Dementia with Lewy bodies —an Investigation of Cause and Consequence

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—an Investigation of Cause and Consequence

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Abstract

Dementia with Lewy bodies (DLB) is today considered to be the second most common primary neurodegenerative dementia after Alzheimer's disease. However, the disease has only been a clearly defined entity for 13 years. Due to its recent recognition, DLB is still not as extensively studied as are other major dementia disorders such as Alzheimer's disease (AD), vascular dementia, and fronto-temporal dementia.

In summary, this thesis demonstrates important differences between AD and DLB. Paper I and II focus on the ultimate consequences of the disease, including resource consumption and impact on quality of life, and demonstrate much more severe consequences of DLB. Paper III and IV focus on diagnosis and prediction of disease progression through CSF analysis, and demonstrate a robust increase of CSF Ca and Mg in DLB but not in AD. Furthermore, CSF t-tau, a marker of AD and neurodegeneration, is demonstrated to increase mortality in DLB, but not in AD. These DLB specific CSF findings give us further understanding of the factors that may trigger the disease and determine disease course. Furthermore, CSF Mg and Ca may be a valuable tool in making a DLB diagnosis, especially when the considered differential diagnosis is AD.

Key words
dementia, Alzheimer's disease, Lewy body disease, dementia with Lewy bodies, health economy, quality of life, health related quality of life, cerebro spinal fluid, trace elements, calcium, magnesium, diagnosticts, T-tau, survival, mortality

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Dementia with Lewy bodies

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List of papers

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II Bostrom, F., L. Jonsson, L. Minthon, and E. Londos. Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. Alzheimer Dis Assoc Disord. 2007. 21 (2): 150–4.

III Bostrom, F., O. Hansson, L. Gerhardsson, T. Lundh, L. Minthon, E. Stomrud, H. Zetterberg, and E. Londos. CSF Mg and Ca as diagnostic markers for dementia with Lewy bodies. Neurobiol Aging. 2009. 30 (8): 1265–71.

IV Bostrom, F., O. Hansson, L. Gerhardsson, T. Lundh, L. Minthon, E. Stomrud, H. Zetterberg, and E. Londos. CSF T-tau predicts survival in dementia with Lewy bodies. Submitted for publication in "Dementia and Geriatric Cognitive Disorders"

Contents

Abbreviations

Alzheimer's disease	AD
Alzheimer's Disease with Vascular components	AD-Vasc
A Quick Test	AQT
Cerebrospinal Fluid	CSF
Dementia with Lewy bodies	DLB
Lewy Body	LB
Lewy Neurites	LN
Mini Mental State Examination	MMSE
Parkinson's Disease	PD
Rapid Eye Movement	REM
Vascular dementia	VASC
Quality of life	QoL

1 Dementia with Lewy bodies — Introduction

1.1 Historical perspective

In 1817, the British physician James Parkinson wrote “An Essay on the Shaking Palsy”[1], thereby recognizing, for the first time, the disease later named “Parkinsons disease” by Jean-Martin Charcot. In 1861 to 1862, Charcot and Vulpian stated, with regard to the disease described by Dr Parkinson: ” In general psychic features are definitely impaired” and “The mind becomes clouded and the memory is lost”. Thus, a condition resembling dementia with Lewy bodies is described for the first time. In 1912, Friedrich Henry Lewy described intra neuronal inclusions in patients with Parkinson’s disease [2] In 1919 these came to be called “corps de Lewy” by Tretiakoff, who also noted that the inclusions were predominant in the substantia nigra [3]. Dr Lewy continued his research, and in 1923 he described widespread cortical Lewy bodies in certain patients i [4], the majority of whom had developed marked mental alteration.

The first study that directly linked dementia to widespread Lewy body pathology was published in 1961 [5]. The two case reports in this study featured many symptoms typical for DLB. In the 1980s, a series of case reports were published, and in 1984 Kosaka and colleagues suggested that these represented a new disease entity; diffuse Lewy body disease [6]. Increased knowledge and research led to a general recognition of Lewy body associated dementia, and in 1995, a consensus report laid out the diagnostic criteria for dementia with Lewy bodies (DLB) [7]. These criteria were updated in 2005 [8]. Thus, although the link between dementia and Lewy bodies has been known for some time, the disease has only been a clearly defined entity for 14 years. Due to its recent recognition, DLB is still not as extensively studied as are other major dementia disorders such as Alzheimer’s disease (AD), vascular dementia, and fronto-temporal dementia. However, more and more research is done each year. In 2007, 385 new research articles were indexed in PubMed, compared to 130 ten years earlier (Figure 1).

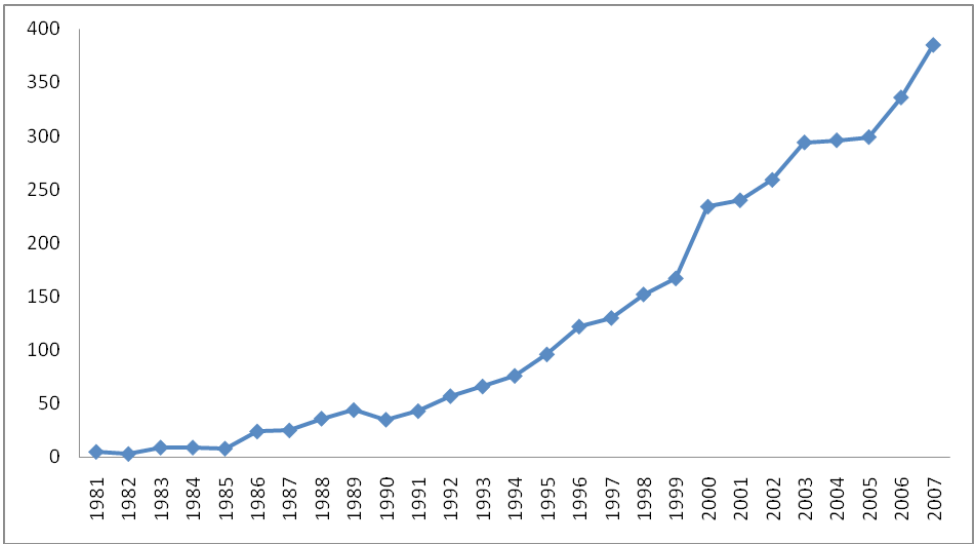

Figure 1. ***Number of articles published on dementia with Lewy bodies.***
All articles indexed in PubMed with the search terms "dementia" and "Lewy body disease" or "Dementia with Lewy bodies" each year.

1.2 Epidemiology

Dementia with Lewy bodies (DLB) is today considered to be the second most common primary neurodegenerative dementia after Alzheimer's disease. However, the exact prevalence is disputed as study results vary; a recent review noted prevalence estimates from 0 to 5 % with regard to the general population, and from 0 to 30.5% of all dementia cases [9]. DLB usually presents in late adulthood between the ages of 60 to 90, and there are no known differences regarding gender or ethnicity [9], although most DLB studies include a majority of male patients [10, 14].

1.3 Pathogenesis

1.3.1 Pathology

The Lewy body (LB) is an eosinophilic intraneuronal inclusion that was first observed in the basal forebrain and nucleus dorsalis n. vagi of patients with Parkinson's disease (PD). In typical localized PD, LBs and the related Lewy neurities (LN) occur primarily within cholinergic neurons in nucleus basalis Meynert as well as in monoaminergic neurons in locus coeruleus and the substantia nigra. In DLB, LBs and LNs are also found in the neocortex. There is, however, a significant pathological overlap between DLB and PD. The LNs and the neocortical LBs are harder to identify as

they lack the clear halo of the typical subcortical LB [6]. DLB patients also frequently exhibit concomitant AD pathology, primarily amyloid plaques, in addition to LBs and LNs. In contrast to AD, however, the typical DLB brain does not present tangles.

1.3.2 α-synuclein aggregation

The LB and the LN consists mainly of α-synuclein. α-synuklein is an abundant presynaptic brain protein with an unknown physiological role. It is suggested that there is an equilibrium between the "normal" unfolded conformation of α-synuklein and the partially folded conformation [15]. In α-synucleinopathies, ie DLB, Parkinson's disease and multiple system atrophy, in vitro studies suggest that this equilibrium may be pushed towards the partially folded configuration by different factors such as charged metal ions, herbicides, and pesticides. The product depends on the exact environmental conditions, but may result in oligomerisation and aggregation into insoluble fibrils that form intracellular inclusions. However, the precise role of α-synuclein containing inclusions remains elusive, and several lines of evidence suggest that the neurotoxic effect is primarily caused by soluble oligomers, before the α-synuclein forms fibrills and aggregates to inclusions [15, 17]. In fact, cortical LBs do not correlate with disease severity [18, 19], and they have even been suggested to sequester neurtoxic α-synuclein oligomers, and thus *protect* against neurodegeneration [17].

1.4 Clinical features and diagnostic criteria

1.4.1 A case report

This is a brief account of a male patient who presented with many symptoms typical of DLB.

The patient was born in 1936. He worked as a glass cutter until 1997, when his coworkers noted that he had started to measure and cut incorrectly, without noticing it himself. In 1998, the patient started having difficulty sleeping and was experiencing mood swings. During the night, he could become physically abusive, and was increasingly unable to separate dreams from reality. During the day, his moods shifted between sadness, silence or anger and he was never perceived as being happy. The patient visited his general practitioner, who prescribed an antidepressant (Citalopram). The patient took this medication for two years without showing any improvement.

The patient's wife noticed that his driving skills deteriorated and he became involved in several minor incidents. Once, the patient suddenly became desoriented while

driving, and at another time he drove into a fence. In 2000 the patient conceded that he could no longer estimate distances and agreed to stop driving. The patient was convinced that his visual disability was due to poor corrective lenses but neither an optician nor an ophthalmologist could find anything wrong. In 2002 the patient started seeing people that were not there. This occured with increasing frequency and he often made comments such as "When are the guests going home?" or "I told them to leave, but they don't listen!" His wife also felt that the patient was more withdrawn and he was often observed staring into space or sleeping during the day.

The patient visited his general practitioner for a routine checkup. Except for a slightly elevated blood-glucose concentration, nothing unusual was found in the patient's physical or blood status.

The patient's family was troubled by his declining functional abilities, though they fluctuated greatly, and the family sometimes thought that the patient was pretending his inabilities.

In 2004 the patient again visited his general practitioner together with his wife and daughter. The doctor noted a loss of short term memory and an inability to find his way in familiar surroundings. He could, for instance, lose his way on his way to the bathroom, especially at night. Furthermore, the patient developed a typical Parkinsonian gait with decreased arm swing as well as masked face and clear cogwheel rigidity in his arms. A CT-scan of the brain showed nothing abnormal. In 2005 the patient's wife again contacted the general practitioner and reported a further decline in memory and a 5–7 kg weight loss over the past year. The patient was referred to a memory outpatient ward. The dementia specialist concluded that the patient suffered from probable dementia with Lewy bodies. An attempt to medicate with Galantamin (acetylcholine esterase inhibitor) was discontinued due to diarrhea. In August 2006 the patient began alternating between a two week stay at a nursing home and two weeks in his own home. The admitting nurse noted that the patient was totally dependent on assistance in all activities of daily living. In Jan 2007 the patient died of an unclear, acute condition. The post mortem examination showed a thrombosis in v. femoralis and bilateral pulmonary embolism. At inspection, the cerebral cortex was appraised as being generally thin, though no further neuropathological examination was done.

The spouse believes that the patient was aware of his disabilities through to the end. This caused him grief and he would sometimes talk about taking his own life. He never had any trouble recognizing his family members, and even when the disease progressed, he recognized which football teams were on TV, and could recognize and enjoy talking to his old football mates.

1.4.2 Diagnostic criteria

DLB can be viewed as in a continuum between AD and PD, both from a clinical and pathological perspective (Figure 2).

In accordance with the general definition of dementia, the DLB patient suffers from progressive disabling mental impairment. Furthermore, the DLB patient has a set of characteristic clinical features that are summarized in the current DLB consensus criteria [8] according to Table 1. These criteria enable a diagnosis of *possible* or *probable* DLB. A *definate* diagnosis requires a post mortem examination. Using the older DLB criteria [7], studies of diagnostic accuracy have revealed acceptable specificity (71 to 95 %), but generally lower sensitivity (18 to 83 %) [20, 21]. In a recent prospective study, 86 % of the patients with probable DLB had diffuse cortical Lewy bodies [22].

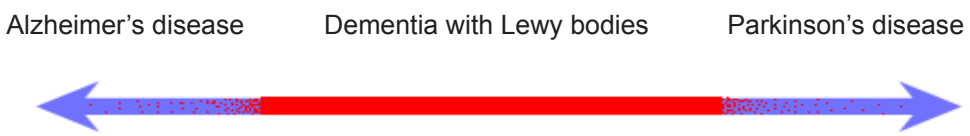

Figure 2. *DLB in a continuum. Dementia with Lewy bodies can be viewed as is in a continuum with Parkinson's disease and Alzheimer's disease, both from a clinical and pathological perspective.*

1.4.2.1 Core features

Fluctuating cognition is thought to depend on fluctuations in attention and alertness and is the most difficult core feature to ascertain. The typical clinical presentation is increased total sleeping time, daytime drowsiness, episodes of staring into space and periods when the patient's thoughts seem incoherent. This feature can be visualized on an EEG as a greater variability in delta-band power in parietal electrodes [23].

Visual hallucinations are often recurrent and elaborate. As the disease progresses, the severity of this symptom typically progresses from mild, often illusion-like, hallucinations, which the patient know are not real, to complex forms without insight. The visual hallucinations may be linked to a reduced blood flow in the cortex of lobus occipitalis as visualized by functional brain imaging [24].

Parkinsonism has to be primary, i.e. not iatrogenic or caused by a localized cerebral infarction [7]. Furthermore, dementia symptoms must appear prior to, or up to one

year after occurrence of parkinsonism, otherwise a diagnosis of PD or PD with dementia (PDD) is more likely. In DLB, parkinsonism is most commonly presented as bradykinesia, facial masking and rigidity. Resting tremor is not as common as in PD [25]. DLB patients often benefit from a tentative L-dopa treatment, though they generally do not respond as well as PD patients [26].

1.4.2.2 Suggestive features

REM sleep behavior disorder can precede dementia onset by many years and is manifested as vivid dreaming and motor activity, without the muscle atonia present in normal dreaming. The patients "act" out their dreams, both verbally and motorically, sometimes violently which may cause the spouse to sleep in a separate bedroom [27, 28].

Severe neuroleptic sensitivity is thought to be caused by a downregulation of D2 receptors. A "stress" test is not recommended as this may cause irreversible damaging to the patient, even fatal reactions haven been described already at low doses [29].

DaT-Scan (functional imaging of the Dopamine Transporter) estimates the presynaptic dopaminreceptor activity and thus provides an estimation of intact dopaminergic neurons in substantia nigra, which are decreased in DLB but not in AD [30]. DaT-scan helps in distinguishing DLB from AD when there are diagnostic uncertainties.

1.4.2.3 Supportive features

In addition to the core and suggestive features of DLB, there are some clinical features that are typical, but not diagnostic [8]. *Repeated falls and syncope* and *transient, unexplained loss of consciousness* may be linked to s*evere autonomic dysfunction* which causes hypotension following orthostatic challenge [31]. In addition, the autonomic dysfunction leads to decreased sympathetic cardiac innervation which can be visualized as *Low uptake on MIBG myocardial scintigraphy.* Other common symptoms of autonomic dysfunction are urinary incontinence, obstipation, impotence as well as eating and swallowing difficulties. *Hallucinations in other modalities, depression* and *systemized delusions* may easily be confused with primary psychiatric diagnoses if the symptoms are not recognized as part of DLB. In contrast to AD patients, DLB patients typically have a *relative preservation of medial temporal lobe structures on CT/MRI* and a *reduced occipital activity on SPECT/PET.* Finally, a routine EEG often demonstrates *prominent slow wave activity on EEG with temporal lobe transient sharp wave.*

Table 1. Current DLB consensus criteria.
Two core features or one core feature and one suggestive feature have to be present for a *probable* DLB diagnosis. One core feature or one suggestive feature is sufficient for a *possible* DLB diagnosis. A *certain* diagnosis requires post mortem examination.

Core features
Fluctuation Cognition
Visual Hallucinations
Parkinsonism
Suggestive features
REM sleep behavior disorder
Severe neuroleptic sensitivity
Low presynaptic dopamine receptor activity in basal ganglia
Supportive features
Repeated falls and syncope – Transient, unexplained loss of consciousness – Severe autonomic dysfunction –Hallucination in other modalities – Systemized delusions – Depression – Relative preservation of medial temporal lobe structures on CT/MRI – Reduced occipital activity on SPECT/PET – Low uptake on MIBG myocardial scintigraphy – Prominent slow wave activity on EEG with temporal lobe transient sharp waves.

1.4.3 Cognitive profile of the DLB patient

Commonly used cognitive tests, such as MMSE [32], cannot be used to distinguish DLB from other dementias, and DLB patients will often score highly on these tests even when dementia is evident. The DLB patient's memory is often relatively preserved while attention, executive and visospatial abilities falter [33, 34]. *Mental slowing* is often obvious and can be demonstrated in cognitive tests, such as AQT [35].

1.4.4 Bio-markers of DLB

In AD, the CSF markers T-tau, P-tau and Aβ42 are commonly used to aid in diagnosis. However, discrepant quantities of these CSF AD markers have been found in DLB. Yet, the overall trend is values somewhere between AD and controls, and these markers cannot be used to reliably differentiate between DLB and AD [36–38]. Moreover, methods for determining CSF α-synuclein have been developed [39], but have not yet demonstrated any potential as diagnostic markers for DLB. Thus, there have been no reliable cerebrospinal fluid or genotypic biomarkers available to support a diagnosis of DLB in vivo [8], prior to the projects in this thesis.

2 Aims of the thesis

A general model of disease research in humans is presented in Figure 2. The original aim of this thesis was to explore the uppermost "level", in other words the general interaction of DLB with the individual and society (Paper I and II). The third study was aimed at investigating the metal profile in DLB patients' cerebrospinal fluid (CSF) and plasma, bearing in mind that earlier life exposition may alter this metal pattern. However, the results of paper III yielded a new hypothesis for the importance of increased CFS Ca and Mg, two physiologically regulated trace elements, in the pathogenesis of DLB. To further explore this hypothesis, a fourth study was conducted (Paper IV) to determine the influence of these CSF metal on disease course. In addition, CSF AD markers were included as possible determinants, as concomitant AD-pathology is known to increase mortality in DLB.

Paper I To compare QoL in patients with DLB and patients with AD. The secondary aim of this study was to investigate determinants of QoL in DLB such as cognition, behavioural disorders, disability, age, co-morbidity, institutionalisation and whether the patient is living together with a caregiver or alone.

Paper II To compare costs of care, including formal and informal costs, for patients with AD and DLB. The secondary aim was to assess determinants of costs of care in DLB.

Paper III To investigate the metal pattern in the CSF of patients with DLB compared to controls, AD patients and patients with AD-Vasc.

Paper IV To explore CSF levels of AD associated bio-markers and CSF metal concentrations as determinants of survival among DLB patients.

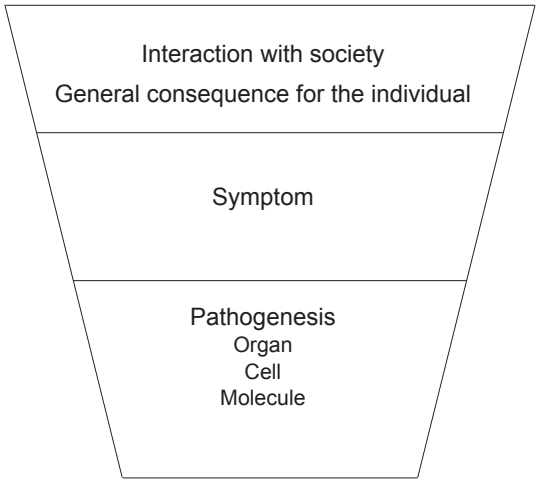

Figure 3. ***A general model of disease research in Homo sapiens.***
This model is an attempt to comprise all research regarding a single illness. A modification of the World Health Organization's model for functioning, disability and health [40].

3 Materials

All four studies in this thesis include patients with clinically probable DLB according to the consensus criteria [8]. Although a post mortem examination is required to make a certain diagnosis, the high specificity of the diagnostic criteria produced a representative DLB group [20, 21, 22].

Paper I and II

Thirty-four patients with DLB, attending regular visits to the memory clinic, University Hospital MAS, Malmö, Sweden, were included. These patients were matched with 34 patients with AD according to gender, age and cognitive function. The AD patients were selected from a group of 272 patients attending regular visits to six memory clinics in Sweden, Finland and Norway.

Paper III

CSF and plasma samples were obtained from 29 patients with DLB, 174 with AD and 90 with clinical criteria for AD and a history of at least one suspected cerebrovascular insult and/or minor ischemic insult on computerized tomography without any clear causative effect on the development of clinical dementia (AD-Vasc). All included patients were admitted to the memory clinic, University Hospital MAS between 1999 and 2003.

Paper IV

47 DLB and 157 AD patients admitted to the memory clinic, University Hospital MAS, as well as 49 healthy volunteers were included in a longitudinal prospective study between 1999 and 2003.

Table 2. Demographics and cognitive function of study subjects in respective group.

Study	Diagnosis[a]	N	Gender[b] male/female	Age[c] median (range)	MMSE[d] median (range)
I and II	DLB	34	19/15	78 (64-87)	20 (0-29)
	AD	34	19/15	79 (63-92)	20 (0-30)
III	DLB	29	17/12	74 (54-84)	23 (14-29)
	AD	174	52/122	74 (52-86)	22 (2-30)
	AD-Vasc	90	33/57	77 (57-87)	22 (6-30)
	Controls	49	15/34	73 (60-87)	30 (27-30)
IV	DLB	47	25/22	77 (55-89)	23 (10-30)
	AD	159	39/120	76 (52-86)	21 (2-29)
	Controls	49	15/34	73 (60-87)	30 (27-30)

[a] DLB = Dementia with Lewy Bodies, AD = Alzheimer's Disease, AD-Vasc = Alzheimer's Disease with Vascular components.

4 Methods

4.1 Paper I and II

The DLB and AD group were evaluated in their homes or at a memory clinic together with their primary caregiver; the spouse in 20 cases, the patient's child in 11 cases and a sibling in three cases.

Psychometric tests

Cognitive function was assessed with the Mini Mental State Examination (MMSE) [41]. Behavioural disturbances were measured with the Neuropsychiatric inventory (NPI) [42] which includes questions regarding presence and severity of hallucinations, agitation, depression, anxiety, apathy, euphoria, desinhibition, irritability, aberrant motor behaviour, sleep disorder, and eating disorder. These disturbances can be analyzed either as one variable or item by item.

Measurement of disability

The DLB patients were examined in regard to dependency in Activities of Daily Living (ADL) with the Disability Assessment for Dementia scale (DAD) [43]. This instrument includes questions regarding 4 domains related to basic self-care (hygiene, dressing, continence, and eating) and 6 domains related to instrumental activities of daily living (meal preparation, telephoning, going on outings, management of finance and correspondence, management of medications, leisure activities, and housework).

Comorbidity

Co- morbidity was assessed in the DLB group using 12 domains: Hypertension, heartfailure, thyroid disease, diabetes, autoimmune disorder, cancer, hyperlipidemia, ischemic heart disease, stroke, asthma, COPD, and migraine. Information regarding the prevalence of Parkinson's disease (PD) was gathered in the AD material, but was not analysed as co-morbidity in these studies as it is not possible to suffer from both PD and DLB.

Resource utilisation

Resource use was measured with the "Resource Utilisation in Dementia" instrument (RUD Lite) [44], which contains questions concerning use of community care services, type of accommodation, the employment status of the patient and primary caregiver, medical care, and informal care. Informal care was divided into lost pro-

ductive time or leisure time depending on if the primary care giver was aged above or below 65 years of age. Lost production was estimated according to mean salaries in Sweden (197 SEK /h) [45], and lost leisure time was assessed according to studies by the Swedish Road Administration that measured how much Swedish drivers were willing to pay to reduce travel time (28 SEK /h) [46].

Quality of life

At, present, no validated DLB-specific QoL instrument is available. Thus, in this study we used the QoL-AD [47] and EQ5D [48]. Both instruments were administered to both patients and caregivers.

The QoL-AD is a QoL instrument specifically developed for use with patients with AD. Thirteen domains (physical health, energy, mood, living situation, memory, family, marriage, friends, self, ability to do chores, ability to do things for fun, money and life as a whole) are rated on a four-point scale, 1 being poor and 4 being excellent.

The EQ-5D is a generic QoL instrument in which the respondents are asked to rate their current health status in five dimensions; mobility, hygiene, usual activities, pain/discomfort and anxiety/depression. For each of the possible health states, a utility weight can be assigned through an algorithm that has been developed based on a time trade-off study in the United Kingdom [49]. The utility weight is a number <1, where 0 equals death and 1 equals perfect health, indicating the attractiveness of the health state based on the preferences of the general population. The EQ-5D also includes a visual analogue scale (VAS), anchored at perfect health (100) and death (0). Thus, three values representing QoL were acquired with these two instruments.

Statistical analyses

The Mann-Whitney U test was used to analyse differences between the AD and DLB group with respect to demographics and test results. Linear regression analysis was used to analyse determinants of QoL and resource utilisation, and Spearman rank-order correlation was used to compare the three acquired QoL values and to correlate resource utilisation with the significant determinants from the regression analysis.

4.2 Paper III and IV

Metal concentration in plasma and CSF

The total concentrations in CSF and plasma of metals were determined by inductively coupled plasma-mass spectrometry [50]. In brief, the samples are injected into

an argon plasma that holds about 10 000 K – or approximately twice the temperature of the face of the sun. At this temperature, all present metals are ionized. Thereafter, the metal ions are separated on the basis of their mass-to-charge ratio and a detector receives an ion signal proportional to the concentration of respective metal.

Protein analysis in CSF and plasma

Albumin levels in CSF and serum were measured by immunonephelometry, which is an antibody-antigen based method. CSF total-tau (T-tau), phosphorylated tau (P-tau) and Aβ42 concentrations were measured with xMAP method and the INNOBIA AkzBio3 kit (Innogenetics) as described by Olsson and colleagues [51]. The xMAP method is based on fluorescent beads that bind receptors, for example antibodies, for the desired analyte. The beads can also be colored differently. In this study, three different beads were used to bind receptors for T-tau, P-tau and Aβ42 respectively. The beads are put in solution with the substrate (CSF in this case), and bind their respective analytes. They then pass through a sensor with lasers of two different wavelengths that detect: 1 which beads pass through (=which analyte), and 2 how many detector molecules are bound to them (=how much analyte).

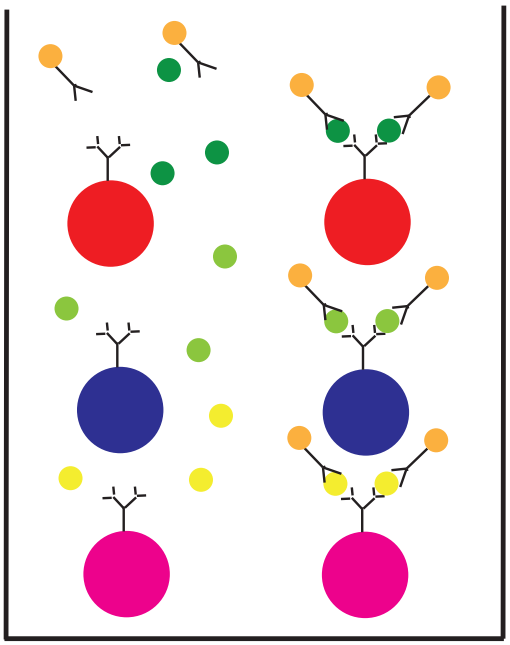

Figure 4. A graphical illustration of the simultaneous binding of three different analytes to their repectuiv fluorescent bead and tracer molecules.

Statistical analysis

The Mann-Whitney U test was used to analyse differences between the AD and DLB group with respect to demographical data. Differences in metal concentrations between DLB and AD, AD-Vasc and controls was assessed with non-parametric Kruskal-Wallis one-way analysis of variance followed by the non parametric Mann Whitney U-test for continuous variables since the metal concentrations were not normally distributed.

Spearman's rank order correlation was performed post hoc to analyze the relationship between the two metals that were significantly increased in the DLB patients compared to the controls. The Youden method [52] was used to establish the optimal cut-off point to assess the diagnostic accuracy of the different metal concentrations in distinguishing DLB from AD. Kaplan Meier survival curves were constructed to estimate the survival distributions between groups and generalized Wilcoxon was used to compare survival distributions between groups. Cox proportional hazard models were used to determine the effects of covariates on survival time.

5 Results and comments

Paper I

Patients with Lewy Body dementia use more resources than those with Alzheimer's disease

A person with the most common form of dementia, AD, costs on average 172000 SEK annualy, compared to 87000 SEK for an average elderly person [53]. A prognosis for future dementia prevalence is presented in figure 5. Total annual costs for care of dementia was in 2008 estimated to about 50 billion SEK [54]. In 2030 it will have increased to around 60 billion SEK with the same cost per patient. For comparison, the total Swedish health care budget 2005 was 223 billion SEK [55]. It is therefore essential to direct interventions effectively. The first step towards being able to do this is to map costs for individual diseases and the different determinants of resource use.

The resource use in dementia with Lewy bodies is poorly studied; only one small study, (n=15), has assessed the additional resource utilisation in DLB compared to AD [56] The additional annual cost of care of DLB compared to AD was estimated at 19,564 USD, about 151 000 SEK (16 100 EUR).

Results

1 The DLB patients cost about twice as much as the AD patients annually, 348 000 SEK compared to 169 000 SEK ($p < 0.001$).

2 The primary reason for the differences in resource use was a higher frequency of assisted living in the DLB group.

3 The AD patients with a higher cognitive function used less resources compared to those with lower cognitive function. This trend was not seen in the DLB group.

4 Disability in instrumental activities of daily living (I-ADL) was correlated to resource use in the DLB group ($p = 0.001$, $r^2 = 0.277$).

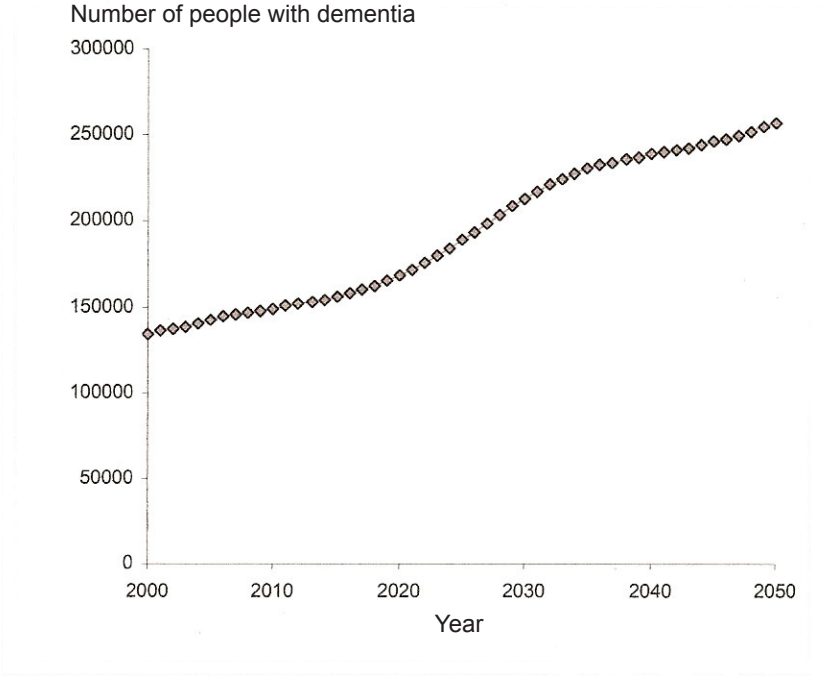

Figure 5. ***Prognosis for future dementia prevalence.***
With permission from the Swedish Health authority [53]

Comments

The major difference between the DLB and AD group was utilization of assisted living. This is not surprising, however, as community care services dominate in cost-of- illness studies [57].

In dementia in general, cognitive decline measured with MMSE score and cost of care are strongly correlated [58, 59]. This study demonstrates, however, that cognitive function measured with MMSE is not as important a determinant of cost of care in DLB as in AD patients. A clinical impression is that MMSE scores are fairly high even when the DLB patients have evident dementia. Thus, MMSE is probably not as sensitive to specific cognitive impairment in DLB as in AD.

Loss of independence has been established as a determinant of cost of care in patients with AD [60]. We show that this correlation is particularly strong among DLB patients when only I-ADL is assessed. It is possible that resource consumption decreases if independance according to I-ADL improves, but further prospective studies are needed.

Paper II

Patients with dementia with Lewy bodies have more impaired quality of life than patients with Alzheimer's disease

The reasons for treating disease can be divided into two categories: 1) to prolong life and 2) to improve the patients' quality of life (QoL). The measurement of QoL poses fundamental definitional problems and at the core of the discussion is the lack of consensus and a gold standard. This study focuses on health related QoL, i.e. how the disease affects the patient's QoL. This is, to our knowledge, the first study of QoL in DLB. In previous studies of AD, however, QoL has been demonstrated to be severely affected compared to healthy controls [61]. In this study, both the patients and the caregivers estimate of the patient's QoL is recorded.

Results

1 The DLB patients in this study have lower QoL than the AD patients regardless of instrument or whether patient or caregiver-reported QoL was used (Table 2).

2 Two AD patients and 8 DLB patients scored negative values on EQ-5D utility, possibly indicating a QoL state that is worse than death.

3 NPI score, independency in I-ADL and whether the patient was living with the primary caregiver as well as presence of apathy and delusions were found to be determinants of QoL in DLB.

Comments

The focus of this study is on caregiver reported QoL as patient-reported QoL has been shown not to correlate with cognition or progression of the disease in patients with dementia [62, 63], even though most healthy subjects would probably strongly prefer a health status with intact cognitive function to a state with severe cognitive impairment. The caregivers may be in a better position to provide estimates that reflect how patients might have interpreted their QoL had they been cognitively intact. Caution must however be taken when interpreting caregiver reported QoL, as it is not only affected by factors concerning state of the patients, but also by factors concerning the caregiver, such as caregiver burden and caregiver depression [64, 65]. As in several previous studies, we found that caregiver-reported QoL was considerably lower than patient-reported QoL for all measurements [47, 64, 66, 67].

Cognitive function was not a determinant of QoL in DLB in this study. Thus, in the clinical setting and in clinical trials, the patients' QoL, and improvement thereof, cannot be estimated simply with a measurement of cognitive function, but must be measured directly with instruments designed for this purpose.

Table 3. ***Patient and caregiver rated health related quality of life.***

	DLB	AD	Difference (p)#	Difference (p)¤
EQ-5D utility				
Completed, patient % (n)	71 (24)	94 (32)		
Completed, caregiver % (n)	100 (34)	100 (34)		
Patient-rated utility *	0.38 ±0.38	0.87 ±0.17	0.0000003	0.000002
Caregiver-rated utility *	0.24 ±0.30	0.56 ±0.29	0.0000007	0.000004
VAS scale				
Completed, patient % (n)	65 (22)	79 (27)		
Completed, caregiver % (n)	100 (34)	97 (33)		
Patient-rated utility *	55 ±17	76 ±19	0.0002	0.001
Caregiver-rated utility *	43 ±22	53 ±20	0.037	0.22
QoL-AD				
Completed, patient** % (n)	68 (23)	88 (30)		
Completed, caregiver** % (n)	94 (32)	100 (34)		
Patient-rated utility *	2.29 ± 0.41	2.89 ± 0.45	0.00002	0.0001
Caregiver-rated utility *	2.01 ± 0.35	2.35 ± 0.45	0.002	0.012

* Mean ± standard deviation
** Counted as completed if 1 or less questions missing
# Using Mann Whitney U-test
¤ Corrected for multiple comparison

Paper III

CSF Mg and Ca as diagnostic markers for dementia with Lewy bodies

In both AD and PD divalent trace elements are thought to play a role in the pathogenesis of the diseases. Furthermore, in DLB, preclinical studies suggest a role for divalent trace elements in converting α-synuclein from the harmless β-sheet conformation, to the harmful folded conformation that has a tendency to form neurotoxic oligomers [15, 68–70]. In addition, α-synuclein has been demonstrated to form annular oligomers and to interact with the lipid surface of neurons when Ca is present

[71]. Furthermore, neurons that express Ca-buffering proteins are spared in DLB [72]. Prior to this study however, there have been no clinical data to support a disturbed metal homeostasis in the DLB patient's brain.

Results

1 CSF Mg and Ca were increased in DLB ($p < 0.001$) compared to both AD patients and controls. In addition CSF Cu may be increased among DLB patients.

2 The same trends were present in plasma in DLB, however there was no correlation between CSF and plasma levels in the individual DLB patient.

3 CSF-Mg and CSF-Ca correlated strongly within the DLB group ($r_s = 0.74$, $p < 0.001$)

4 A combination of CSF-Ca and CSF-Mg could distinguish DLB patients from AD patients with high sensitivity and specificity , 93 % and 81 % respectively.

5 The plasma levels of the analyzed metals were unable to discriminate DLB from AD with small areas under the receiver operating characteristic curve (≤ 0.71).

Comments

The elevated CSF trace element concentrations found in this study supports a role for Ca, Mg and possibly Cu in the formation of harmful α-synuclein oligomers that eventually lead to DLB.

Further studies are needed to assess the cause of these disturbances. One may however speculate that two major possibilities exist: 1 A high CSF Ca and Mg predisposes for DLB. 2 High CSF Ca and Mg are caused by disease specific processes. In case 2 one may further speculate whether increased CSF Mg and Ca influences the development and course of the disease or not.

In either case, CSF Ca and Mg may be valuable tools in distinguishing DLB from AD with a sensitivity and a specificity of 93 % and 81 % respectively. For comparison, the routinely used CSF AD markers T-tau and Abeta42 have a combined sensitivity and specificity of 88 % and 89 % in distinguishing AD from controls [73]. If CSF Ca and Mg are used to distinguish DLB from AD with an estimated AD prevalence of 60 % and a DLB prevalence of 15 % of all dementia cases, the positive predicitive value of CSF Mg and Ca would be 53 % and the negative predictive value would be 99 %. In the clinical setting however, most AD patients would not be considered for DLB, and the positive predictive value would be much higher. Possibly, CSF Mg and Ca could be analyzed when there are diagnostic uncertainties in order to distinguish which patients would be suitable for further examination with DaT-scan.

Paper IV

CSF T-tau predicts survival in dementia with Lewy bodies

In post mortem diagnosed patients, DLB has been demonstrated to increase mortality to a greater extent than AD, in spite of a similar progression rate of cognitive decline [74]. Furthermore, concomitant post mortem AD pathology predicted earlier death [74, 75]. Whether CSF AD markers such as Abeta42, P-tau and T-tau also predict earlier death among clinically diagnosed DLB patients has not been studied.

In paper III, we demonstrated disturbed trace element homeostasis in DLB patients compared to both controls and AD patients [12]. These results hint at a possible pathogenic or disease modifying role for Ca, Mg and possibly Cu in DLB.

Results

1 Both DLB and AD patients had greatly shortened survival (relative risk 8 and 10 respectively, $p < 0.001$). There were however no significant differences between the DLB and AD patients.

2 CSF T-tau predicted shorter survival among DLB patients ($p = 0.024$, Exp (B) = 1,3 per 100 ng/L T-tau), model significance $p = 0.020$), but not among AD patients or controls.

3 CSF Ca, Mg and Cu did not influence survival in this study.

Comments

Most studies of dementia disorders focus on level of function. Although many patients and caregivers would agree that this is a central problem, it has become increasingly evident that DLB, as well as AD, are correctly viewed as life shortening diseases. In this study, the 5 year survival rate was about 50 % for the patients with dementia compared to 94 % in the control group, and 83 % in the general population (75–79 years) [76]. For comparison, a newly diagnosed malignant neoplasy has a 5 year survival rate of about 60 %, and breast cancer a 5 survival rate of 86 % [77]. Furthermore, survival is an objective measurement of disease course, and measuring determinants thereof may give us further knowledge about the underlying mechanisms of the disease.

CSF T-tau may be viewed as a marker of neurodegeneration or a marker of AD. Both theories could explain the main finding of this study; increased rate of neuronal degeneration would lead to earlier death, as could concomitant AD pathology [74]. However, if CSF T-tau indeed is a marker of rate of neuronal damage, then T-tau should

predict survival in the AD group as well. This is not the case in this study. Thus, the results of this study contradict the theory that T-tau is a marker of the intensity of neuronal degeneration.

This study gives little further knowledge of the role of CSF trace elements in DLB. Although these factors did not influence survival in this study, additional, larger studies need to be conducted, and other study groups should be included, such as "preclinical" DLB patients with RBD, and other DLB linked symptoms, to determine whether CSF trace element disturbances are a "trigger factor" for the disease.

6 Final conclusion

In conclusion, this thesis demonstrates important differences between AD and DLB. Paper I and II focus on the ultimate consequences of the disease, including resource consumption and impact on quality of life, and demonstrate much more severe consequences of DLB. Paper III and IV focus on diagnosis and prediction of disease progression through CSF analysis, and demonstrate a robust increase of CSF Ca and Mg in DLB but not in AD. Furthermore, CSF t-tau, a marker of AD and neurodegeneration, is demonstrated to increase mortality in DLB, but not in AD. These DLB specific CSF findings give us further understanding of the factors that may trigger the disease and determine disease course. Furthermore, CSF Mg and Ca may be a valuable tool in making a DLB diagnosis, especially when the considered differential diagnosis is AD.

7 Summary in Swedish/ Populärvetenskaplig sammanfattning på svenska

Lewy body demens – en undersökning av orsak och konsekvens

Fredrik Boström

Lewy body demens anses i dag vara den näst vanligaste degenerativa demenssjukdomen efter Alzheimers sjukdom. Vård av patienter med demens utgör en av de största samhällskostnaderna. Den totala kostnaden för demenssjukdomar i Sverige uppskattades till 50 miljarder kronor år 2005 och beräknas vara 60 miljarder kronor år 2030. Som en jämförelse kan nämnas att den samlade sjukvårdsbudgeten år 2005 var 223 miljarder kronor. Därför är det viktigt att använda resurser på ett optimalt sätt för demenssjuka. Detta kräver dock att vi kartlägger kostnader för olika sjukdomar och vilka faktorer som styr dessa kostnader. Den första studien undersöker resursutnyttjande och omfattar inte bara kommunal och medicinsk vård, utan även anhörigs obetalda omvårdnad. Studien visade att DLB patienter är betydligt mer kostsamma än AD-patienter och använder ungefär dubbelt så mycket resurser vid jämförbar hjärnfunktionsnivå.

Livskvalitet hos patienter med Lewy body demens och deras närstående var ett helt outforskat område innan studie 2. Studien visar att DLB patienter har en livskvalitet som är betydligt sämre än vid Alzheimers sjukdom, samt vilka hjärnfunktionsstörningar som påverkar livskvaliteten. Dessutom visar studien att patienter med Lewy body demens har bättre livskvalitet om de bor med sina närstående.

Man kan ta prov på vätskan som omger hjärnan (=likvor) via en kanyl i ryggslutet. Denna vätska säger ofta mer om vad som händer i hjärnan än vad blodprov gör, då den inte avgränsas från hjärnan av den så kallade blod-hjärnbarriären. I studie 3 analyserade vi förekomst av spårämnen i likvor, då man anser att dessa kan spela en central roll vid utveckling av vissa demenssjukdomar. Analysen visar att patienter med Lewy body demens skiljer sig markant från Alzheimerpatienter och friska kontroller vad gäller två viktiga spårämnen – Calcium och Magnesium. Intressant nog vet man från provrörsförsök att proteinet som orsakar Lewy body demens (α -synuclein) ombildas till skadliga former då man tillsätter just dessa två spårämnen. Våra fynd skulle alltså kunna utgöra en central pusselbit i förståelsen för varför sjukdomen utvecklas. Oavsett om avvikelserna påverkar sjukdomsprocessen är avvikelserna så distinkta att förmodligen kan användas i diagnostiskt syfte för att särskilja Lewy body demens från Alzheimers sjukdom med hög statistisk säkerhet.

Det är tidigare känt att samtidig DLB och Alzheimerpatologi ger ett snabbare och mer aggressivt sjukdomsförlopp. Med stöd av detta och föregående studies resultat valde vi därför att i studie 4 undersöka hur Alzheimermarkörer och metallkoncentrationer i likvor påverkar sjukdomsförloppet. Vi fann att överlevnad hos patienter med Lewy body demens kan förutses med en Alzheimermarkör (t-tau). Detta kan bero på att markören skvallrar om samtidiga Lewy body demens och Alzheimerprocesser i patientens hjärna, men kan också bero på att markören är förhöjd hos patienter med intensivt cellsönderfall i hjärnan.

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REVIEW ARTICLE

Patients with Lewy body dementia use more resources than those with Alzheimer's disease

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SUMMARY

Objectives The purpose of this study was to compare resource use and costs in patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) and to assess determinants of costs of care in DLB.

Method Thirty-four patients with DLB were included in a cross-sectional study. The patients were matched with respect to age, gender and Mini Mental State Examination (MMSE) score to 34 patients with AD. Both groups were examined using Resource Utilisation in Dementia (RUD Lite), MMSE and the Neuropsychiatric inventory (NPI). The DLB patients were additionally examined using the Disability Assessment for Dementia Scale (DAD).

Results Costs of care in patients suffering from DLB was on average 348,000 SEK (37,500€) per year compared to 169,000 SEK (18,200€) in the AD group ($p < 0.001$). Within the DLB group, care costs correlated significantly ($r_c = 2.77$, $p < 0.001$) with dependency in instrumental activities of daily living measured with DAD, whereas MMSE and NPI were not significantly correlated to resource use in the DLB group.

Conclusions DLB patients use more resources, and are more costly than AD patients. Dependency in instrumental activities of daily living is strongly correlated to resource use in DLB patients.

KEY WORDS — cost of care; resource utilisation; dementia; dementia with Lewy bodies; Alzheimer's disease; disability in dementia

INTRODUCTION

The global direct costs for dementia have been estimated at 156 billion USD (131 billion €) in 2003 based on a worldwide estimated prevalence of 27.7 million demented persons (Wimo *et al.*, 2006). The total cost for dementia disorders in Sweden was estimated to 38.4 billion SEK, (4.09 billion €) in the year 2000 (Socialstyrelsen, 2001). In comparison, the total Swedish health care budget the same year was 170 billion SEK (18.10 billion €) (Socialstyrelen, 2005).

Dementia with Lewy Bodies (DLB) is considered to be the second most common degenerative dementia disorder after Alzheimer's disease (AD). Patients suffer from motor, cognitive and psychiatric symptoms, as described in the consensus criteria (McKeith *et al.*, 1996), which were revised in 2005 (McKeith *et al.*, 2005).

The 1996 consensus criteria are considered to be specific for the diagnosis of DLB although not particularly sensitive (Holmes *et al.*, 1999). Using these criteria, the prevalence of DLB has been estimated to be up to 30.5% of all dementia cases, and up to 5% in the general population aged >75 years (Zaccai *et al.*, 2005).

The annual resource utilisation in AD has been estimated to be on average 172,000 SEK (18,300€, 22,000 USD), ranging from 60,700 SEK (6,460€, 8,000 USD) in mild dementia to 375,000 SEK (39,900€, 49,300 USD) in severe dementia (Jönsson *et al.*, 2006). Only one earlier study has assessed the additional resource utilisation in DLB compared to AD (Murman *et al.*, 2003). This study

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estimated the average difference between AD and DLB in annual costs to about 125,000 SEK (13,300€, 16,400 USD). The determinants of cost of care in DLB have not yet been examined.

OBJECTIVE

The primary aim of this study was to compare costs of care, including formal and informal costs, for patients with AD and DLB. The secondary aim was to assess determinants of costs of care in DLB.

MATERIAL AND METHODS

Thirty-four patients with a clinical DLB diagnosis were randomly selected and included from May to July 2005 in a cross-sectional study at the Neuropsychiatry clinic, University Hospital MAS, Malmö, Sweden.

Thirty-four AD patients were selected from a sample of 272 patients from centres in Sweden, Finland and Norway. The complete AD study is further described in Jönsson *et al*. (2006). The AD patients were matched individually to the DLB patients according to gender, MMSE score and age. The matching was conducted by calculating a distance score between each possible pair of AD-DLB patients with matching gender. The distance score was equal to the weighted sum of the squared differences in age and MMSE scores (MMSE scores were given a five-fold higher weight than age, to ensure groups were primarily matched with respect to MMSE scores). Patients were then matched by selecting the AD–DLB patient pairs with the lowest distance scores.

In this study resource utilisation includes direct medical care, prescription drugs and social support costs as well as informal support services, usually provided by family.

The DLB diagnosis was confirmed using the revised DLB criteria (McKeith *et al*., 2005). The AD patients fulfilled the ICD-10 criteria for Alzheimer's disease.

Data collection

The AD and DLB patients were examined using similar methods. The collection procedure of the AD group data has been described in detail elsewhere (Jönsson *et al*., 2006).

In the DLB group the subjects were either examined in their homes or at the Neuropsychiatry clinic UMAS, Malmö together with their primary caregiver (in 20 cases the spouse, in 11 cases the patient's child and in three cases a sibling). Cognitive function was assessed using MMSE (Folstein *et al*., 1975). Behavioural disturbances were measured using the Neuropsychiatric inventory (NPI) (Cummings *et al*., 1994). Dependency in Activities of Daily Living (ADL) was assessed using the Disability Assessment for Dementia scale (DAD) (Gelinas *et al*., 1999)which includes 40 items: 17 related to basic self-care and 23 to instrumental activities of daily living. The number of years since diagnosis was used as an estimate of disease duration.

Resource use was measured using the Resource Utilisation in Dementia (RUD Lite) instrument (Wimo, 1998) which contains questions concerning use of community care services, type of accommodation, the employment status of the patient and primary caregiver, medical care and informal care. In addition, information regarding current medical therapy and co-morbidity was gathered. Informal caregiving time was subdivided to lost production, if the primary caregiver was employed, and lost leisure time in all other cases.

Co- morbidity was assessed in the DLB group using the same 12 domains used in the AD material (Table 1). These 12 domains were analysed as a single variable. Information regarding prevalence of Parkinson's disease (PD) had been gathered in the AD material, but was not analysed as co-morbidity in this study as a PD diagnosis is in conflict with a DLB diagnosis.

Memantine was not included in drug costs as this drug was not registered when the AD data was collected.

Statistical analysis

For statistical analysis SPSS version 12.0.1 was used. The Mann–Whitney *U*-test was used to analyse differences between the AD and DLB group with respect to costs, age, gender, MMSE scores, NPI scores, co-morbidity and years since diagnosis. Spearman rank-order correlation was used to correlate DAD, B-ADL and I-ADL results with resource utilisation. A stepwise linear regression analysis was used to analyse MMSE, NPI and I-ADL as determinants for resource utilisation in DLB.

Ethics

This study was approved by the ethics committee of Lund University. The participating primary caregivers gave written informed consent to participation in the study. The participating patients gave written informed consent to participation in the study when

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Table 1. Between-group comparisons of demographic data, numbers of years since diagnosis, co-morbidity, and test score results

	DLB mean(range)	AD mean(range)	Difference (p)
n	34	34	1
Gender[a] (male/female)	19/15	19/15	1
Age[a]	77.4 (64–87)	78.2 (63–92)	0.92
Years since diagnose	2.85 (0.91–5.95)	2.07 (0–7.78)	0.039*
Co-morbidity	0.88 (0–3)[d]	1.06 (0–4)[d]	0.752
Hypertension(n)	12	11	–
Heart failure(n)	4	6	–
Thyroid disease(n)	4	1	–
Diabetes(n)	3	3	–
Autoimmune disorder(n)	2	0	–
Cancer(n)	2	2	–
Hyperlipidemia(n)	2	3	–
Ischemic heart disease(n)	1	4	–
Stroke(n)	0	2	–
Asthma(n)	0	1	–
COPD(n)	0	1	–
Migraine(n)	0	2	–
MMSE[a]	17.3 (0–29)	16.9 (0–30)	0.92
NPI-brief (max 30)	6.29 (0–17)[b]	3.50 (0–11)[b]	0.048*
Delusions	0.62[c]	0.50[c]	0.622
Hallucinations)	1.06[c]	0.26[c]	<0.001***
Agitation/aggression	0.29[c]	0.35[c]	0.371
Dysphoria	0.62[c]	0.35[c]	0.233
Anxiety	0.74[c]	0.53[c]	0.411
Euphoria	0.03[c]	0.03[c]	0.966
Apathy	1.26[c]	0.68[c]	0.021*
Desinhibition	0.15[c]	0.09[c]	0.727
Irritability/labilit)	0.24[c]	0.41[c]	0.206
Aberrant motor activity	0.41[c]	0.29[c]	0.503
DAD	15.03 (0–37)	Not done	–
B-ADL	8.88 (0–20)	Not done	–
I-ADL	6.15 (0–18)	Not done	–

All results are presented as mean (range) if not otherwise stated.
[a]Matched variables.
[b]Total brief NPI results.
[c]Results of examined items in the brief NPI. Range 0–3.
[d]Co-morbidity added to a single variable.
*$p = <0.05$.
***$p = <0.001$.

possible. This study was carried out in accordance with the Helsinki Declaration.

RESULTS

Material

Demographic data, numbers of years since diagnosis, co-morbidity, and test score results are presented in Table 1.

Resource utilisation and costs

Resource utilisation, prices (unit costs) and calculated costs are presented in Table 2a, Table 2b, and Table 2c and Figure 1. Total costs were higher ($p < 0.001$) in patients suffering from DLB, namely 348,000 SEK (37,500€, 45,800 USD) per year compared to 169,000 SEK (18,200€, 22,200 USD) for the AD patients. Accomodation constituted the greatest difference in resource utilisation between the DLB and AD patients. The DLB patients also utilised more outpatient care, informal care, community services and pharmaceutical therapy. The AD patients utilised more inpatient care. Informal care more than 16 h per day was adjusted to 16 h, ($n = 2$) in the AD group and ($n = 1$) in the DLB group.

In six cases in the AD group the primary caregiver was unable to specify the average duration of the help provided with B-ADL, I-ADL or supervision. In these cases the duration of that particular item was imputated using the means of other positive

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Table 2a. Community services and assisted living expenses

	Unit cost SEK	DLB resource utilisation	AD resource utilisation	DLB cost SEK	AD cost SEK
Accommodation		*Days/year*	*Days/year*		
Block of service flats	575	11 (0–365)	22 (0–365)	6176 (0–20 9875)	12346 (0–209875)
Group living	1080	150 (0–365)	11 (0–365)	162313 (0–394200)	11594 (0–394200)
Nursing home	1479	0	11 (0–365)	0	15878 (0–539835)
Sum				168489 (0–394200)	39817 (0–539835)
Community services		*Times per year*	*Times per year*		
Home help, per visit	228	149 (0–1536)	63 (0–1040)	34036 (0–350208)	14297 (0–237120)
Home delivered meals	84	16 (0–372)	34 (0–364)	1331 (0–31248)	2826 (0–300576)
Day center visit	237	–	26 (0–260)	0	6162 (0–61620)
Transportation	172[a]	22#(0–360)	4.9 (0–52)	3736 (0–61920)	846 (0–8944)
Sum				39112 (0–350208)	24131 (0–267696)
Sum				207603 ± 194306 (0–575173)	63949 ± 136876 (0–539835)

[a]per hour #h/year.

Table 2b. Medical care

	Unit cost SEK	DLB resource utilisation	AD resource utilisation	DLB cost SEK	AD cost SEK
Inpatient care		*Days/year*	*Days/year*		
Geriatrics and respite care	3004	0	6.11 (0–204)	0	18377 (0–612816)
Internal medicine	3313	3.7 (0–84)	0	12083 (0–278292)	0
Surgery	4846	0.4 (0–12)	0	1710 (0–58152)	0
Sum				13793 (0–278292)	18377 (0–612816)
Outpatient care		*Times per year*	*Times per year*		
Physician visit[a]	1110	2.1 (0–24)	2.56 (0–12	2350 (0– 6632)	2872 (0–19464)
Nurse visit	368	8.8 (0–96)	9.9 (0–260)	3246 (0–35328)	3658 (0–95680)
Day care	405	22.2 (0–240)	6.12 (0–104)	9005(0–97200)	2478 (0–42120)
Sum				14602 (0–97200)	9008 (0–95680)
Drugs	–	–	–	18141 (1966–31020)	11450 (0–24257)
Sum				46536 ± 59712 (6454–315967)	38836 ± 106719 (0–632632)

[a]Calculated using the distribution of specialist visits and general practitioner visits in the AD material.

Table 2c. Informal care

	Unit cost SEK	DLB resource utilisation	AD resource utilisation	DLB cost SEK	AD cost SEK
Informal care		Hours/year	Hours/year		
Lost production (per h)	197	272 (0–4746)	183 (0–1825)	53536 (0–934867)	35953 (0–359525)
Lost leisure time (per h)	28	1429 (0–6753)	1079 (0–10463)	40017 (0–189091)	30218 (0–292973)
Sum				93553 ± 173855 (0–934867)	66170 ± 95646 (0–359525)
Sum all costs				347692 ± 229255 (24831–955718)	168955 ± 188344 (14061–676237)

(Table 2 a–c) All prices are in SEK. Unit cost is from (Jönsson *et al*., 2003) and is presented per day unless otherwise stated. The prices are adjusted to 2005 consumer price index (KPI) (Statistiska Cenralbyrån, 2005). Resource utilisaiton and cost are presented as *mean* (*range*) unless otherwise stated.

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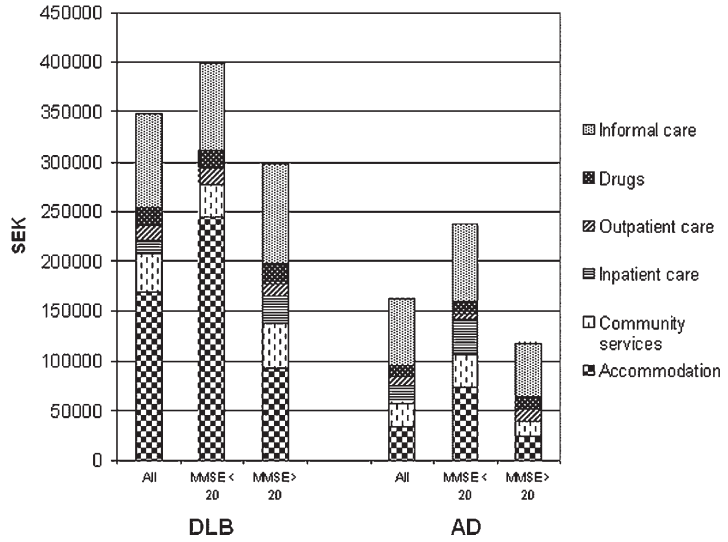

Figure 1. MMSE score and costs of care in DLB and AD. The DLB and AD group are divided at MMSE = 20 (median), creating four equally large groups ($n = 17$). Mann–Whitney *U*-test was used to assess significant differences. DLB > 20 *vs* DLB < 20, $p = 0.139$; AD > 20 *vs* AD < 20, $p = 0.016$*; DLB > 20 *vs* AD > 20, $p = 0.001$***; DLB < 20 *vs* AD < 20, $p = 0.018$*. Note: ∗, $p = <0.05$; ∗∗∗, $p = <0.001$.

responders in the same category. In addition, an analysis of costs of care among the 28 AD patients without any missing data was performed. The cost of these patients was on average 188,000 SEK (20,200€, 24,700 USD) annually, slightly more than the average cost in the complete AD group.

Determinants of costs of care

To describe costs in relation to cognitive function, the DLB and AD groups were subdivided into two equally large groups with better (MMSE > 20) and worse cognitive function (MMSE < 20). DLB patients had significantly higher costs of care compared to AD patients in the cognitively better group (MMSE > 20). In the DLB patients with MMSE score above and below 20 the costs of care was not significantly different. In contrast, costs in the AD group increased significantly with decreasing MMSE scores (Figure 1).

The DLB group scored significantly higher on the NPI brief scale than the AD group. A comparison between DLB and AD regarding the distribution of NPI scores in the ten examined domains is presented

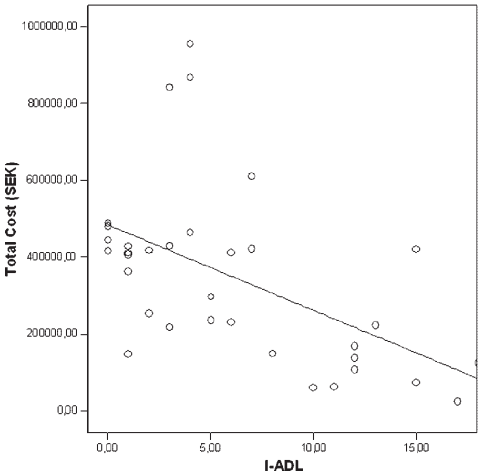

Figure 2. Correlation between I-ADL and care costs in the DLB group. Dependency in I-ADL assessed by the Disability Assessment in Dementia Scale (DAD) correlates significantly ($r_s = 0.569$, $p < 0.001$**) with costs in the DLB group. Note: ∗∗, $p = <0.01$.

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in Table 1. The NPI domain giving the highest average score among the DLB patients was apathy.

Within the DLB group costs of care correlated significantly with dependency in instrumental activities of daily living (I-ADL) measured with DAD ($r_s = 0.569$, $p < 0.001$**, where ** means $p = <0.01$) (Figure 2). Costs also correlated significantly with dependency in basic self care (B-ADL) ($r_s = -0.507$, $p = 0.002$**), and the complete dependency in daily living score on DAD ($r_s = -0.530$, $p = 0.001$**).

Finally MMSE, NPI and I-ADL were entered as variables in a stepwise regression analysis as determinants of costs. I-ADL was found to be the only significant determinant of costs in this model ($p = 0.001$, $r^2 = 0.277$).

DISCUSSION

Only one earlier study has assessed resource utilisation in DLB patients (Murman *et al*., 2003). This study was limited by small sample size of patients with DLB ($n = 15$) and an unmatched larger body of patients with AD. The present study of 34 patients with DLB and 34 matched patients with AD has a considerably larger sample size of patients with Lewy bodies.

A possible weakness in this study is the time span of four years between the gathering of data of the AD and DLB groups. Two adjustments were made due to this: memantine was removed from the cost analysis of DLB patients as it was not registered when the AD material was gathered and all prices where adjusted to current consumer price index (Statistiska Centralbyrån, 2005). Furthermore, DLB was probably more recognised when the DLB patients were examined as DLB was not defined until 1996. This possibility is supported by some of the AD patients in the complete sample having symptoms of Parkinson's disease, and may have been diagnosed with DLB had they been examined a few years later. This possibility would cause an underestimation of the differences between AD and DLB in this study.

There was a significant difference in years since diagnosis in the DLB and the AD group. Two regression analyses were performed to investigate the influence of years since diagnosis as a determinant of costs in the AD and DLB group. Years since diagnosis did however not influence costs in the AD or in the the DLB group.

In the earlier study (Murman *et al*., 2003), the additional annual cost of care of DLB compared to AD was estimated to 19,564 USD, about 151,000 SEK (16,100€). Our study complies very well with these figures, estimating the average difference between AD and DLB in annual costs of care to 179,000 SEK(19,300€, 25,600 USD). A higher frequency of assisted living seems to be the primary reason for DLB patients being more expensive than AD patients. This is not surprising considering community care services dominate in cost of illness studies (Jönsson *et al*., 2006). Among the AD patients the highest cost was informal care, however still less than in the DLB group.

Drug consumption constituted a small amount of the total costs of care, 5,6% in the DLB group and 7,3% in the AD group. These results are in accordance with other studies where drug consumption in patients with degenerative dementia has been shown to be low compared to other costs (Ostbye and Crosse, 1994; Jönsson *et al*., 2006).

In this study we show that cognitive function measured with MMSE may not be as important a determinant of costs of care in DLB as in AD patients. In general in dementia, cognitive decline measured with MMSE score and cost of care are strongly correlated (Jönsson *et al*., 1999, 2006). The AD patients follow this estimation and are more expensive with lower MMSE score. In contrast, the DLB patients with higher cognitive functionioning (MMSE > 20) are already very expensive, and the cost of care does not increase significantly for those with poorer cognitive function (MMSE < 20).

In the complete AD sample ($n = 272$), NPI has earlier been shown to be a weak determinant for cost of care in patients with AD (Jönsson *et al*., 2006). This trend was not evident in the DLB group in this study.

A clinical impression is that apathy in DLB, in contrast to in AD, is a common and stigmatising neuropsychiatric symptom. This impression was supported by this study where the DLB group was significantly more apathetic than the AD patients. As a consequence apathy was further examined as a determinant for costs of care. In DLB patients ($n = 21$) with apathy, the annual cost was 397,000 SEK (42,900€, 52,200 USD) compared to 135,000 SEK (14,500€, 17,800 USD) in AD patients ($n = 15$) with apathy ($p < 0.001$). In patients without apathy the average cost was 267,000 (28,800€, 35,100 USD) in DLB ($n = 13$) and 196,000 SEK (21,100€, 25,800 USD) in AD patients ($n = 19$). As costs of care in DLB patients with apathy was almost three times as high as in AD patients with apathy, this factor needs to be further studied, as it may be a determinant for care costs.

Loss of independence has been established as a determinant of costs of care in patients with AD (Livingston *et al*., 2004). We show that ADL measured with DAD correlates strongly with costs of care. This correlation is even stronger when only I-ADL is assessed.

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Assessing the causes of decreased independence in I-ADL among DLB patients was not the aim of this study. However, considering that MMSE and NPI are not evident determinants for costs of care in this study, increasing dependency in ADL is probably not explained simply by a faltering cognitive function or increasing behavioural disturbances. Parkinsonism has been demonstrated as a determinant for costs of care in patients with DLB (Murman *et al*., 2003). This could imply that parkinsonism is important to independence in I-ADL in DLB. It is however clear that determinants for independence in I-ADL in DLB patients are poorly investigated and needs to be further studied.

An explanation as to why the DLB patients in this MMSE matched material utilise more resources may be that a low MMSE score signals further progression of their dementia than it does in the AD group.

To find determinants of future costs of care in DLB, future studies may need to focus on onset of symptoms of the disease, since these possibly occur years before changes show on a routine test such as the MMSE.

We also suggest that measurement of independence in daily living, primarily I-ADL, is used in addition to other variables when making economic evaluations of patients with DLB. The question is to what extent an increase in independence in I-ADL leads to a decrease in costs of care. This has to be examined in future interventional studies.

CONCLUSION

In summary this study shows that DLB patients utilise more resources, and consequently are more costly than AD patients in a matched material, and that dependency in activities of daily living, especially I-ADL, is strongly correlated to costs of care in DLB patients. Furthermore, our results imply that MMSE and NPI are probably not as good determinants for care costs in DLB as in AD.

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II

Patients With Dementia With Lewy Bodies Have More Impaired Quality of Life Than Patients With Alzheimer Disease

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Abstract: The primary aim of this study was to compare quality of life (QoL) in patients with Dementia with Lewy Bodies (DLB) and patients with Alzheimer disease (AD). The secondary aim of this study was to investigate determinants of QoL in DLB. Thirty-four patients with DLB at the Neuropsychiatry clinic, University Hospital MAS, Malmö, Sweden, were included in a cross-sectional study. These patients were matched to 34 patients with AD. Two QoL instruments, the EQ-5D instrument and the Quality of Life-Alzheimer disease (QoL-AD) instrument, were applied in this study. Both instruments were administered to both patients and caregivers. Patients with DLB in this study have significantly lower QoL than patients with AD regardless of instrument or whether patient or caregiver-reported QoL was used. Furthermore, this study shows that important determinants of QoL in DLB include Neuropsychiatric Inventory score, independency in instrumental activities of daily living, whether the patient is living with the caregiver and the presence of apathy and delusions.

Key Words: dementia with Lewy Bodies, DLB, quality of life, QoL

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Dementia is established as one of the major challenges of this century owing to the enormous burden these pathologies impose on patients, caregivers, and society. In subjects over 65 years of age, crude prevalence rates for dementia in Europe vary between 5.9% and 9.4% with an exponential increase with age.[1] In 2 European population-based studies, the prevalence of Dementia with Lewy Bodies (DLB) was estimated to 21.9% (Finland) and 30.5% (UK) of all dementia disorders.[2] DLB is today considered to be the second most common degenerative dementia disorder after Alzheimer disease (AD).

The core criteria of DLB are fluctuating cognition, visual hallucinations, and spontaneous features of Parkinsonism. Other typical symptoms of DLB are rapid eye movement sleep behavior disorder and severe neuroleptic sensitivity.[3,4] Taking into account the difference in clinical manifestation of DLB and AD, it is expected that the diseases differ in consequence for the patient, caregiver, and society. This study focuses on quality of life (QoL) of patients with DLB. Despite of an increasing interest in QoL studies, QoL research in AD is still considered to be in its infancy.[5] QoL in DLB is previously unstudied.

QoL is an elusive concept that has been defined and assessed in various ways. Health-related QoL is a somewhat narrower concept relating to the impact of physical and mental disorders and disability on the general well being of a person. One problem is that there is no gold standard when measuring QoL. In this study, we use 2 widely used instruments, one generic and one specifically developed to assess QoL in patients with AD.

AIM

The primary aim of this study was to compare QoL in patients with DLB and patients with AD. The secondary aim of this study was to investigate cognition, behavioral disorders, disability, age, comorbidity, institutionalization, and whether the patient is living together with a caregiver or alone as determinants of QoL in DLB.

MATERIALS AND METHODS

Study Design

A total of 34 patients with DLB attending regular visits at the memory clinic, University Hospital MAS, Malmö, Sweden, were prospectively interviewed according to the same protocol as 272 patients with AD who attended regular visits at 6 memory clinics in Sweden, Finland, and Norway, earlier described by Jonsson et al.[6] From the 272 patients with AD, 34 were selected to match

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the 34 patients with DLB according to sex, age, and cognitive function.

The matching was conducted by calculating a distance score between each possible pair of AD-DLB patients with matching sex. The distance score was equal to by the weighted sum of the squared differences in age and Minimental State Examination (MMSE) scores (MMSE scores were given a 5-fold higher weight than age, to ensure groups were primarily matched with respect to MMSE scores). Patients were then matched by selecting the AD-DLB patient pairs with the lowest distance scores (Table 1).

The DLB diagnosis was confirmed using the revised DLB criteria[4]: (1) Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function, (2) at least 2 core features or 1 core feature and 1 suggestive feature have to be present. Core features are: fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations that are typically well formed and detailed, and spontaneous features of parkinsonism. Suggestive features are: rapid eye movement sleep behavior disorder, severe neuroleptic sensitivity, abnormally low uptake in basal ganglia on single photon emission computed tomography dopamine transporter scan, and abnormally low uptake on [123I]meta-iodobenzylguanidine (MIBG) myocardial scintigraphy. The patients with AD fulfilled the ICD-10 criteria for AD.

TABLE 1. Between-group Comparisons of Demographic Data, Comorbidity, and Test Score Results

	DLB Mean (Range)	AD Mean (Range)	*P* for Difference
N	34	34	
Sex (male/female)†	19/15	19/15	1
Age†	77.4 (64-87)	78.2 (63-92)	0.92
Comorbidity	0.88 (0-3)¶	1.06 (0-4)¶	0.752
Hypertension (n)	12	11	—
Heart failure (n)	4	6	—
Thyroid disease (n)	4	1	—
Diabetes (n)	3	3	—
Autoimmune disorder (n)	2	0	—
Cancer (n)	2	2	—
Hyperlipidemia (n)	2	3	—
Ischemic heart disease (n)	1	4	—
Stroke (n)	0	2	—
Asthma (n)	0	1	—
COPD (n)	0	1	—
Migraine (n)	0	2	—
MMSE†	17.3 (0-29)	16.9 (0-30)	0.92
NPI-brief (max 30)‡	6.29 (0-17)§	3.50 (0-11)§	0.048*
Delusions	0.62‖	0.50‖	0.622
Hallucinations	1.06‖	0.26‖	< 0.001**
Agitation/aggression	0.29‖	0.35‖	0.371
Dysphoria	0.62‖	0.35‖	0.233
Anxiety	0.74‖	0.53‖	0.411
Euphoria	0.03‖	0.03‖	0.966
Apathy	1.26‖	0.68‖	0.021*
Desinhibition	0.15‖	0.09‖	0.727
Irritability/lability	0.24‖	0.41‖	0.206
Aberrant motor activity	0.41‖	0.29‖	0.503
DAD	15.03 (0-37)	Not done	—
B-ADL	8.88 (0-20)	Not done	—
I-ADL	6.15 (0-18)	Not done	—
Caregiver living with patient#	15	22	
Special living††	15	4	

All results are presented as mean (range) if not otherwisely stated.
†Matched variables.
‡A brief version of the NPI.
§Total brief NPI results.
‖Severity of each symptom (range 0-3).
¶Comorbidity added to a single variable.
#Number of patients living with their primary caregiver.
††Number of patients with assisted living such as service flats, group living, or nursing home.
*$P \leq 0.05$; **$P \leq 0.01$.

Data Collection Procedure

The examination of the patients with DLB was designed similar to the data collection procedure in the AD group.[6]

The DLB and AD groups were examined in their homes or at a memory clinic together with their primary caregiver.

The primary caregiver to the patients with DLB was in 20 cases the spouse, in 11 cases the patient's child, and in 3 cases a sibling. Cognitive function was assessed using MMSE.[7] Behavioral disturbances were measured using the Neuropsychiatric Inventory (NPI).[8] Patients with DLB were in addition examined regarding dependency in activities of daily living (ADL) using the Disability Assessment for Dementia scale[9] which includes 40 items: 17 related to basic self-care and 23 to instrumental activities of daily living (I-ADL).

Comorbidity was assessed in the DLB group using the same 12 domains used in the AD material. Information regarding prevalence of Parkinson disease had been gathered in the AD material, but was not analyzed as comorbidity in this study as a Parkinson disease diagnosis is in conflict with a DLB diagnosis.

QoL Instruments

Two QoL instruments, the EQ-5D instrument[10] and the Quality of Life-Alzheimer disease (QoL-AD) instrument,[11] were applied in this study. Both instruments were administered to both patients and caregivers.

The EQ-5D is a generic QoL instrument in which the respondent is asked to rate their current health state on 5 dimensions (mobility, hygiene, usual activities, pain/discomfort, and anxiety/depression), with 3 possible levels for each dimension. For each of the possible health states, a utility weight can be assigned through an algorithm that has been developed on the basis of a time trade-off study in the United Kingdom.[12] The utility weight is a number < 1, where 0 equals death and 1 equals perfect health, indicating the attractiveness of the health state based on the preferences of the general population. In contrast to the 2 other QoL scales used in this study, it is possible to obtain negative values of QoL using this method. The EQ-5D also includes a visual analog scale (VAS), anchored at perfect health (100) and death (0). Thus 2 values representing QoL are acquired using this instrument. Kendall coefficient of concordance regarding

EQ-5D measurments has been estimated to W = 0.984 ($P < 0.001$).[10]

The QoL-AD is a QoL instrument specifically developed for use in patients with AD. Thirteen domains (physical health, energy, mood, living situation, memory, family, marriage, friends, self, ability to do chores, ability to do things for fun, money, and life as a whole) are rated on a 4-point scale, 1 being poor and 4 being excellent. The maximum score is 52 and the minimum 13. The Internal consistency reliability for QoL-AD ranges from 0.84 to 0.88 for patient and caregiver-reported QoL in cognitively impaired patients.[11,13]

Patient and caregiver-reported QoL were analyzed separately as this study focused on caregiver-reported QoL.

Statistical Analysis

For statistical analysis SPSS 12.0.1 was used. Spearman rank order correlation was used to assess correlations between QoL-AD and the 2 values representing QoL that was acquired using EQ-5D as these values were not normally distributed. The Mann-Whitney *U* test was employed to test for differences in QoL scores between groups. Two linear regression analyses were done on caregiver-reported EQ-5D utility with an exclusion criterion for the examined determinants of $P < 0.10$. The first regression analysis included NPI score, independency in I-ADL, age, comorbidity, institutionalization and whether the patient is living with primary caregiver. The second regression analysis included all NPI items as separate variables.

RESULTS

Ninety-four percent of the DLB patients' caregivers and 97% of the AD patients' caregivers were able to complete both QoL instruments adequately. Corresponding figures for patient reports were 59% in the DLB group and 76% in the AD group.

Demographic data and assessed possible determinants of QoL in DLB and AD are presented in Table 1. The patients with DLB scored significantly higher on the brief NPI and were significantly more apathetic than the patients with AD. The higher prevalence of hallucinations in the DLB group compared with the AD group was expected as this symptom is included in the DLB criteria.

Patient and proxy-rated health-related QoL in DLB and AD are presented in Table 2 and Figure 1. Two patients with AD and 8 patients with DLB scored negative values on EQ-5D utility. The correlations between EQ-5D utility scores, EQ-5D VAS scale and QoL-AD for all patients (DLB and AD) are presented in Table 3.

Table 4 presents 2 regression models of NPI score, independency in I-ADL and whether the patient was living with the primary caregiver were found to be significant determinants of QoL in DLB in the first regression analysis. Apathy and delusions were found to be determinants of QoL in DLB in the second regression analysis (Table 4).

TABLE 2. Patient and Caregiver-rated Health-related QoL. (Mean ± Standard Deviation)

	DLB	AD	Difference (*P*)*	Difference (*P*)†
EQ-5D utility				
% completed, patient (n)	71 (24)	94 (32)		
% completed, caregiver (n)	100 (34)	100 (34)		
Patient-rated utility	0.38 ± 0.38	0.87 ± 0.17	< 0.0001	< 0.0001
Caregiver-rated utility	0.24 ± 0.30	0.56 ± 0.29	< 0.0001	< 0.0001
VAS scale				
% completed, patient	65 (22)	79 (27)		
% completed, caregiver	100%	97 (33)		
Patient-rated utility	55 ± 17	76 ± 19	0.0002	0.001
Caregiver-rated utility	43 ± 22	53 ± 20	0.037	0.22
QoL-AD				
% completed, patient‡	68 (23)	88 (30)		
% completed, caregiver‡	94 (32)	100 (34)		
Patient-rated utility	2.29 ± 0.41	2.89 ± 0.45	< 0.0001	0.0001
Caregiver-rated utility	2.01 ± 0.35	2.35 ± 0.45	0.002	0.012

*Using Mann-Whitney *U* test.
†Corrected for multiple comparison (Bonferroni).
‡Counted as completed if 1 or less questions are missing.

DISCUSSION

This is to our knowledge the first study to describe quality of life in patients with Lewy Body Dementia. The DLB and AD patients were not selected from the same population. There are some compatibility limitations to this method, however, the same investigational protocol was used, thus the data produced were considered to be comparable.

The strong correlations that were found between 3 QoL measures (QoL-AD, EQ-5D utility, and VAS scores) are in line with previous findings in AD.[6,14,15] In this study, the EQ-5D questions, excluding the VAS scale, were easier to answer than the QoL-AD questions; only

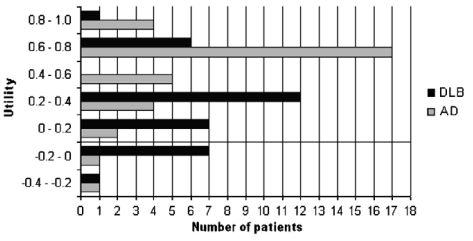

FIGURE 1. Caregiver reported EQ5D utility in DLB and AD. Interpretation of utility score: 1 = perfect health, 0 = death.

TABLE 3. Pearson Correlation of Used QoL Instruments in All Studied Patients

	EQ-5D (Patient)	VAS (Patient)	QoL-AD (Patient)	EQ-5D (Caregiver)	VAS (Caregiver)	QoL-AD (Caregiver)
EQ-5D (patient)	1	0.49 (0.11)*	0.56 (0.10)*	0.48 (0.10)*	0.109 (0.13)	0.30 (0.12)†
VAS (patient)		1	0.59 (0.10)*	0.45 (0.11)*	0.33 (0.13)†	0.40 (0.12)*
QoL-AD (patient)			1	0.51 (0.10)*	0.207 (0.13)	0.56 (0.10)*
EQ-5D (caregiver)				1	0.60 (0.08)*	0.64 (0.07)*
VAS (caregiver)					1	0.60 (0.08)*
QoL-AD (caregiver)						1

Correlations are presented as *r*(SE).
*Correlation is significant at the 0.01 level (2-tailed).
†Correlation is significant at the 0.05 level (2-tailed).
Grey cells represent comparisons of patient and caregiver reported quality of life.

5.9% patients in the AD group and 29.4% of the patients in the DLB group were unable to complete the EQ-5D, compared with 32.4% of the AD patients and 35% of the DLB patients who were unable to complete the QoL-AD scale. The patients with DLB were to a greater extent unable to answer questions regarding QoL adequately compared with the patients with AD, although the patients with DLB and AD were matched regarding cognitive function. It was not the aim of this study to investigate the reason for this difference, however one may speculate that the greater prevalence of apathy in the DLB group may play an important role. Another possible contributing factor is poorer conversational skills among patients with DLB as reported by Ferman et al.[16] This result implicates the limits of trying to assess the general level of ability in dementia using only measurements of cognitive function.

The focus of this study is on caregiver-reported QoL as patient-reported QoL has been shown not to correlate with cognition or progression of the disease in patients with dementia,[14,17] even though most healthy subjects would probably strongly prefer a health state with intact cognitive function to a state with severe cognitive impairment. The caregivers may be in a better position to provide estimates that reflect how patients might have interpreted their QoL had they been cognitively intact. Caution must, however, be taken when interpreting caregiver-reported QoL, as it is not only affected by factors concerning state of the patients, but also by factors concerning the caregiver, such as caregiver burden and caregiver depression.[18,19] As in several previous studies, we found that caregiver-reported QoL was considerably lower than patient-reported QoL for all measurements.[6,11,15,18]

Whether to use proxy-reported QoL in patients with dementia is a debated issue. However, in this study the DLB patients have significantly lower QoL than the AD patients regardless of whether patient or caregiver-reported QoL was used. A possible reason for this difference is a higher prevalence of behavioral disorders in the DLB group compared with the AD group. Our clinical impression is that apathy is particularly stigmatizing and prevalent in patients with DLB. This impression is supported by apathy being significantly more prevalent in the DLB group compared with the AD group, and also that apathy was associated with lower QoL within the DLB group in the multiple regression analysis. Another possible explanation of the difference in QoL in these cognitively matched DLB and AD groups is that a decreased cognitive level signals farther progression of the disease in DLB than it does in AD.

In 6% of the patients with AD and 24% of the patients with DLB the caregiver-rated EQ-5D scores corresponded to below-zero utility values according to the UK scoring algorithm. This indicates that the general population sample used to obtain the scoring algorithm considered these health states to be worse than death. The finding that almost 1 in 4 patients with DLB are in health states considered equal to or worse than death is alarming. The corresponding figure for the AD group was 6%, markedly less compared with the DLB group.

We found that NPI score, dependency in I-ADL, and whether the patient was living with the caregiver were significant determinants of QoL in DLB. NPI score and whether the patient was living with the caregiver were

TABLE 4. Linear Regression Analyses of Proxy Rated EQ-5D Utility in DLB

	Model 1	Model 2: NPI Items
Exclude Variables	MMSE score, Age, Special Living, Total Morbidity	Hallucinations, Agitation, Depression, Anxiety, Euphoria, Desinhibition, Irritability, Aberrant Motor Behaviour, Sleep disorder, Eating disorder
N	34	34
	B (*P*)	B (*P*)
NPI	−0.008 (0.003)	—
I-ADL	0.019 (0.015)	—
Living with patient	0.161 (0.042)	—
Delusions*	—	−0.035 (0.018)
Apathy*	—	−0.037 (0.001)
(constant)	0.198 (0.035)	0.472 (< 0.001)
R^2	0.524	0.363

Two linear regression analyses where obtained using backward elimination with a removal limit of $P < 0.10$. The full NPI was used in these analyses.
*NPI item.

also found to be determinants for QoL in the complete AD group (n = 272) whereas I-ADL was not assessed in the AD study.[6] ADL and I-ADL have, however, been shown to be determinants of QoL in dementia in other studies.[20,21]

Apathy and delusions were the only NPI items that were individually significant determinants of QoL in DLB. Earlier studies indicate that apathy may be a general determinant of QoL in dementia.[22] Delusions were not as prevalent in the DLB group as apathy, but may be a specific determinant of QoL in DLB. There are no earlier reports of delusions as a determinant of QoL in dementia.

Cognitive function was not a determinant of QoL in DLB in this study. Cognitive function as a determinant of QoL in DLB has not previously been studied. In other dementias, cognitive function correlates with QoL in some studies,[14,23] but not in others.[6,21]

The results of this study and an earlier study of resource utilization in DLB versus in AD,[24] indicate that the consequences of DLB and AD differ greatly; a DLB diagnosis predicts an almost 3-fold increase in resource utilization and a significantly lower QoL compared with AD. These results underline the importance making a correct differential diagnosis of degenerative dementia, as the diagnosis is likely to influence the gravity and type of problems that will have to be addressed during the course of the disease.

The QoL in caregivers to patients with DLB was not studied here, but should be examined in future studies as it is affected in other dementia disorders.[25,26]

To examine whether the extensive impairment of QoL in DLB is reversible, interventional studies that include QoL as an outcome measures are needed.

In summary, the results of this study suggest important differences in quality of life between patients with DLB and AD, and that important determinants of quality of life in DLB include NPI score, independency in I-ADL, whether the patient is living with the caregiver and the presence of apathy and delusions.

The present study is limited by a small sample size. More research is needed to confirm the findings of this study and to further examine other possible determinants of QoL in DLB such as motor dysfunction and autonomic dysfunction.

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CSF Mg and Ca as diagnostic markers for dementia with Lewy bodies

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Abstract

Accumulating evidence implicates a role for altered metal homeostasis in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD). However, few investigations have addressed this issue in dementia with Lewy bodies (DLB). The aim of the present study was to investigate metal concentrations in cerebrospinal fluid (CSF) and plasma from patients with DLB and other neurodegenerative disorders. To that end, CSF and plasma samples were collected from 29 patients with DLB, 174 patients with AD, 90 patients with AD with minor vascular components, and 51 healthy volunteers. Total concentrations of Mg, Ca, Mn, Fe, Cu, Zn, Rb, Sr, and Cs were determined using mass spectrometry. Patients with DLB had elevated Ca and Mg levels in CSF and Mg levels in plasma as compared to all other groups ($p < 0.001$). Furthermore, a combination of CSF-Mg and CSF-Ca could distinguish DLB from AD with a sensitivity of 93% and a specificity of 85%. Cu levels in both CSF and plasma tended to be higher in DLB compared to the other groups, but these trends failed to reach significance after correction for multiple comparisons. Mn, Fe, Zn, Rb, and Sr concentration in CSF or plasma were similar in all groups. The observed elevations of CSF-Mg, CSF-Ca and CSF-Cu may contribute to or be associated with the neurodegenerative process in DLB. Furthermore, determination of CSF-Mg and CSF-Ca concentration may be a valuable tool in distinguishing DLB from AD.

Keywords: Alzheimer's disease; Dementia with Lewy bodies; Cerebrospinal fluid; Trace elements; Metals; Alpha synuclein; Lewy body disease

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia disorder. Clinically, DLB is characterized by fluctuating cognition, visual hallucinations, and spontaneous features of Parkinsonism in addition to progressive dementia. Other typical symptoms of DLB that may help in distinguishing DLB from other dementing illnesses are disturbed sleep, especially in the rapid eye movement phase, and severe sensitivity to neuroleptic drugs (McKeith et al., 1996, 2005).

The neuropathologic findings of DLB show a wide anatomic range. Lewy bodies (LB) and Lewy neurites, mainly composed of α-synuclein in an aggregated state (Baba et al., 1998; Tamamizu-Kato et al., 2006), are found from the brain stem to the cortex. In addition, in many cases there is concurrent Alzheimer's disease (AD) pathology in the form of β-amyloid (Aβ)-containing senile plaques. The invariable finding of LB in definite DLB has put much focus on the involvement of α-synuclein in the pathogenesis of the disease. Together with other neurodegenerative diseases that are characterized by abnormal α-synuclein aggregation, such as Parkinson's disease (PD) and multiple system atrophy, DLB has been designated a synucleinopathy (Weisman and McKeith, 2007). Similarly to the putative pathogenic role

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of Aβ in AD (Blennow et al., 2006), abnormal α-synuclein oligomerization and aggregation have been proposed to be a primary cause of this group of disorders (Weisman and McKeith, 2007).

Several neurodegenerative diseases, including AD and PD, are characterized by modified copper and zinc homeostasis in the brain (Lovell et al., 1998) and in the cerebrospinal fluid (CSF) (Molina et al., 1998; Basun et al., 1991; Jimenez-Jimenez et al., 1998). These changes seem to contribute either directly or indirectly to increased oxidative stress, an important factor in neuronal toxicity (Morgan et al., 2004). Furthermore, copper and zinc are also involved in inflammatory reactions, e.g. in the synthesis and secretion of interleukin-2, which may play a role in neurodegeneration (Todorich and Connor, 2004). When coupled to misfolded Aβ, this modified metal homeostasis appears to be an important factor in the pathological progression of AD, a line of reasoning that may hold true also for the toxicity of α-synuclein (Uversky et al., 2002)

Still, very little is known about the role of metals in DLB. To address this question, we undertook a study comparing metal concentrations in the CSF and plasma of DLB patients compared to AD patients, patients with AD and minor vascular components (AD-Vasc) and healthy volunteers.

2. Objective

The aim of this study was to investigate the metal pattern in the cerebrospinal fluid (CSF) of patients with DLB compared to controls, AD patients and patients with AD-Vasc.

3. Method and material

CSF and plasma samples were obtained from 29 patients with DLB, 174 with AD and 90 with AD-Vasc. All patients who had completed a full investigation of medical history, cognitive test (MMSE), computerized tomography of the brain, measurement of relative cerebral blood flow, blood, and CSF analyses, were selected consecutively from patients attending the Neuropsychiatry Clinic, University Hospital MAS, Malmö, Sweden between 1999 and 2003. The patients fulfilled the clinical criteria for AD (NINCDS-ADRDA) (McKhann et al., 1984) or the consensus criteria for DLB (McKeith et al., 1996, 2005). No patient fulfilled the NINCDS-AIREN or DSM IV criteria for vascular dementia. AD-Vasc was defined as fulfillment of the clinical criteria for AD and a history with at least one suspected cerebrovascular insult and/or minor ischemic insult on computerized tomography without any clear causative effect on the development of clinical dementia. In addition MMSE score, CSF and plasma was gathered from 51 healthy volunteers. EDTA was used as anticogulant for the plasma collection. All plasma and CSF samples were stored at −80 °C until analysis. The total concentrations in CSF and plasma of magnesium (Mg), calcium (Ca), manganese (Mn), iron (Fe), copper (Cu), zinc (Zn), rubidium (Rb), strontium (Sr), and cesium (Cs) were determined by inductively coupled plasma-mass spectrometry (ICP-MS; Thermo X7, Thermo Elemental, Winsford, UK) in accordance with Gerhardsson and colleagues (submitted for publication). To ensure the accuracy of the analytical methods and results, samples with 2% HNO_3 and quality control (QC) samples were analyzed along with the collected samples (Seronorm Trace Elements Serum Lot MI0181; SERO AS, Billingstad). The background contamination of the collection vessels was below the detection level of the analytical method used, and the obtained values for the QC samples showed good agreement with the recommended concentrations. Albumin levels in CSF and serum were measured by immunonephelometry on a Beckman Immage Immunochemistry system (Beckman Instruments). The albumin ratio (Q(alb)) was calculated as CSF albumin/serum albumin.

3.1. Statistical analysis

SPSS 14.0 was used for statistical analysis. Since the metal concentrations were not normally distributed a non-parametric Kruskal–Wallis one-way analysis of variance was performed followed by Mann–Whitney *U*-test for continuous variables to analyze differences between DLB and controls, AD patients and AD-Vasc patients. Adjustment for multiple comparisons was performed using the Bonferroni method. Spearman's rank order correlation was performed post hoc

Table 1
Between-group comparisons of demographic data

	DLB	AD	AD-Vasc	Controls	Significant differences $p < 0.05$ (DLB vs. other)
N	29	174	90	49	
Gender male/female (*n*)	17/12	52/122	33/57	15/34	DLB vs. controls, AD
Age[1]	74 (54–84)	74 (52–86)	77 (57–87)	73 (60–87)	No
Disease duration (yrs)[1a]	2 (0–8)	2 (0–10)	2 (0–8)	na	No
MMSE (score 0–30)[1a]	23 (14–29)	22 (2–30)	22 (6–30)	30 (27–30)	DLB vs. controls
CSF-Albumin (g/L)[2a]	0.29 + −0.16	0.27 + −0.11	0.28 + −0.12	0.25 + −0.08	No
S-Albumin (g/L)[2a]	35.5 + −3.11	36.4 + −3.61	35.9 + −3.70	36.0 + −2.45	No
Q(alb)[2a] ($\times 10^{-3}$)	8.2 + −3.2	7.3 + −2.4	7.8 + −3.6	7.4 + −3.2	No

Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), Alzheimer's disease with minor vascular components (AD-Vasc), number (*N*), not applicable (na) mini mental state examination (MMSE), in cerebrospinal fluid (CSF-), in serum (S-) [1]median (range) [2]mean (S.D.) [a]DLB $n = 26$–28, AD $n = 166$–174, AD vasc = 83–90, controls $n = 48$–49.

to analyze the relationship between the two metals that were significantly increased in the DLB patients compared to the controls. The Youden method (Youden, 1950) was used to establish the optimal cut-off point to assess the diagnostic accuracy of the different metal concentrations in distinguishing DLB from AD.

4. Results

Demographics, MMSE, CSF-Alb, S-Alb and Q(alb) are presented in Table 1. Two controls were excluded due to low MMSE score (<26). Comparably more male patients were present in the DLB group than among the controls and the AD patients. There were no significant differences between male and female patients regarding metal concentrations in plasma or CSF in any group (data not shown). The blood–brain barrier function, reflected by Q(alb) was similar in all groups.

Mg, Ca and Cu differed in concentration in CSF samples from DLB patients compared to the other groups (Tables 2 and 3 and Fig. 1), however, after correction for multiple comparisons differences in CSF Cu concentrations failed to reach significance. Yet, DLB patients displayed higher Ca and Mg levels in CSF when compared to all other groups in a statistically robust manner ($p < 0.001$). Furthermore, CSF-Mg and CSF-Ca correlated strongly within the DLB group ($r_s = 0.74$, $p < 0.001$) (Fig. 2). In addition, Cs in CSF was elevated among the DLB patients compared to the AD patients ($p < 0.001$) but not compared to the controls or the AD-Vasc patients. Rb and Cs CSF levels were borderline significantly increased in DLB compared to AD and AD-Vasc, respectively. Mn, Fe, Cu, Zn, Rb and Sr concentrations in CSF did not differ between DLB patients and the other groups (Table 2).

Patients with DLB had significantly increased Mg levels in their plasma compared to controls and AD patients ($p < 0.001$), as well as compared to AD-Vasc patients ($p < 0.05$), and showed increased Ca in their plasma compared to AD-Vasc patients ($p < 0.05$). In addition, P-Cu was elevated among the DLB patients compared to patients with AD and AD-Vasc ($p < 0.05$) but not compared to controls (Table 3). All DLB patients had P-Mg and P-Ca values within the normal reference range used at the local laboratory for clinical practice (Mg 0.7–1.2 mM; Ca 2.2–2.6 mM).

There was no significant correlation between CSF and plasma levels of Mg or Ca in the DLB group (Ca: $r_s = -0.20$ $p = 0.30$; Mg: $r_s = -0.25$ $p = 0.20$) or among the controls (Ca: $r_s = -0.23$ $p = 0.10$; Mg: $r_s = -0.27$ $p = 0.55$). Furthermore, Q(alb) did not correlate significantly with CSF-Ca or CSF-Mg in the DLB group (Ca: $r_s = 0.31$ $p = 0.13$; Mg: $r_s = -1.45$ $p = 0.48$) or among the controls (Ca: $r_s = 0.39$ $p = 0.13$; Mg: $r_s = -0\text{-}17$ $p = 0.90$).

The CSF-Mg concentration could distinguish DLB patients from AD patients (AD and AD-Vasc) with a sensitivity of 93% and a specificity of 81%, when an optimal cut-off

Table 2
Metal concentrations in CSF

	DLB	Controls	AD-Vasc	AD	DLB vs. controls p	DLB vs. AD p	DLB vs. AD-Vasc p
Mg (mg/L)	32.6 (26.8–38.8)	28.0 (25.2–37.0)	27.3 (23.5–34.0)	27.5 (23.4–35.5)	1.9×10^{-8}***	1.8×10^{-12}***	3.2×10^{-12}***
Ca (mg/L)	56.2 (45.2–67.6)	49.6 (44.0–67.7)	49.8 (42.8–64.4)	49.9 (41.5–67.2)	1.5×10^{-6}***	3.6×10^{-9}***	1.9×10^{-7}***
Mn (μg/L)	0.67 (0.37–2.43)	0.72 (0.41–2.02)	0.63 (0.21–2.04)	0.61 (0.25–3.36)	0.38	0.25	0.57
Fe (μg/L)	224 (148–269)	235 (122–403)	174 (106–438)	192 (100–434)	0.52	0.36	0.093
Cu (μg/L)	20.7 (14.0–140.2)	18.2 (12.9–34.7)	18.4 (8.41–83.71)	17.8 (9.0–109)	0.006*	0.0036*	0.010*
Zn (μg/L)	21.0 (8.1–146)	17.0 (9–103.3)	17.0 (8.41–66.6)	17.6 (9.0–138)	0.39	0.10	0.17
Rb (μg/L)	76.5 (55.5–155)	72.5 (51.2–115.5)	67.5 (46.0–118.1)	66.9 (38.1–121.8)	0.94	0.012	0.054
Sr (μg/L)	15.9 (8.5–34.6)	13.8 (5.1–33.1)	14.4 (6.4–83.8)	13.5 (5.7–65.4)	0.15	0.10	0.11
Cs (μg/L)	0.26 (0.15–0.47)	0.28 (0.14–0.62)	0.22 (0.11–0.43)	0.19 (0.07–0.62)	0.30	0.0002**	0.011

All metal concentrations are presented as median (range). Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), Alzheimer's disease with minor vascular components (AD-Vasc). (*) <0.01; (**) <0.001; (***) <0.0001.

Table 3
Metal concentrations in plasma

	DLB	Controls	AD-Vasc	AD	DLB vs. controls *p*	DLB vs. AD *p*	DLB vs. AD-Vasc *p*
Mg (mg/L)	22.8 (18.5–27.6)	21.1 (18.0–27.5)	21.4 (13.4–25.3)	21.3 (15.4–28.7)	0.00033 **	0.00024**	0.0017*
Ca (mg/L)	102.7 (87.6–123.2)	98.3 (82.5–142.1)	98.0 (71.3113.7)	97.4 (83.0–125.5)	0.003*	0.0017*	0.00044**
Mn (μg/L)	0.99 (0.61–2.50)	0.94 (0.63–2.24)	1.40 (0.51–4.49)	1.45 (0.48–5.95)	0.66	0.079	0.098
Fe (mg/L)	1.53 (0.99–1.88)	1.67 (1.05–3.54)	1.54 (0.75–2.96)	1.61 (0.72–3.24)	0.006*	0.10	0.21
Cu (mg/L)	1.36 (0.98–2.25)	1.26 (0.81–3.43)	1.22 (0.78–2.04)	1.23 (0.79–2.23)	0.038	0.0013*	0.0015*
Zn (μg/L)	771 (605–1348)	846 (535–1371)	854 (555–1197)	872 (573–2500)	0.013*	0.0027*	0.0038*
Rb (μg/L)	299 (225–455)	300 (225–433)	302 (186–438)	294 (171–481)	0.83	0.40	0.69
Sr (μg/L)	31.5 (19.5–79.9)	31.6 (13.1–62.7)	30.4 (14.6–176)	31.2 (12.0–166)	0.77	0.10	0.11
Cs (μg/L)	0.83 (0.50–9.69)	1.06 (0.55–3.71)	1.40 (0.35–9.03)	0.78 (0.36–9.94)	0.18	0.31	0.17

All metal concentrations are presented as median (range). Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), Alzheimer's disease with minor vascular components (AD-Vasc). (*) <0.01; (**) <0.001.

value of 29.3 mg/L was used. Moreover, the CSF-Ca concentration resulted in a sensitivity of 93% and a specificity of 63% for detection of DLB among the demented patients using the optimal cut-off value 50.7 (Fig. 3). A combination of the two variables yielded a sensitivity of 93% and a specificity of 85% when a positive result was defined as a combination of CSF-Mg ≤ 27.3 mg/L and CSF-Ca ≤ 48.0 mg/L. The plasma levels of the analyzed metals were unable to discriminate

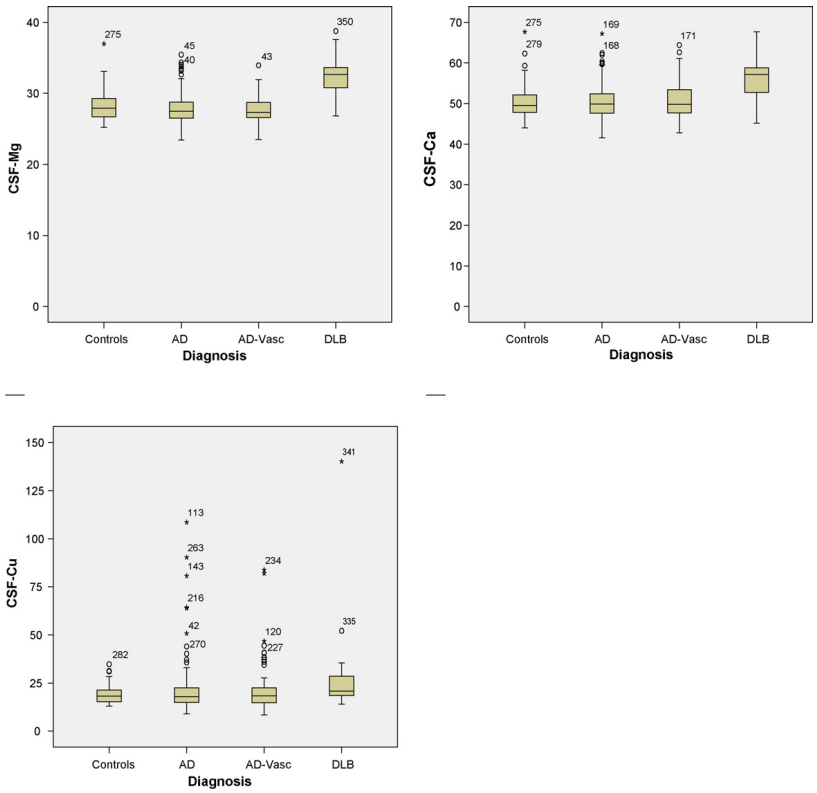

Fig. 1. CSF concentrations of Mg, Ca and Cu. Ca and Mg are in (mg/L), Cu in (μg/L).

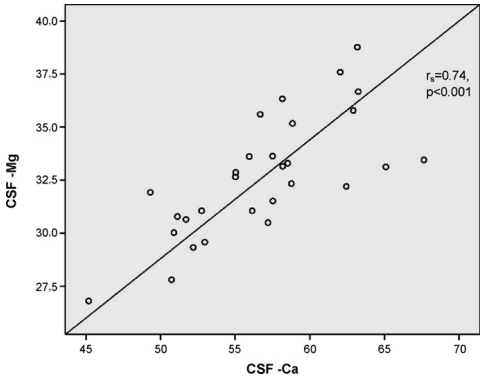

Fig. 2. Correlation between cerebrospinal fluid Mg and Ca levels among DLB patients (mg/L).

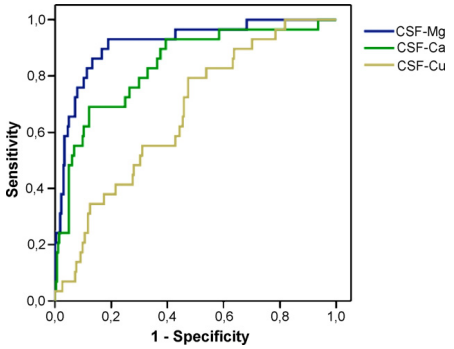

Fig. 3. Receiver operating characteristic (ROC) curves of CSF-Mg, CSF-Ca and CSF-Cu for differentiation of DLB patients from all patients with Alzheimer's disease (ADVasc and AD). The areas under the ROC curve for the analyzed metals with 95% confidence interval were: CSF-Mg, 0.92 (0.86–0.97), CSF-Ca 0.84 (0.76–0.92) and CSF-Cu 0.66 (0.57–0.76), respectively.

DLB from AD with small areas under the receiver operating characteristic curve ($\leq$0.71).

5. Discussion

There is to our knowledge no prior study of metals in DLB patients' CSF or plasma. This study included more male than female DLB patients, a trend seen in most studies of DLB. However, there were no significant differences between genders regarding metal concentration in CSF or plasma in any of the studied groups.

The main findings of this study are that CSF Mg and Ca are elevated in DLB compared to all other groups in a sensitive and specific manner that allow the use of these variables as a diagnostic tool in distinguishing DLB from AD. Moreover, Cu levels in the CSF of the DLB patients was increased in a less robust fashion. Similar trends were observed for the plasma levels of these three metals, although some comparisons failed to survive adjustment for multiple testing. Notably, none of the DLB patients had laboratory findings compatible with hypercalcemia or hypermagnesemia. This metal pattern is likely to be specific for DLB patients as earlier studies have shown normal Ca, Mg and Cu concentrations in CSF in Parkinson's disease (PD) and AD patients. (Basun et al., 1991; Jimenez-Jimenez et al., 1998; Forte et al., 2004; Gerhardsson et al., submitted for publication). The albumin concentration in CSF is about 0.8% compared to that of serum. Consequently, CSF-Alb should not substantially be able to influence the amount of bio-available metal ions in CSF and could not be the explanation of the observed differences in CSF metal concentration.

The Ca concentration in plasma is about twice as high as that in CSF. Therefore, it would be logical that disrupted blood–brain barrier integrity could explain the increased Ca concentration in DLB patients' CSF. However, there was no difference in BBB integrity measured with Q(alb) (Frolich et al., 1991) between the three groups, and no correlation between Q(alb) and CSF-Ca levels. Furthermore, AD-Vasc patients had the same levels of these metals in their CSF as controls (Gerhardsson et al., submitted for publication.). Other DLB specific pathologic changes in the blood–brain barrier that do not influence CSF-alb may contribute, such as α-synuclein that has been shown to form pore-like structures in cell membranes in vitro (Lashuel et al., 2002). The Mg concentration in plasma and CSF are very similar, but the Mg^{2+} ion is in contrast to Ca^{2+} enriched intracellularly. Therefore, a possible source of the elevated Mg levels in CSF in DLB could be widespread cellular damage, possibly due to the cytotoxic properties of some alpha synuclein species (Smith et al., 2005). The strong correlation between CSF Ca and Mg suggests that the changes in these two metals are somehow connected in DLB. The cause-and-effect relationships between the altered metal pattern in CSF and the development of the disease are, however, difficult to hypothesize as both Ca and Mg are two essential trace elements, intricately regulated by homeostasis.

The increased Ca, Mg and Cu concentration in DLB patients CSF may contribute to the long-term development of the disease through affecting α-synuclein aggregation and micro-vascular function. This idea is supported by the results that cortical neurons that express Ca-sequestering proteins are spared in DLB (Gomez-Tortosa et al., 2001). Furthermore, the formation of α-synuclein oligomers is accelerated by the presence of both Mg (Lowe et al., 2004), Ca (Nielsen et al., 2001) and Cu (Gaggelli et al., 2006) in vitro. Finally, α-synuclein has been demonstrated to form annular oligomers and to interact with the lipid surface of neurons when Ca is present (Tamamizu-Kato et al., 2006). These mechanisms are thought to be important steps in the formation of neurotoxic

α-synuclein aggregates and thereby the pathogenesis of the disease. Furthermore, α-synuclein has been demonstrated to enhance Ca^{2+} influx through voltage dependent Ca^{2+} channels in vitro (Adamczyk and Strosznajder, 2006). This mechanism may potentiate the toxic effect of an increased extracellular Ca level in DLB patients.

Both micro-vascular pathology and blood–brain barrier dysfunction increase during aging. These changes are diminished by Ca-channel blockers (Farkas and Luiten, 2001), indicating a possible pathogenic role for an increased extracellular Ca level in interrupting the micro-vascular and BBB function of the brain. The possible pathogenic or symptom-modifying roles of Ca and Mg may be even further aggravated by both metals often being elevated in the same patient, given the high correlation between CSF-Mg and CSF-Ca. However, it is not possible to predict in which patients CSF levels of Ca and Mg will be elevated with plasma concentrations, as metal concentrations in these two fluids do not correlate.

In summary, this study shows that Mg, Ca and Cu levels in CSF are elevated in patients with DLB compared to controls, patients with AD and patients with AD-Vasc, and that CSF-Mg, and CSF-Ca can be a valuable tool in distinguishing DLB from AD. More studies are needed to verify the results of this study and to compare PD and DLB with regard to Mg, Ca and Cu concentration in CSF.

Disclosure statement

The authors reported no conflicts of interest. This study was approved by the ethics committee of Lund University and was carried out in accordance with the Helsinki Declaration.

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IV

CSF T-tau is associated with shorter survival in dementia with Lewy bodies

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Abstract

Pathology typical for Dementia with Lewy bodies (DLB) has been demonstrated to increase mortality to a greater extent than Alzheimer's disease (AD) pathology. However, mortality in DLB has also been shown to increase with concomitant AD pathology. Furthermore, in a recent publication, we showed that there is a robust and specific increase of CSF Calcium and Magnesium in DLB patients compared to both AD patients and controls. Thus, in order to explore the influence of CSF AD markers and trace element concentrations on mortality in DLB, we undertook a longitudinal prospective study of 47 clinically diagnosed DLB and 157 AD patients as well as 49 healthy volunteers. Both AD and DLB had increased mortality compared to healthy controls (RR 10 and 8, $p < 0.001$). Increased levels of CSF T-tau was associated with increased mortality among DLB patients ($p < 0.05$) but not among AD patients or controls. Gender, age, MMSE score, Aβ42 concentration and P-Tau, and CSF trace element concentrations did not influence survival in the obtained models.

Keywords: Dementia with Lewy bodies, Lewy body disease, Alzheimer's disease, Cerebrospinal fluid, Mortality, Survival

Introduction

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia disorder [1]. DLB has been designated an α-synucleinopathy together with Parkinson's disease and multiple system atrophy. These disorders are thought to be characterized by pathological α-synuclein turnover [2], in difference to Alzheimer´s Disease (AD), in which Aβ accumulation and deposition, and possibly tau phosphorylation, are thought to be central pathogenic steps [3].

DLB has been demonstrated to shorter survival to a greater extent than AD, in spite of a similar progression rate of cognitive decline [4]. However, concomitant AD pathology predicts earlier death in post mortem diagnosed DLB [4, 5]. Three CSF AD markers are commonly used; T-tau, P-tau and Aβ42. T-tau is hypothesized to reflect rate of neuronal degeneration, and high P-tau and low Aβ42 correlates to formation of tangles and plaques respectively [3, 6]. Discrepant quantities of these CSF AD markers have been found in DLB, however, the overall trend is values somewhere between AD and DLB [7–9], and whether the CSF AD markers predict earlier death among clinically diagnosed DLB patients has not been studied.

The authors of this article recently demonstrated a disturbed trace element homeostasis in DLB patients, with a robust and specific increase of CSF Calcium (Ca) and Magnesium (Mg) compared to both controls and AD patients [10]. These results hint at a possible pathogenic or disease modifying role for divalent ions in the DLB patients juxtaneuronal environment.

In order to explore the influence of concomitant AD pathology and CSF trace elements on disease course, we undertook a study of the commonly used CSF biomarkers for AD as well as CSF metal concentrations as possible determinants of survival in clinically diagnosed DLB. The mortality rate of people with dementia is known to increase with age [11]. This is undoubtedly connected with the mortality rate according to age in a population in general. Thus, we included a control group of healthy volunteers to get a more specific picture of the influences of AD and DLB on mortality and the determinants thereof.

Aim

The primary aim of this study was to explore CSF levels of AD associated bio-markers and CSF metal concentrations as determinants of survival among DLB patients.

Method and material

47 DLB and 157 AD patients admitted to the Neuropsychiatry Clinic, University Hospital MAS, Malmö, between 1999 and 2003 were included in a longitudinal prospective study. All patients who had completed a full investigation, together with their primary caregiver, were included. The patients fulfilled the consensus criteria for DLB [1, 12], or the clinical criteria for AD (NINCDS-ADRDA) [13]. In addition 49 healthy volunteers were included.

The study subjects underwent a baseline investigation of medical history, physical and neurological examination, computerized tomography (CT) of the brain, measurement of relative cerebral blood flow, and cognitive function (MMSE) [14]. Furthermore, CSF and plasma samples were collected.

CSF total-tau (T-tau), phosphorylated tau (P-tau) and Aβ42 concentrations were measured with xMAP technology and the INNOBIA AkzBio3 kit (Innogenetics) as described by Olsson and colleagues [15].

The total concentrations in CSF of Mg, Ca, and copper (Cu) were determined by inductively coupled plasma-mass spectrometry (ICP-MS; Thermo X7, Thermo Elemental, Winsford, UK) in accordance with Gerhardsson and colleagues [16].

Statistical analysis

SPSS 16.0 was used for the statistical analyses. To avoid bias of non-normal distributions , the Mann-Whitney U test was used to analyse differences between the AD and DLB group with respect to demographical data. Kaplan Meier survival curves were constructed to estimate the survival distributions between groups and generalized Wilcoxon was used to compare survival distributions between groups. Cox proportional hazard models were used to determine the effects of covariates on survival time. In order to determine the influence on mortality of covariates, two Cox regression analyses were performed with backward removal with a removal limit of $p = 0.10$. The first analysis comprised CSF biomarkers of Alzheimer pathology, ie T-tau, P-tau, and Aβ42 as well as the possible confounding factors age, MMSE score at baseline, and gender. The second regression analysis comprised CSF Ca, Mg and Cu concentrations.

Results

Demographic data, cognitive status at baseline and a between groups comparison of the analyzed covariates are presented in Table 1. Comparably more male patients were present in the DLB group than among the controls and the AD patients. There was a tendency towards a greater rate of cognitive decline among the DLB patients compared to the AD patients, this trend did however not reach significance (Mann Whitney U test; $p = 0.08$).

Both the DLB and AD group had markedly shorter survival compared to controls, relative risk 8 and 10 respectively ($p < 0.001$ both). There was a trend towards younger age at death in DLB compared to AD ($p = 0.08$) (figure 1). Furthermore, there was a non-significant tendency towards increased mortality during follow up in the DLB compared to the AD group when disease duration was calculated from the first contact with the specialist clinic ($p = 0.13$) (Figure 2).

The multivariate Cox proportional hazard model revealed that DLB patients with elevated levels of CSF T-tau had an increased risk of early death ($p = 0.022$, Hazard Ratio (HR) = 1.36 per 100 ng/L T-tau, 95 % CI = 1.05–1.78), model significance $p = 0.036$). However, this was not the case among AD patients or controls. Gender, age, MMSE score, P-tau concentration and Aβ42 concentration did not influence survival in the obtained model. A higher baseline CSF T-tau was observed among the DLB patients who where deceased compared to those that survived at follow up (Mann Whitney U test; $p = 0.024$)

The used method was unable to construct a Cox regression model of the influence of metal covariates on survival (with $p \leq 0.05$) for any group.

Discussion

This is the first study to analyze the influence of CSF markers on survival among DLB patients. This study included more male than female DLB patients, a trend seen in most studies of DLB. However, gender did not influence mortality in any of the studied groups.

The main finding of this study was that the elevated level of CSF T-tau was associated with earlier death among DLB patients, but not among AD patients or healthy controls. There is to our knowledge no study of the intra-individual variance of T-tau in DLB. However, CSF T-tau seems to be remarkably stable over time in both in subjects with minor cognitive impairment and AD [17, 18]. Thus, it is more likely that CSF T-tau reflects the nature than the stage of the disease. A possible explanation of

the association between earlier death and elevated CSF T-tau could be that increased T-tau in the DLB group reflect concomitant AD pathology, which is known to increase mortality among DLB patients [4]. Furthermore, T-tau concentration in CSF may reflect the intensity of neuronal degeneration in the DLB group, as is thought to be the case in all chronic neurodegenerative disorders. Thus, CSF T-tau is sometimes referred to as a "state" marker of the neurodegenerative disorder. This argument is largely based on comparisons between different brain diseases, such as Creutzfeld-Jakob's Disease, in which both the rate of neuronal damage and T-tau is very high, compared to AD, where both are comparably lower [19]. T-tau is also a dynamic marker of traumatic brain injury [20], and the magnitude of the tau elevation is related to clinical outcome [21]. In addition, one earlier small study (n = 21) suggests an association between mortality and CSF T-tau in AD [22]**.** However, the present, comparably larger, study (AD n = 159) failed to demonstrate a correlation between T-tau and mortality among the AD patients. Thus, although the hypothesis on T-tau as a marker of the aggressiveness of neurodegenerative dementias could explain the main finding of this study, the hypothesis needs further testing.

CSF Mg and Ca have been demonstrated to be specifically increased among DLB patients compared to AD patients and controls [10]. The results of the present study implicate that these changes may not correlate to disease stage or rate of disease progression. However, these results must be interpreted with care due to a small sample size. Furthermore, even if disease progression is not affected by CSF trace elements, CSF metal changes may yet be a crucial "trigger" factor in the development of the disease. Another possibility is that CSF Ca and Mg are increased due to DLB specific disease processes, but neither influences the development nor the course of the disease.

Both AD and DLB are associated with shorter survival, both in this as well as in earlier studies [11, 23–25]. There was however no significant difference in survival time between the AD and DLB patients in the present study. This result is in contrast to an earlier larger study in which DLB patients had shorter survival, but similar cognitive decline [4]. However, in contrast to the present study, which comprised clinically diagnosed patients, DLB diagnosis was made post mortem, making the studies not entirely compatible.

In the DLB group, there was a tendency towards a more rapid MMSE decline as well as a trend towards a shorter survival (not significant), measured as time to death after the first contact with a specialist clinic. This may signal a later debut, but a more aggressive course of the disease. Thus, further, larger, studies are needed to further explore mortality and rate of cognitive decline in of clinically diagnosed DLB.

Disease onset is measured in most clinical trials of dementia disorders. It is however an elusive concept, prone to recall biases on the part of patients and informants, and lack of understanding that certain symptoms may represent dementia. Although an earlier report suggest good interrater reliability of standardized estimation of disease onset [26], the most important problem is that there is no gold standard to evaluate the validity of proxy or patient reports. Another difficulty is deciding what symptoms to look for as a sign of disease onset. For instance, subjective memory problems often present years after anamnestic REM sleep behavior disorder in DLB. To avoid the subjective and elusive concept of estimated disease onset, we used date of admission as an objective surrogate.

In summary, this study shows that CSF T-tau, a marker of AD and neuronal degeneration, is associated with increased mortality in dementia with Lewy bodies and that CSF metal concentrations may not influence disease progression in DLB.

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Disclosure Statement

The authors reported no conflicts of interest. This study was approved by the Ethics Committee of Lund University and was carried out in accordance with the Helsinki Declaration.

Table 1. Demographic data and analyzed covariates

	DLB	**AD**	**Controls**	**Significant differences** p <0.05 (DLB vs other)
Number	47	159	49	
Gender male/female (n)	25/22	39/120	15/34	DLB vs AD, Controls
Age at onset [a] (years)	77 (55-89)	76 (52-86)	73 (60-87)	No
MMSE [a] (at baseline)	23 (10-30)	21 (2-29)	30 (27-30)	DLB vs AD, Controls
Follow up time [a] (years)	4 (0-7)	5 (0-7)	5 (1-7)	DLB vs AD, Controls
Deceased	55 %	52 %	6 %	DLB vs Controls
Cognitive decline (MMSE score /year) [a]	2 (1.33-18) [b]	1.5 (-4-12)	Not applicable	No
T-tau (ng/L) [a, c]	270 (86-786)	545 (181-2144)	245 (64-698)	DLB vs AD
P-tau (ng/L) [a c]	73 (37 -115)	77 (30-203)	57 (22-132)	DLB vs Controls
Aβ42 (ng/L) [a c]	469 (228-834)	392 (259-781)	746 (377-995)	DLB vs AD, Controls
Ca (mg/L) [a d]	56.2 (45.2-67.6)	49.7 (42.6-62.6)	49.6 (44.0-67.7)	DLB vs AD, Controls
Mg (mg/L) [a d]	32.6 (26.8-38.8)	27.3 (23.4-35.5)	28.0 (25.2-37.0)	DLB vs AD, Controls
Cu (µg/L) [a d]	20.7 (14.0-140.2)	18.2 (8.4-108.6)	18.2 (12.9-34.7)	DLB vs AD, Controls

DLB = Dementia with Lewy bodies; AD = Alzheimer's disease;
MMSE = Mini mental state examination;
[a] median (range), [b] n=35, [c] DLB n=34, AD n=159, Controls n=49 [d]DLB n=29, AD n=159, Controls n=49.

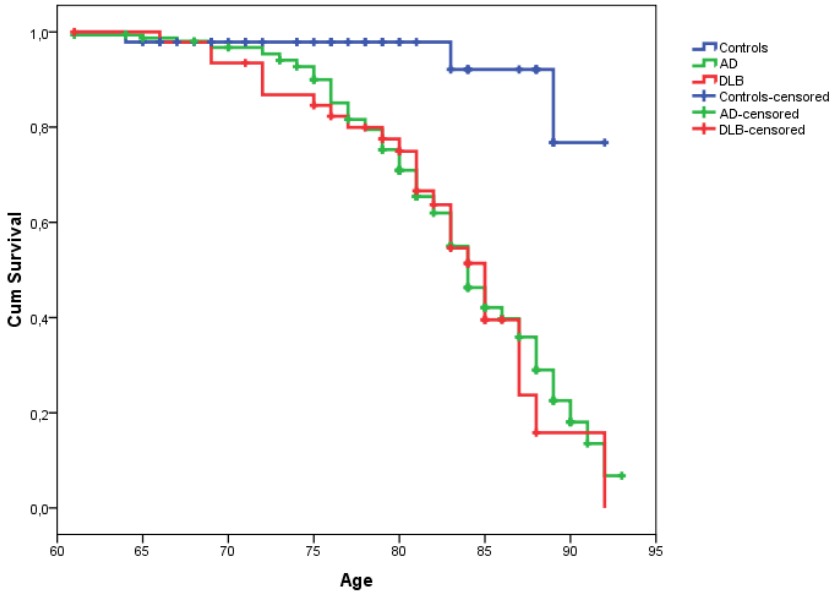

Figure 1. Kaplan Meier Survival curves comparing mortality for DLB and AD. There was no difference in age at death (X^2 0.012, p = 0.92. Mean age at death was 80 (66–92) yrs in the DLB group and 81 years (61–92) in the AD group. Controls vs other p <0.001.

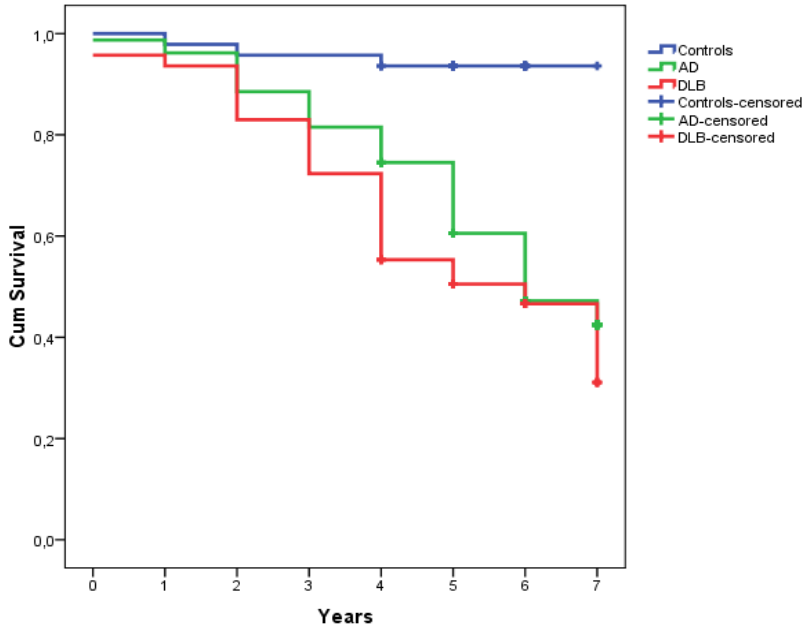

Figure 2. Kaplan-Meier survival curves comparing the survival among DLB and AD patients as well as healthy controls, with a reference point from the first contact with the specialist clinic. Mean survival was 7.02 (6.28–7.76) years in the AD group compared to 5.59 (4.71–6.48) yrs in the DLB group (X^2 = 2.34, p = 0.13). The controls lived longer than both dementia groups (p <0.0001 both)

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