner was ever hurt and if the patient told the bed-partner about dreams where he or she was attacked and had to defend him/her selves and if the patient woke up and told about a dream and the details from the dream mirrored the patients movements during sleep.

Biomarkers

Imaging

A structural MRI was performed in 185 cases. This was mainly to identify cerebrovascular disorder and other structural lesions. In a subgroup of 26 patients we acquired SPECT images of the striatum after injection of ¹²³I-FP-CIT.

Blood tests

Electrolytes, haematological, liver, kidney and thyroid blood tests were performed to exclude organic causes of dementia and blood-cells and plasma were stored for future research.

CSF

In a subsample of participants a lumbar puncture was performed to exclude organic causes of dementia and CSF was stored for future analysis. CSF was not used for diagnosing AD at baseline.

Statistics

We applied the software package SPSS version 15 for all analyses. A p-value of 0.05 was considered statistically significant. Analyses in papers 1 and 2 consisted of rates and proportions using 95% confidence intervals.(CI) Between-group comparisons were made using one-way ANOVA for parametric variables with post-hoc comparisons using Scheffe tests and chi-square for categorical data. In paper 2 the proportion with sleep disorders was compared between groups using Fisher's exact test and odds ratios with confidence intervals. Between-group comparisons of continuous data were made using the Mann-Whitney U test as the data were not normally distributed. For our third paper cognitive scores were calculated as standardized z-scores with zero as the mean value and 1 as the standard deviation for the 3 domains: Memory, Attention/Executive and Visuospatial. The memory cognitive z-scores were calculated from the CVLT-2 total score list 1-5, list A short delay and list A long delay. Attention/Executive cognitive z-scores were calculated from the serial 7s from the MMSE, Trail making test A and B and all items from the Stroop tests. Visuospatial cognitive z-scores were calculated from the Silhouette test only due to skewed data on the Cube test.

The two-step cluster analysis procedure was used as a data driven approach for classifying patients in groups according to NPI hallucinations frequency times intensity score, parkinsonism as UPDRS-3 score, fluctuations score and RBD score. The two-step clustering procedure is based on a sequential pre-clustering procedure, followed by agglomerative hierarchical clustering method in a predetermined number of clusters.(Chiu, Fang, Chen, Wang, & Jeris, 2001; Zhang, Ramakrishnon, & Livny, 1996) In order to determine the optimal number of clusters we chose the number of clusters that minimized Akaike's information criterion. To test the robustness of the final cluster solution the sample was split in two random samples and re-clustered using the same number of clusters as in the whole-sample clustering procedure. Finally the agreement of the sub-sample clusters with the whole-sample cluster was calculated. Statistical significances between clusters for categorical variables were tested with Pearson's Chi-square tests. Student's t-tests were applied to test statistical

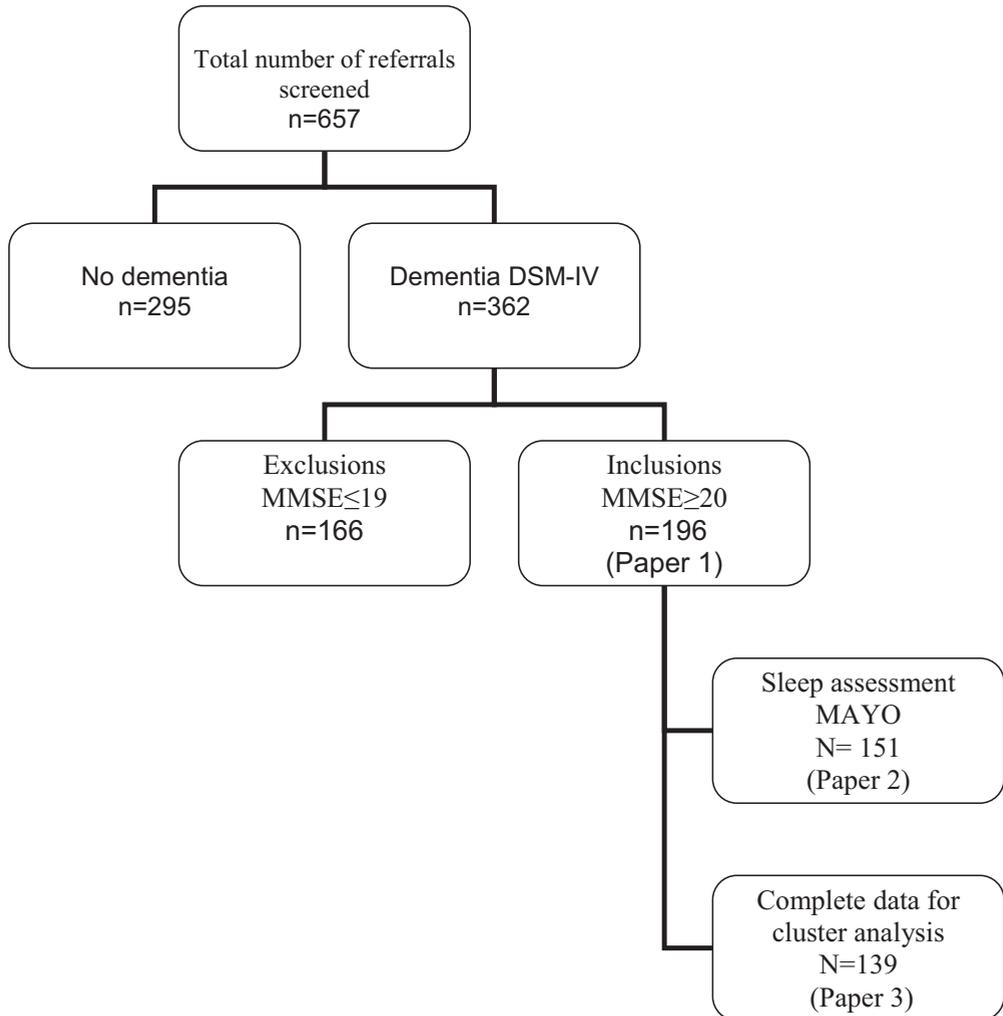
differences between normally distributed continuous data and Mann-Whitney U test for continuous nonparametric data. Kruskal-Wallis tests were applied for one way analysis of variance of nonparametric data and one way analysis of variance for normally distributed data. Post hoc analyses applied Mann-Whitney U tests for continuous data and Pearson's Chi-square tests for categorical data.

Ethics and legal issues

The DemVest-study is approved by the Regional Committee for Medical and Health Research Ethics in Western Norway and the Data Inspectorate of Norway. Financial support was received from the Regional Health Authorities of Western Norway, Helse-Vest RHF and the Norwegian Research Council. The patients provided written consent to participate in the study after the study procedures had been explained in detail to the patient and a caregiver, usually the spouse or off-spring. Participants in the Mayo Clinic Study of Aging provided written consent; the full protocol as well as the sharing of data was approved by the Mayo Foundation Institutional Review Board.

RESULTS

During the 2 year inclusion period we screened 657 subjects of whom 196 (29.8%) fulfilled the inclusion criteria (Fig 1, Tab 8). 461(70.2%) cases were excluded and reasons for exclusion were: 166 had moderately or severe dementia, 102 were not willing to participate, 79 had mild cognitive impairment, 48 had normal cognition, 24 had depression and pseudo-dementia, 14 had newly diagnosed somatic or terminal disorder, 11 had bipolar disorder or psychosis, 7 had other neurological disorder, 4 had delirium and there were missing data in 6 cases. Of the excluded cases diagnosed with dementia(n=267), 91(34.0%) were diagnosed with AD, 22(8.2%) with DLB, 27(10.1%) had VaD, 6(2.2%) had mixed dementia and 121(45.3%) had unspecified dementia. Thus, the frequencies of DLB and AD were lower and VaD was higher among the excluded compared to included subjects, and the diagnostic distribution differed significantly. Data from all 196 participants and their primary caregivers were analyzed in **paper 1**. In **paper 2** participants with a sleep partner who completed the MSQ (n=151) were included and in **paper 3** only persons with a complete dataset for the core and suggestive DLB symptoms (n=139) were included: 129 participants from baseline examination and an additional 10 who had a complete dataset at 12-months follow-up.

Figure 1 Flowchart of inclusions and exclusions in the DemVest-Study

Paper 1

Frequency and case identification of Dementia with Lewy bodies using the revised consensus criteria

Two of the authors independently reviewed all available information and kappa for a diagnosis of probable DLB versus non-DLB was 0.73.

The frequency of DLB was 39/196 (20%) of whom 31 (16%) had probable and 8 (4%) possible DLB. The frequency of probable DLB increased by 25% as compared to the 1996 criteria applying the revised 2005 criteria. The frequency of DLB did not differ significantly across dementia severity as measured with mean CDR scores or age bands.

Paper 2

Frequency and Correlates of Caregiver Reported Sleep Disturbances in a Sample of Persons with Early Dementia

We found a significantly higher frequency of sleep disturbances in LBD, i.e. both DLB and PDD combined, as compared to AD and normal controls. In LBD sleep disturbances were found in 89% compared to 64% in AD ($p=0.008$). The most striking difference was the much higher proportion with probable REM sleep behaviour disorder and excessive daytime sleepiness in LBD compared to the other groups. Having any sleep disturbance in mild dementia correlated with both anxiety ($p=0.025$) and depression. ($p=0.029$)

Paper 3

Core and suggestive symptoms of Dementia with Lewy Bodies cluster in persons with mild dementia

Finally in the third paper we found that the core features of DLB (visual hallucinations, parkinsonism and cognitive fluctuations) and the suggestive feature RBD clustered in our participants with mild dementia. The analysis identified four clusters and the agreement of the sub-sample clusters with the whole-sample cluster was 91% (127/139). In cluster 1 (n=21,) participants had high scores for hallucinations, parkinsonism and fluctuations and an intermediate score for RBD and we labelled this cluster the Lewy Body Dementia (LBD) cluster. In cluster 2 (n=17, xx%) participants had intermediate scores for hallucinations, parkinsonism and fluctuations but a high score for RBD and this cluster is labelled the RBD cluster. In cluster 3 (n= 81, xx%) participants had low or zero scores for all DLB symptoms and this cluster was labelled the non-LBD cluster. Finally in cluster 4 (n=20, xx%) participants had high fluctuation scores and low scores for hallucinations, parkinsonism and RBD and consequently this cluster was labelled the Cognitive Fluctuation (CF) cluster. Participants in the LBD-cluster had significantly more impaired visuospatial abilities ($p=0.002$) as compared to the other clusters. Cut-off values for the core features and RBD were suggested.

DISCUSSION

Findings in context

Here we take the opportunity to discuss issues that have not been previously discussed in the three published papers, to present and discuss data reanalyzed for this thesis and to discuss our findings compared to the most recent data published, i.e. data published after the 3 papers were submitted.

Our main findings in this thesis were that 1) 20% of the participants in the DemVest-cohort fulfilled the revised clinical criteria for DLB. 2) 71% of the dementia participants had caregiver reported sleep disturbances as compared to 56% of the normal controls, and the caregivers reported more sleep disturbances among the LBD patients as compared to AD patients. Finally, 3) we found that the DLB symptoms cluster in individuals with mild dementia, providing empirical support for the diagnosis DLB.

The frequency of DLB

196 participants fulfilled DSM-IV diagnostic criteria for dementia and all these were then evaluated according to the core features of DLB, i.e. visual hallucinations, motor parkinsonism, fluctuations in cognition and consciousness and RBD. 31 participants (15.8%) were given a diagnosis of probable DLB. They had 2 core features or 1 of the core features plus RBD. 8 participants (4.1%) were given a diagnosis of possible DLB because they had one core feature of DLB without fulfilling diagnostic probable criteria for any other subtype of dementia.

Table 4 Number of participants fulfilling the two sets of diagnostic criteria

Diagnosis	Probable DLB		Possible DLB	
	1996	2005	1996	2005
Criteria	1996	2005	1996	2005
Number	25	31	13	8
Visual hallucinations	24	25	3	2
Parkinsonism	11	14	8	5
Fluctuations	17	18	3	2
RBD		10		0
123I-FP-CIT SPECT		3		0
Neuroleptic sensitivity		0		0

Some of the participants diagnosed with a non-DLB dementia also fulfilled criteria for possible DLB, i.e. they had one core feature or RBD, but as we choose to put only one diagnosis for each participant, these data have not been analyzed and are not included in this thesis. In the revised consensus criteria severe neuroleptic sensitivity and a positive CIT-SPECT/ DaTSCAN are included as suggestive features of DLB. In our cohort no participants reported severe neuroleptic sensitivity and overall only 13 (6.6%) participants were treated with neuroleptics at baseline. Unfortunately, it was not possible to examine all the included participants with a DaTSCAN, and thus only 26 scans were performed at baseline. 3 participants were given a diagnosis of probable DLB based on having one core feature and a positive DaTSCAN.

To our knowledge no previous studies had reported on the frequency of DLB according to the revised clinical criteria at time of publication. Recently an Italian group reported findings from Italian memory clinics originally applying the 1996 criteria, reanalyzing their data according to the revised criteria. They reported an increase in the proportion with probable DLB from 78/102 to 82/102, an increase of about 4 % as compared to 25 % in our study. The Italian study applied both

retrospective and prospective cases and did not report on how sleep disturbances like RBD was screened for and diagnosed.(Farina, et al., 2009)

Our findings are comparable to epidemiological studies applying stringent methodology to detect DLB according to the original criteria,(Rahkonen, et al., 2003; Stevens, et al., 2002) although many studies have reported much lower frequencies.(Zaccai, et al., 2005) Nevertheless, our findings are probably still an underestimation of the true frequency of all cases fulfilling the revised clinical DLB criteria because 1) all participants were only given one diagnosis. If the non-DLB cases had been given a secondary dementia diagnosis, many cases would fulfil the possible DLB criteria in addition to the AD criteria. A substantial proportion of those diagnosed as having possible DLB fulfil criteria for probable DLB after one year.(O'Brien, et al., 2009) 2)Applying a DaTSCAN in all participants would probably have yielded more participants with a probable or possible DLB diagnosis. 3)Finally, we did not have access to cardiac scintigraphy, which has demonstrated high sensitivity for diagnosing DLB.(Yoshita, et al., 2006)

In a study with autopsy verified diagnosis it was shown that in persons with mild DLB only few of them expressed the core features. As a consequence one might expect that many of our cases diagnosed as non-DLB will eventually develop into a more typical phenotype during follow-up,(Tiraboschi, et al., 2006) at least among the cases with one core or suggestive feature diagnosed with another subtype of dementia. A 12 months follow-up study of persons with possible DLB applying CIT-SPECT /DaTSCAN found a positive scan at baseline to have high predictive power for a clinical probable DLB diagnosis at 12 months follow-up and a negative scan to have a high predictive power for diagnosing AD at 12 months.(O'Brien, et al., 2009)

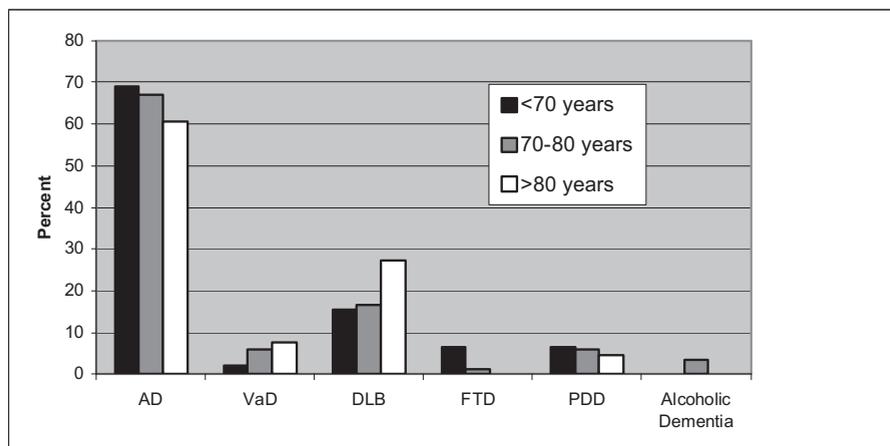
The lower than expected prevalence and incidence of DLB in previous studies might reflect the fact that DLB is not readily detected on memory based screening instruments alone. It is known that cognitive fluctuations are hard to detect reliably without specific screening instruments.(Mega, et al., 1996) Visual hallucinations occurring in individuals without memory problems may not always be considered as

part of a dementia diagnosis clinically. In persons presenting with motor parkinsonian symptoms a detailed cognitive and ADL screening are not always performed. In addition sleep disturbances in dementia is normally not included in the clinical interview and examination and therefore new screening instruments to detect the specific features of DLB need to be developed to more reliably detect this condition.

The prevalence and incidence of DLB is still not known in different populations. Therefore more rigorously designed studies are needed to establish the prevalence and incidence of DLB in different geographical areas, age groups and populations. Screening-instruments for DLB should include neuropsychological tests for attention, visuospatial function and executive function and not rely exclusively on memory based tests. A structured interview for the carer should be added to the diagnostic evaluation. Standardized scales to measure parkinsonism, hallucinations, fluctuating cognition and consciousness, neuroleptic sensitivity and REM sleep behaviour disorder should be included according to recommendations in the last consensus paper.(I. G. McKeith, et al., 2005) In addition cut-off points on clinical rating scales are needed as only one study for fluctuations have reported this.(Ferman, et al., 2004)

The proportion of DLB across age bands

The proportion of persons with DLB did not differ significantly across the three age bands; <70 years, 70-80 years and >80 years. A trend was shown, the proportion of persons with DLB being higher in the >80 years group, i.e. the oldest age group.

Figure 2. Baseline diagnoses in 3 age bands

A systematic review of prevalence and incidence studies in DLB showed that different age groups were included, i.e. >65 years and >75 years, in different studies. (Zaccai, et al., 2005) The Finnish study by Rahkonen et al. found the DLB frequency in their dementia cohort in the 75+ group to be 22%, and the UK study from London found the frequency of DLB in the 65+ group to be 31%. Unfortunately, the studies referred in this review have applied different methodology and different adaptations of the diagnostic criteria, making direct comparison between studies of different age groups in different studies difficult. However, the best methodologically studies in this review found a higher proportion in the 65+ group (Stevens, et al., 2002) than in the 75+ group (Rahkonen, et al., 2003) when including persons with both probable and possible DLB, opposite the trend in our study. In Stevens et al. visual hallucinations were mandatory for a DLB diagnosis and as such a specific adaptation to the 1996 criteria were introduced in this study. Diagnosis relied both on a clinical examination and case records and specific instruments to detect the core and suggestive features of DLB were not applied. Their screening instrument, the Short-CARE, might not have detected mild cases as only individuals who needed assistance were detected. In the Finnish study by Rahkonen et al. the proportion with DLB and other dementias was reported in 5 years intervals from 75 to 90+. The highest proportion of DLB (50%)

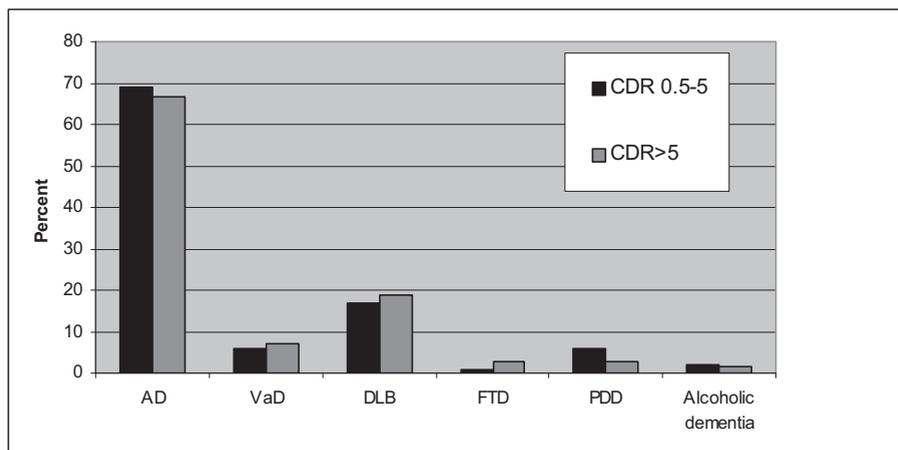
were found in the 80-84 years age group, comparable to our findings. In the Hisayama Study, (Matsui, et al., 2009) a study of incident dementia with pathological diagnostic verification, Matsui et al. found a low incidence of DLB across the age bands from 65 years to 85+, as opposed to AD where they found increasing incidence with age. VaD was found to be the second most common form of dementia as known from other Asian dementia studies, with higher frequencies of VaD and lower DLB frequencies.

Our study was not powered to explore the proportion of DLB as compared to other dementias in the different age groups. Finding the true frequency of DLB in the different age bands in different communities would inform clinicians on where to look for the diagnosis and researchers on possible risk factors and provide insight into the complex relationship between age-related changes and disease-related pathologies.

Proportion of DLB across severity groups

Dementia severity was measured by the Clinical Dementia Rating scale (CDR) which is composed of the subitems: memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care. The proportion of persons with DLB did not differ significantly in two severity groups based on mean total CDR score (5.2); CDR 0.5-5 and CDR >5.

Figure 3. Baseline diagnoses in two severity groups based on mean CDR-scores



For this thesis we recalculated the CDR scores with an online algorithm from the following web site: <http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html> giving new sum scores for each participant; 0 (no cognitive impairment), 0.5 (Mild cognitive impairment), 1 (mild dementia), 2 (moderately severe dementia) or 3 (severe dementia). These previously unpublished data are presented below in table 5. The proportion of DLB patients did not differ significantly across these new CDR severity groups. Of note, some patients had CDR=2, i.e. moderate dementia, despite the inclusion of only mild dementia and more importantly a large proportion scored 0.5 on the CDR scoring signifying MCI, but all were fulfilling the criteria for dementia and had impairment in their ADL-functioning due to impaired cognition. This is due to the inclusion criterion being based on MMSE score of 20 or higher, rather than the composite score being the basis for CDR scoring.

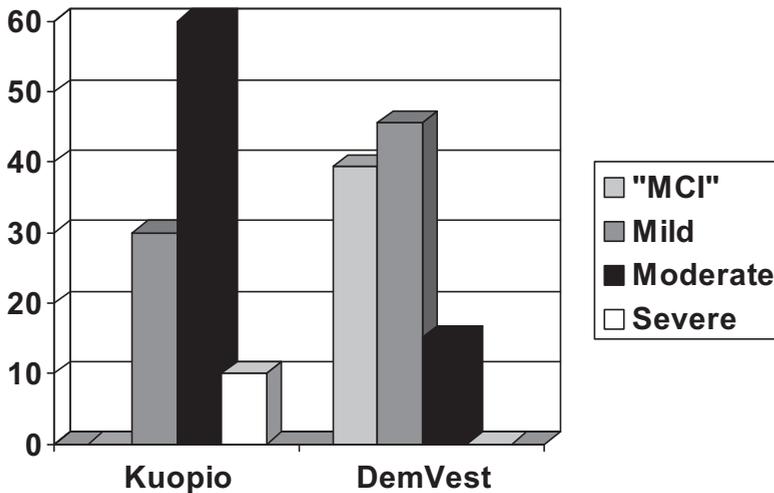
Table 5 New CDR scores

CDR	0.5	1.0	2.0	p-value
AD (%)	40.9	53.5	5.5	0.254
DLB (%)	39.4	45.5	15.2	0.144

P-values based on Pearson chi-square test

In the Finnish study Rahkonen et al. included all stages of dementia in the community making comparison to our data difficult. They concluded that their DLB patients were at a less severe stage and had a shorter duration of symptoms as compared to other types of dementia. This might reflect the fact that diagnosing DLB in severe dementia is difficult due to the fact that in advanced dementia the phenotype is rather similar independent of the initial type of dementia. These findings contrasts the findings from our study where we only included cases with mild dementia referred to an out-patients clinic based on a MMSE score of 20 or above. To conclude, we still do not know if the frequency of DLB is different in different dementia severity groups and further studies specifically designed to address this question are welcome.

Figure 4 The proportion with different severity stages of DLB in two studies



Comparing the two sets of clinical diagnostic criteria

In the revised clinical diagnostic criteria for DLB from 2005 a set of features are included as “suggestive features” to increase sensitivity: RBD, severe neuroleptic sensitivity and a CIT-SPECT/DaTSCAN or PET imaging demonstrating reduced uptake of dopamine transporter. In our study neuroleptic sensitivity was not reported. All the included participants were screened for RBD with the MSQ but only a small proportion underwent a DaTSCAN. The core features and RBD were rated independently by two of the authors yielding a Cohen’s kappa, a statistical measure of inter-rater agreement for categorical data, of 0.73, i.e. substantial agreement. Probable and possible DLB was diagnosed according to the revised and original criteria and the two results were compared. One limitation is that the two sets of criteria were not applied independently and blinded to the opposite criteria by the two raters. More cases fulfilled criteria for probable DLB with the revised criteria because RBD (n=4)

and CIT-SPECT (n=2) made these convert from possible to probable DLB, i.e. the revised criteria were more sensitive for the clinical diagnosis of probable DLB.

Gender

In the α -synucleinopathies a male predominance has been reported in several cohorts including DLB, although this has not always been confirmed in community-based studies. In PD a male predominance is established.(Alves, et al., 2009) In the Finnish community based study from Kuopio only 13% of the DLB patients were male.(Rahkonen, et al., 2003) Others have found an equal sex distribution(Farina, et al., 2009) and in a systematic review of prevalence and incidence studies of DLB no relation to sex was found.(Zaccai, et al., 2005) In our study the proportion of males was significantly higher in DLB (49%) as compared to AD (30%) $\chi^2=5.060$, $p=0.024$. Our finding is comparable to case reports reporting a male predominance in DLB and this is known also in other α -synucleinopathies like PD, MSA and RBD.(Alves, et al., 2009; Boeve, et al., 2003) To establish if a male predominance holds true in DLB a larger community-based study with appropriate design will be needed.

The frequency of sleep disturbances and clinical correlates

In paper 2 we reported on the frequency of caregiver reported sleep disturbances in mild dementia and normal controls. Clinical correlates of sleep disturbances were explored in the dementia cohort. Only those participants who had a sleep-partner at the baseline examination were included in the analysis for the second paper. The control group was comprised of participants in the Mayo Clinic Study of Aging(Roberts, et al., 2008) who are largely of northern European heritage. They are randomly selected community dwelling residents of Olmsted County, Minnesota, who do not carry a diagnosis of dementia. They completed the same sleep assessments as the patients in

Norway. The Kokmen Short Test of Mental Status (STMS)(Kokmen, Naessens, & Offord, 1987; Tang-Wai, et al., 2003) (range 0-38 and cut-off point for dementia 29/38) was used as the mental status examination in the Mayo Clinic Study of Aging rather than the MMSE. MMSE scores were calculated from the STMS scores based on a nomogram involving several thousand subjects (unpublished data, Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA).

The LBD group comprised 29 persons with mild DLB and 10 persons with mild PDD and thus the power to detect differences in the frequency of sleep disturbances between the dementia subtypes, i.e. between LBD and AD, was increased. For this thesis we have chosen to present the additional sleep-data concerning DLB and PDD separately as well, see table 6 & 7 below. The frequency of insomnia in DLB as compared to AD was no longer statistically significant, probably reflecting that our study was not adequately powered to find such a difference. Statistics have now been included for the frequency of somnambulism, and although the numbers are small, there are significant differences between diagnostic groups.

Table 6 Characteristics of the study groups

	LBD	DLB	PDD	AD	p-value ¹
N (%)	39* (26.5)	29 (19.2)	10 (6.6)	97 (63.6)	
Age	78.0 (7.7)	79.0 (7.9)	75.2 (6.7)	74.5 (7.3)	0.009
Male	25(64.1)	16 (55.2)	9 (90)	33 (35.1)	0.082
Education	9.1 (2.7)	9.2 (2.7)	8.9 (3.1)	9.6 (3.1)	0.518
Duration of symptoms	3.1 (2.2)	3.5 (2.2)	2.1 (1.7)	2.3 (1.5)	0.003
MMSE	23.9 (2.7)	23.4 (2.7)	25.5 (1.9)	23.9 (2.3)	0.292
CDR	0.93 (0.51)	0.98 (0.56)	0.75(0.27)	0.86(0.36)	0.659
Total NPI severity (SD)	8.41 (5.52)	9.4 (5.3)	5.5 (5.4)	6.44(5.25)	0.008
Hypnotics	4 (10.0)	3 (10.3)	1 (10)	6 (6.3)	0.695
AChEI	9 (22.5)	8 (27.6)	1 (10)	44 (45.8)	0.088
Memantine	2 (5.0)	2 (6.9)	0	1 (1.1)	0.134

Numbers represent number of subjects (%) or mean score and standard deviation.*29 DLB cases and 10 PDD cases. Differences between groups were analyzed with Fisher's exact tests for categorical data and Mann-Whitney tests for continuous data.

¹AD vs. DLB.

Table 7 Frequency of sleep disturbances in patients with mild dementia

	LBD	DLB	PDD	AD	¹p-value
N (%)	39 (25.8)	29 (19.2)	10 (6.6)	97 (64.2)	
Any*	31 (88.6)	23 (79.3)	8 (80)	55 (56.7)	0.031
pRBD	15 (38.5)	9 (31.0)	6 (60)	9 (9.3)	0.006
pPLMS	7 (21.2)	6 (23.1)	1 (14.3)	8 (8.9)	0.081
pRLS	12 (30.8)	8 (27.6)	4 (40)	13 (13.4)	0.069
EDS	13 (40.6)	10 (41.7)	3 (37.5)	15 (16.7)	0.013
Insomnia	17 (47.2)	12 (44.4)	5 (55.6)	23 (24.0)	0.053
pSRLC	14 (42.4)	11 (42.3)	3 (42.9)	17 (18.7)	0.019
pOSA	9 (25.7)	9 (34.6)	1 (10)	13 (14.9)	0.045
SW	6 (15.4)	4 (14.3)	2 (25)	1 (1.1)	0.010

* Any sleep disturbance. Numbers represent number of subjects (%). Differences between groups were analyzed with Fisher's exact tests. ¹AD vs. DLB.

We found a higher frequency of all sleep disturbances in the mild dementia cohort (71%) as compared to the normal controls (56%) applying the NPI and the MSQ. The NPI reports the frequency of aberrant night time behaviour, included difficulties falling asleep or staying asleep, during the last four weeks and the MSQ reports the frequency of sleep disturbances that have occurred on at least 3 occasions, i.e. during an indefinite time frame, and thus the frequency of insomnia is registered within a much shorter time frame as compared to other sleep disturbances reported here. The frequency of sleep disturbances applying the NPI sleep item has been previously reported in dementia and normal controls, but unfortunately neither the Cache County Study (M. Steinberg, et al., 2006) nor the Nakayama Study (Ikeda, et al., 2004) both community based dementia studies applying the NPI, reported the frequency of aberrant sleep behaviour. In the Cardiovascular Health Study, a large US population based dementia study, Lyketsos et al. reported finding significantly higher frequency of sleep disturbances applying the NPI in participants with dementia (27.4 %) as compared to their MCI group (13.8 %) $p < 0.001$. Unfortunately, they did not report the frequency of sleep disturbances from the general population (Lyketsos, et al., 2002). Recently, findings from a UK community based neuropathology dementia cohort, the MRC CFAS study, was reported. Surprisingly, the authors found the same frequency of sleep disturbances in their normal controls (43.8 %) as in the dementia participants

(42.0 %). Both the dementia participants and their caregivers were asked about “difficulty getting or staying asleep at night or problems falling asleep during the day, ”(Savva, et al., 2009) which reflect the rather wide definition of sleep problems in this study not asking for specific sleep disorders or applying the NPI sleep item. To our knowledge data from the MAYO sleep questionnaire has not yet been published from any other dementia cohort.

The frequency of having any sleep disturbances in mild LBD was higher (89%) than in mild AD (64%) and in normal controls. (56%) Previously the frequency of sleep disturbances in DLB has not been extensively studied. Data not available to us at the time of publication were recently reported from Italian memory clinics.(Farina, et al., 2009) In their cohort of DLB patients, comprising only 4.8 % of the dementia patients, sleep problems were reported in 44.1 % as compared to 79 % in our cohort. 25.5 % had insomnia, about half the frequency in our study with 44 % in DLB, 12.7 % had RBD as compared to 31 % in our study and hypersomnia in the daytime was reported in 10.8 % as compared to 42 % with EDS in our study. Direct comparison between the studies is difficult as the Italian study applied the 1996 criteria and reported 48 % use of neuroleptics as compared to only 13 % in our study. Importantly, they did not report how sleep problems were screened for or diagnosed.

We found that depression and anxiety correlated with sleep disturbances in mild dementia thus demonstrating the clinical significance of sleep disturbances in dementia. To our knowledge this has not previously been reported.

Four clusters revealed in mild dementia

The results are based on a proportion of the participants from paper1(n=129) plus an additional 10 at 12 months follow up. To be included in these analysis participants needed a complete dataset for the NPI hallucinations item, a complete UPDRS-3 score, a fluctuation score and a RBD score. Using objective, rater-independent statistical procedures, thereby avoiding the risk for circularity inherent in a purely clinical

diagnostic approach, we identified 4 clusters in our mild dementia cohort based on scorings on continuous scales for hallucinations, fluctuations, motor parkinsonism and RBD. The NPI hallucination item was applied, including hallucinations for all modalities. For this thesis we reviewed the first 13 participants reporting scoring 1 or more on the NPI hallucinations item: 12 of 13 (92%) reported visual hallucinations and 5 of these in addition reported auditory hallucinations. 1 of 13 reported auditory and gustatory hallucinations only. The fluctuation score was composed of two different scales; 120 participants completed the Clinician Assessment of Cognitive Fluctuations and a subgroup of 39 completed the Mayo Fluctuation Questionnaire. The two scales were combined to one common fluctuation score by multiplying the Mayo score by 4 yielding a 0-16 total fluctuation score for all participants. The concordance between the two scales have not been examined and they may thus measure different aspect of cognitive fluctuations.

The RBD score was based on the four questions regarding RBD from the MSQ but only a small proportion of the participants scored more than 1 point here. Thus some other scoring of RBD like the RBDQ-HK(Li, et al. 2010) a 13 item scale scored 0-100 would be more appropriate for future research. This scale probably would have to be made available in a caregiver/ bed-partner version to be appropriate in dementia research.

Different cognitive profiles in clusters

Standardized Z scores for the three cognitive domains memory, attention/executive and visuospatial were calculated. We found the Z-score for the visuospatial cognitive factor in the LBD cluster to be significantly more impaired as compared to the non-LBD cluster. (-0.36 vs. 0.14, $p=0.002$) Memory was more impaired in the non-LBD cluster, although not significant. These findings are in accordance with previous findings comparing cognitive profiles in DLB and AD.(Collerton, et al., 2003)

Table 8 Cognitive z- scores in clusters

	Cluster1 LBD	Cluster2 RBD	Cluster3 Non-LBD	Cluster4 CF	p-value
Memory	0.26(1.32)	0.12(1.30)	-0.11(0.9)	0.12(1.1)	0.664
Visespatial	-0.32(0.62)	0.06(0.80)	0.14(0.69)	-0.02(0.85)	0.029*
AttExecutive	-0.10(0.39)	0.15(0.60)	-0.03(0.51)	-0.06(0.55)	0.717

Scores are mean and SD Z-scores. Overall p-values are calculated from Kruskal-Wallis test, post hoc tests Mann Whitney U tests. *Cluster 1 vs. cluster 2 significant at p=0.07 Cluster 1 vs. cluster 3 significant at p=0.002 Cluster 1 vs. cluster 4 significant at p=0.106

Thresholds for core and suggestive features of DLB

Based on median scores for the core symptom of DLB and RBD scales we proposed cut-off values on these scales to designate what is sufficient for a DLB diagnosis.

Scoring 1 or more on the NPI hallucinations item, fluctuation score and RBD score or 10 or more on the UPDRS-3 scale can be used as a clinical guide to identify the LBD cluster according to our findings. These findings need to be confirmed by others and confirmation of the validity of clusters awaits a biomarker or pathology study.

The definition of cognitive fluctuations

Cognitive fluctuations are not strictly defined regarding content, duration or intensity. The revised DLB criteria recommends using some kind of formal assessment of fluctuations. The One Day Fluctuation Assessment Scale, The Clinician Assessment of Fluctuation and the Mayo Fluctuations Composite Scale are all mentioned as possible tools. It is recommended that the rater has adequate training in applying the scales that are used. (I. G. McKeith, et al., 2005) In our study we applied two different scales, i.e. the Clinicians Assessment of Fluctuations and the MAYO scale both defining different aspects of cognitive fluctuations. The two scales have not been directly compared in the same set of patients and therefore we cannot claim that they actually measure the same phenomena of cognitive fluctuation.

Methodological issues

Cross sectional design

All three papers are based on data collected cross-sectionally, i.e. at one time point, and thus no conclusions regarding causality can be drawn based on our findings. We used data from the baseline examination in the DemVest-study, a prospective dementia study specifically designed to explore all aspects of Dementia with Lewy Bodies during the time span of the disease. The core and suggestive features of DLB are measured at the time of inclusion and participants might therefore fulfil other diagnostic criteria at a different time of examination. To our knowledge, the consistency of these features over time has not been explored. The same features are used as basis for the cluster analysis in paper 3 and the different sleep disturbances are also screened for at the baseline examination and might change over time.

Case selection, recruitment and potential bias

We estimated that the screened subjects represent about 5 % of incident cases in our catchment area during the inclusion period. This is based on the 14% elderly in the counties of Rogaland and Hordaland with a total population of 900000 and an expected incidence of dementia in this group of 1 new cases per 55 elderly/year.(Andersen, et al., 1999) As we screened all referrals to all out patients clinics in a defined area during a two year period we wanted to secure inclusion of a proportion of cases with mild dementia as unselected as possible, although we acknowledge that the proportion of referrals is low as compared to the frequency of new cases in our catchment area during the two year period. The DSM-IV criteria for diagnosing dementia are the most sensitive diagnostic criteria for diagnosing dementia,(Wancata, Borjesson-Hanson, Ostling, Sjogren, & Skoog, 2007) and thus probably few cases are lost applying using these criteria. On the other hand these criteria may be less specific as compared to the ICD-10 criteria. Regarding both AD

and VaD we applied the research diagnostic criteria including cases fulfilling both probable and possible criteria. These criteria are the most specific and least sensitive. Regarding vascular dementia the prevalence is known to vary widely depending on the specific set of criteria applied. The NINDS-AIREN criteria that we applied have been found to be the least sensitive of the criteria for VaD and suggestions to update them have been put forward.(Gold, et al., 2002)

Unfortunately, we did not record how many of the included cases were referred from neurology to one of the participating centres, but based on our clinical impression the neurology departments evaluate rather few cases with preferably younger patients. Thus, we believe that only a small proportion of all included was referred from the neurology departments. Among the included subjects, 53% were included by old age psychiatry and 47% by geriatric medicine clinics. The proportion with DLB was 27.9 % in the cases from Old Age Psychiatry out-patients clinics and 10.9 % from Geriatric Medicine. In Norway it has been shown that the referred cases are younger, but otherwise similar, to the cases with dementia not referred to out-patient clinics.(Gausdal & GjØra, 2007) One might speculate that DLB cases would be referred more often due to higher frequencies of BPSD. A community based survey screening random inhabitants in a defined area found an even higher frequency of DLB as compared to our study when including both probable and possible DLB.(Rahkonen, et al., 2003) This is probably partly due to methodological differences, but the possibility that the prevalence of DLB differs in different populations cannot be ruled out.

Methods of measurement

The NPI was not specifically designed to detect insomnia in mild dementia, and the definition of insomnia includes reduced function during the daytime in addition to the problems getting to or staying asleep. The normal controls answered the NPI-Q, a shorter version which might not detect the same individuals as the full version of the NPI. Although in PD it was reported that clinical interview alone with the patient and bed-partner only detected about half of the cases with RBD,(Gagnon, et al., 2002) the

MSQ has been found to have acceptable sensitivity and specificity to detect the different sleep disturbances. (B. Boeve, personal communication 2009) To formally diagnose conditions like RBD and PLMS a Polysomnography (PSG) must be included in the examination. Different screening measures were applied in dementia and normal controls, i.e. MMSE and Kokmen. The MMSE cut-off for mild dementia might lead to relatively more DLB cases being included since the MMSE is less sensitive for this group, and thus moderately demented patients with DLB might be included in our cohort.

Confounding factors

Only univariate analyses are applied in these three cross-sectional studies. These are known to be subject to a range of possible biases. As an example we did not control for sex, age, education, the different drugs taken by the participants in the three studies, and one might speculate that AChEI would reduce the frequency of core symptoms, sleep disturbances, caregiver distress and disturb the clusterization of the participants. However, there were not major differences between the DLB and AD groups. Still, applying multiple regression analyses controlling for potential biases might have yielded slightly different results.

Conclusions, implications and directions for future research

Conclusions

In geriatric medicine and old age psychiatry combined 20% of persons with mild dementia were diagnosed to have DLB. This made DLB the second most frequent primary dementia disorder in our cohort. We found 80% of the DLB patients to have a sleep disturbance, significantly more than in the AD group and in normal age-matched controls. In DLB, the frequencies of REM sleep behaviour disorder, excessive daytime sleepiness and sleep walking differed from AD. Anxiety and depression were found to be clinical correlates of sleep disturbances in our mild dementia cohort. Finally, in the cluster analysis we identified four clusters: in cluster 1, named the LBD-cluster, participants with a clinical diagnosis of DLB and PDD clustered together based on their scores on scales for hallucinations, fluctuations, motor parkinsonism and RBD, thus providing empirical support for the DLB diagnosis. We provided cut-off scores on scales for the core and suggestive symptoms in DLB and identified a distinct cognitive profile in the LBD- cluster.

Implications for clinical practice

DLB is common in out-patient dementia clinics in Western Norway and is probably among the most common cause of primary degenerative dementia even in other clinical settings. DLB can be diagnosed reliably with the revised clinical criteria and clinical instruments like the NPI, fluctuation inventories, UPDRS-3 and MSQ. Cut-off scores on these scales are provided and can now be applied in other clinical settings like nursing homes, general practice and hospitals. Sleep disturbances in mild dementia are common in DLB and correlated with anxiety and depression and as a consequence should be screened for and treated in the clinic. Clinicians seeing patients

with dementia need to systematically screen for visual hallucinations, cognitive fluctuations, parkinsonism and RBD to diagnose DLB.

Directions for future research

In DLB the sensitivity and specificity of the revised DLB criteria as compared to neuropathology need to be explored to determine if the specificity is acceptable and to determine their positive predictive value in different clinical settings. The stability of the core and suggestive features of DLB over time needs to be explored, in particular the clinical course of patient fulfilling the criteria for possible DLB need to be characterised.. Treatment studies of sleep disturbances and other clinical features in DLB with both pharmacological and non-pharmacological interventions are urgently needed. New biomarkers in CSF for diagnostic and prognostic purposes as well as for ultimately underpinning the development of future disease modifying interventions are needed.

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Appendix

Revised criteria for the clinical diagnosis of DLB

1. **Central feature (essential for a diagnosis of possible or probable DLB)**
 - Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
 - Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
 - Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.
2. **Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB.)**
 - Fluctuating cognition with pronounced variations in attention and alertness.
 - Recurrent visual hallucinations that are typically well formed and detailed.
 - Spontaneous features of parkinsonism.
3. **Suggestive features (If one or more of these is present in the presents of one or more core features a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)**
 - REM sleep behaviour disorder
 - Severe neuroleptic sensitivity
 - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging.
4. **Supportive features (commonly present but not proven to have diagnostic specificity)**
 - Repeated falls and syncope
 - Transient, unexplained loss of consciousness
 - Severe autonomic dysfunction, e.g. orthostatic hypotension, urinary incontinence.
 - Hallucinations in other modalities
 - Systematized delusions
 - Depression
 - Relative preservation of medial temporal lobe structures on CT/MRI scan
 - Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
 - Abnormal (low uptake) MIBG myocardial scintigraphy
5. **A diagnosis of DLB is less likely**
 - In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging.
 - In the presence of any other physical illness or brain disorder sufficient to count in part or in total for the clinical picture
 - If parkinsonism only appears for the first time at a stage of severe dementia
6. **Temporal sequence of symptoms**
 - DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is presented). (Shortened, see reference (I. G. McKeith, et al., 2005) for full text.)

Table 1 Pathological and clinical cohorts reporting the frequency of DLB

First author and reference	N	Criteria for DLB	The frequency of DLB in dementia cohort studied
(Perry, et al., 1990)	N=93, AS	Pathological	19%
(Shergill, Mullan, D'ath, & Katona, 1994)	N=114, CC	Mc Keith 1992	26,3%
		Byrne 1991 probable	7%
		Byrne 1991 possible	16,6%
(CG Ballard, et al., 1993)	N=58, CC	McKeith 1992	24,1% (14 of 58)
(C. Ballard, et al., 1995)	N=124, CC	McKeith 1992	9,7% (12 of 124)
(C. Ballard, et al., 2001)	N=193, CR	McKeith 1996	24% (37 of 154)
(Del-Ser, Munoz, & Hachinski, 1996)	N=73, AS	Pathological	15% (11 of 73)
(Londos, Passant, Brun, & Gustafson, 2000)	N=200, AS	McKeith 1996	24% (48 of 200)
(Chan, Chiu, Lam, & Leung, 2002)	N=102, CC	McKeith 1996	2,9% (3 of 102)
(Lopez, et al., 2003)	N=333, CC	McKeith1996	13,8% (46 of 333)
(Takada, et al., 2003)	N=454;CC	McKeith 1996	2,2%
(Fujihara, Brucki, Rocha, Carvalho, & Piccolo, 2004)	N=141, CC	McKeith 1996	0%*
(Farina, et al., 2009)	N=102, CC	McKeith 1996	4,8%
(Aarsland, et al., 2008) (Paper 1 in thesis)	N=196, CC	McKeith 2005	20%

Note: AS= autopsy series, CC=clinical cohort, CR=case register. *not reported in paper but in e-mail from corresponding author.

Table 2 Community based studies reporting the frequency of DLB

Reference	N	Criteria*	Age	Frequency	Comment
(Stevens, et al., 2002)	107	1	≥65	30.5%	Only patients with VH included
(Rahkonen, et al., 2003)	137	1	≥75	21.9%	Only persons aged 75 or older in Finland.
(Sambrook, et al., 2004)	766	1	>60	3%	Canadian Outcomes Study in Dementia
(Lam, et al., 2008)	2073	1	>70	3.6%**	Thematic Household Study Hong Kong
(de Pedro-Cuesta, et al., 2009)	1194	0	>70	0.8-2%	Reanalysis of Spanish community surveys.
(Shaji, Iype, & Anandan, 2002)	51	1	>60	12%	Kerala India
(Harvey, Skelton-Robinson, & Rossor, 2003)	227	CC	<65	7%	Age below 65 years UK
(Lopez, et al., 2003)	707	1	>65	3.5%	US Cardiovascular Health Cognition Study
(Wakisaka, et al., 2003)	102***	P	>65	41.4%	Community based pathology study Japan
(Matsui, et al., 2009)	275	P	≥65	10.6%	Pathologically verified diagnoses Japan
(de Silva, et al., 2003)	28	1	≥65	3.6%	Semi-urban population India
(Herrera, et al., 2002)	118	1	≥65	1.7%	Brazil
(Yamada, et al., 2001)	142	1	≥65	0.1%	Rural town Japan
(Yamada, et al., 2002)	19	1	≥70	0%	Japanese-Brazilian
(Miech, et al., 2002)	185	0	≥65	3.2%	Cache County Study US
(MRC-CFAS 2001)****	109	P	>70	12%	MRC-CFAS study UK
(Jhoo, et al., 2008)	37	1	>65	0.4%	Korean Longitudinal Study of Health and Aging

Note: *Criteria 1 = McKeith et al. 1996, 0= no criteria, CC= clinical criteria, P=pathological. **DLB+PDD ***29 demented

****("Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales.

Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)," 2001)

Table 3 Studies reporting the incidence of DLB

Study	Age	N*	Criteria**	DLB incidence
(Matsui, et al., 2009) Hisayama- study	65+	828/81	1	1.4 per 1000 persons per year
(de Lau, et al., 2004)	55+	6839	0	0.7 per 1000 person per year (95% CI,0,4-1,0)
(Lopez-Pousa, Vilalta- Franch, Llinas-Regla, Garre-Olmo, & Roman, 2004)	75+	1198/18	0	2% of annual clinical dementia incidence in a memory clinic
(Miech, et al., 2002)	65+	185/6	0	0.1% per year in general population 3.2% per year of all new dementia

*population/DLB ** 1=McKeith 2005 0= no criteria

Table 4 Staging of Lewybody pathology in the human brain

Reference	Year	Comment
(Kosaka, et al., 1984)	1984	<u>Group A:</u> Diffuse type of LBD; cerebral cortex, basal ganglia, diencephalon and brainstem affected by Lewybody pathology <u>Group B:</u> Transitional type between A and C <u>Group C:</u> Brainstem and diencephalon affected like in PD
(Braak, et al., 2003)	2003	<u>Stages 1-2:</u> Presymptomatic; pathology confined to medulla oblongata and olfactory bulb <u>Stages 3-4:</u> Symptomatic phase; affection of the substantia nigra, midbrain and basal forebrain. <u>Stages 5-6:</u> Cognitive failure and dementia, cortex affected.
(Halliday, et al., 2008)	2008	<u>Group 1:</u> Younger patients with distribution of pathology according to the Braak staging. <u>Group 2:</u> Early malignant dementia dominant syndrome <u>Group 3:</u> Older onset, shorter survival and more pronounced Lewy related pathology.
(Beach, et al., 2009)	2009	<u>I</u> Olfactory Bulb <u>Ia</u> Brainstem Predominant <u>Ib</u> Limbic Predominant <u>III</u> Brainstem and Limbic <u>IV</u> Neocortical

Table 5 Validation studies for pathological criteria

Reference	Year	Criteria*	Comment
(Muller, et al., 2005)	2005	2	Modification and simplification of the Braak 2003 criteria
(Leverenz, et al., 2008)	2008	1	49% of cases not classifiable
(Parkkinen, Pirttila, & Alafuzoff, 2008)	2008	1&2	Modifying criteria classifies 96-97%
(Fujishiro, et al., 2008)	2008	1	83% had a distribution of α -synuclein as suggested 48% were demented and 54% had EPS
(Alafuzoff, et al., 2009)	2009	1	More than 95% of clinically probable DLB cases met pathological criteria of intermediate- (12 cases; 29%) or high likelihood DLB (28 cases; 67%).
	2009	2	Inter-observer agreement was 80% (McKeith 2005)
			Inter-observer agreement was 65%(Braak 2003)
			Inter-observer agreement was 78% (Leverentz 2009)
			Inter-observer agreement was 82% (Muller 2005)

Note: *Criteria 1= McKeith 2005 2 = Braak 2003

Table 6 Gene mutations and their clinical phenotypes

Gene mutation	Reference	Clinical phenotype
A53T SNCA	(Yamaguchi, et al., 2005)	PD, PDD or DLB
A30P SNCA	(Polymeropoulos, et al., 1997)	Typical PD
E46K SNCA	(Zarranz, et al., 2004)	PD, PDD or DLB
G209A SNCA	(Morfis & Cordato, 2006)	DLB
Duplication SNCA	(Chartier-Harlin, et al., 2004)	Classic PD
Triplication SNCA	(Singleton, et al., 2003)	PDD and DLB
V70M SNCB	(Ohtake, et al., 2004)	DLB
P123H SNCB	(Ohtake, et al., 2004)	DLB
GBA	(Sidransky, et al., 2009) (Mata, et al., 2008)	PD PD and DLB
LRRK2 (PARK8)	(Zimprich, et al., 2004)	PD, PDD and DLB

Table 7 Demographics and baseline characteristics of included participants

	All*	AD	VaD	DLB	FTD	PDD	p-value
Number(%)	196(100)	128(65.3)	11(5.6)	39(19.9)	4(2.0)	11(5.6)	
Age	76.1(7.8)	75.6(7.7)	78.5(6.6)	78.4(7.9)	65.6(4.3)	76.7(8.2)	0.021 ²
% Male	40.7	29.8	72.7	48.6	75.0	90.0	0.001 ⁶
Education	9.5(2.9)	9.5(2.9)	10.1 (2.1)	9.2(2.6)	10.0(5.4)	8.9(3.1)	0.920
Duration	2.7(2.2)	2.3(1.6)	5.4(5.1)	3.3(2.2)	4.8(2.5)	2.1(1.7)	<0.0005 ³
MMSE	23.9(2.3)	23.8(2.2)	23.4(2.8)	23.7(2.6)	23.5 (4.0)	25.7(2.0)	0.100
NPI ¹	19.6(18.3)	16.4(15.9)	22.7(20.4)	29.7(21.2)	25.5 (18.4)	18.6 (20.2)	0.003 ⁴
UPDRS-3	6.4(10.2)	2.3 (3.7)	7.2(6.0)	13.1(13.3)	3.8 (4.3)	29.5 (11.4)	<0.0005 ⁵
MADRS	7.8 (5.9)	6.9 (5.6)	8.2 (6.6)	9.4 (5.5)	9.75 (8.2)	11.8 (7.8)	0.047 ⁷

Numbers represent number of subjects and frequency or mean and standard deviation. *Included 3 persons diagnosed with alcoholic dementia. ¹NPI scores are total frequency times intensity scores. P-values are based on ANOVA and chi-square tests and post hoc tests on the Bonferroni correction for parametric data and the Kruskal-Wallis test and Mann-Whitney test posthoc for non-parametric data. ²Posthoc analyses: significant difference DLB vs. FTD. ³VaD vs. AD, DLB and PDD. ⁴AD vs. DLB. ⁵AD vs. DLB and PDD. PDD vs. VaD and FTD. ⁶Comparing all dementia subtypes. When comparing sex in DLB vs. AD p=0.024 ⁷DLB vs. AD and PDD vs. AD

Levels of Evidence Class I-IV

“Class I includes prospective, randomized, controlled clinical trials with a representative population and masked outcome. At this level, four criteria must be met: 1 designation of primary outcomes, 2 clear definition of exclusion and inclusion factors, 3 adequate counting of dropouts, and 4 presentation of baseline characteristics that indicate enough similar between groups to make a valid comparison. Class II studies are prospective, matched-group, cohort studies, or an RCT performed in a representative population and with a masked outcome. Class II lacks the four criteria required in class I. Class III evidence indicates all other controlled trials, such as studies based on natural history, in which the outcome assessment is independent of the treatment. Class IV evidence includes uncontrolled studies, case reports, and consensus or expert opinion groups.” (Reference American Academy of Neurology)