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Published in:
Dementia and Geriatric Cognitive Disorders

DOI:
[10.1159/000249145](https://doi.org/10.1159/000249145)

2009

[Link to publication](#)

Citation for published version (APA):
Boström, F., Hansson, O., Blennow, K., Gerhardsson, L., Lundh, T., Minthon, L., Zetterberg, H., & Londos, E. (2009). Cerebrospinal Fluid Total Tau Is Associated with Shorter Survival in Dementia with Lewy Bodies. *Dementia and Geriatric Cognitive Disorders*, 28(4), 314-319. <https://doi.org/10.1159/000249145>

Total number of authors:
8

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Citation for the published paper:
Fredrik Boström, Oskar Hansson, Kaj Blennow, Lars Gerhardsson, Thomas Lundh, Lennart Minthon, Henrik Zetterberg, Elisabet Londos
"Cerebrospinal Fluid Total Tau Is Associated with Shorter Survival in Dementia with Lewy Bodies."
Dementia and geriatric cognitive disorders, 2009,
Volume: 28 Issue: 4, p 314-19

<http://dx.doi.org/10.1159/000249145>

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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 were associated with increased mortality among DLB patients ($p < 0.05$) but not among AD patients or controls. Gender, age, MMSE score, $A\beta_{42}$ 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 {McKeith, 2005 #87}. 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 {Weisman, 2007 #91}, in difference to Alzheimer's Disease (AD), in which A β accumulation and deposition, and possibly tau phosphorylation, are thought to be central pathogenic steps {Blennow, 2006 #113}.

DLB has been demonstrated to shorten survival to a greater extent than AD, in spite of a similar progression rate of cognitive decline {Williams, 2006 #103}. However, concomitant AD pathology predicts earlier death in post mortem diagnosed DLB {Williams, 2006 #103; Jellinger, 2007 #104}. Three CSF AD markers are commonly used; T-tau, P-tau and A β 42. T-tau is hypothesized to reflect rate of neuronal degeneration, and high P-tau and low A β 42 correlates to formation of tangles and plaques respectively {Buerger, 2006 #162; Blennow, 2006 #102}—although two recent studies showed no correlation between CSF tau and neocortical tangle pathology {Engelborghs, 2007 #180; Buerger, 2007 #179}. Discrepant quantities of the CSF AD markers have been found in DLB, however, the overall trend is values somewhere between AD and DLB {Mollenhauer, 2006 #20; Mollenhauer, 2005 #166; Wada-Isoe, 2007 #167}, 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 {Bostrom, 2008 #105}. 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 {Guehne, 2005 #128}. 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 diagnosis was continuously clinically reevaluated, and at study end the patients fulfilled the 2005 consensus criteria for probable DLB {McKeith I, 1996 #4; McKeith, 2005 #87}, or the clinical criteria for AD (NINCDS-ADRDA) {McKhann, 1984 #78}. In addition 49

healthy volunteers were included. All study subjects were followed for a maximum of 7 years.

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) {Folstein, 1975 #115}.

Furthermore, CSF and plasma samples were collected.

CSF total-tau (T-tau), phosphorylated tau (P-tau) and A β 42 concentrations were measured with xMAP technology and the INNOBIA AkzBio3 kit (Innogenetics) as described by Olsson and colleagues {Olsson, 2005 #116}.

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 {Gerhardsson, 2008 #114}.

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 A β 42 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 A β 42 concentration did not influence survival in the obtained model. A higher baseline CSF T-tau was observed among the DLB patients who were 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 patients with clinically probable DLB according to the consensus criteria {McKeith, 2005 #87}. Although a post mortem examination is required to make a certain diagnosis, the high specificity (86%) {Fujishiro, 2008 #172} of the diagnostic criteria produced a representative DLB group. 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.

Furthermore, in contrast to earlier studies, the CSF T-tau levels of the DLB patients were not increased compared to the control subjects {Mollenhauer, 2006 #165; Mollenhauer, 2005 #166}. 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 subjects with minor

cognitive impairment and AD {Zetterberg, 2007 #169; Blennow, 2007 #168}. 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 {Williams, 2006 #103}. 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 {Blennow, 2003 #118}. T-tau is also a dynamic marker of traumatic brain injury {Zetterberg, 2006 #156}, and the magnitude of the tau elevation is related to clinical outcome {Zemlan, 2002 #157}. In addition, one earlier small study (n=21) suggests an association between mortality and CSF T-tau in AD {Wallin, 2006 #121}. 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 {Bostrom, 2008 #105}. 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 {Larson, 2004 #127; Ganguli, 2005 #126; Guehne, 2005 #128; Koedam, 2008 #125}. 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 {Williams, 2006 #103}. 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 {Doody, 2004 #119}, 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.

Acknowledgements

Anna-Carin Björkman and Cecilia Dahl for administration of patients' material. This study was supported by "Swedish Brain Power" and the Swedish research council, Region Skåne.

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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Table 1. Demographic data and analyzed covariates

	DLB	AD	Controls	Significant differences P<0.05 (DLB vs other)
<i>N</i>	47	159	49	
Gender male/female (n)	25/22	39/120	15/34	DLB vs AD, Controls
Age at admission ^a (Years)	75.8 (55-89) ±6.8	75.4 (52-86) ±6.8	73.1 (60-87) ±7.7	No
MMSE ^a (At baseline)	22.7 (10-30) ±5.3	20.2 (2-29) ±4.9	30 (27-30)	DLB vs AD, Controls
Follow up time ^a (years)	4.3 (0-7) ±1.8	5.1 (0-7) ±1.7	5.1 (1-7) ±1.0	DLB vs AD, Controls
Deceased	55%	52%	6%	DLB vs Controls
Cognitive decline (MMSE score /year) ^a	3.5.1 (1.33-18) ^b ±3.7	1.9 (4.0-12.0) ±2.4	na	No
Concomittant medication				
Aspirin	30%	29%	23%	No
Antihypertensives and cardiac therapy	35%	33%	37%	No
Medication	54%	45%	4%	DLB vs Controls
Antidepressant				
Antipsychotics, anxiolytics, sedative/hypnotics	59%	32%	0%	DLB vs AD, Controls
CSF analytes				
T-tau (ng/L) ^{a, c}	318.3 (86-786) ±187.3	663.8 (181-2144) ±332.7	284.9 (64-693) ±154.0	DLB vs AD
P-tau (ng/L) ^{a, c}	73.7 (37 -115) ±19.6	81.2 (30-203) ±29.9	49.0 (22-132) ±13.6	DLB vs Controls
Aβ42 (ng/L) ^{a, c}	479.2 (228-834) ±166.4	397.0 (259-781) ±73.7	438 (377-995) ±132	DLB vs AD, Controls
Ca (mg/L) ^{a, d}	56.8 (45.2-67.6) ±5.2	50.2 (42.6-62.6) ±3.8	50.4 (44.0-67.7) ±4.9	DLB vs AD, Controls
Mg (mg/L) ^{a, d}	32.6 (26.8-38.8) ±8.8	27.7 (23.4-35.5) ±2.0	28.4 (25.2-37.0) ±2.3	DLB vs AD, Controls
Cu (μg/L) ^{a, d}	24.4 (14.0-140.2) ±23.2	12.6 (8.4-108.6) ±21.0	19.3 (12.9-34.7) ±5.3	DLB vs AD, Controls

Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), number (N), not applicable (na) mini mental state examination (MMSE),. ^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

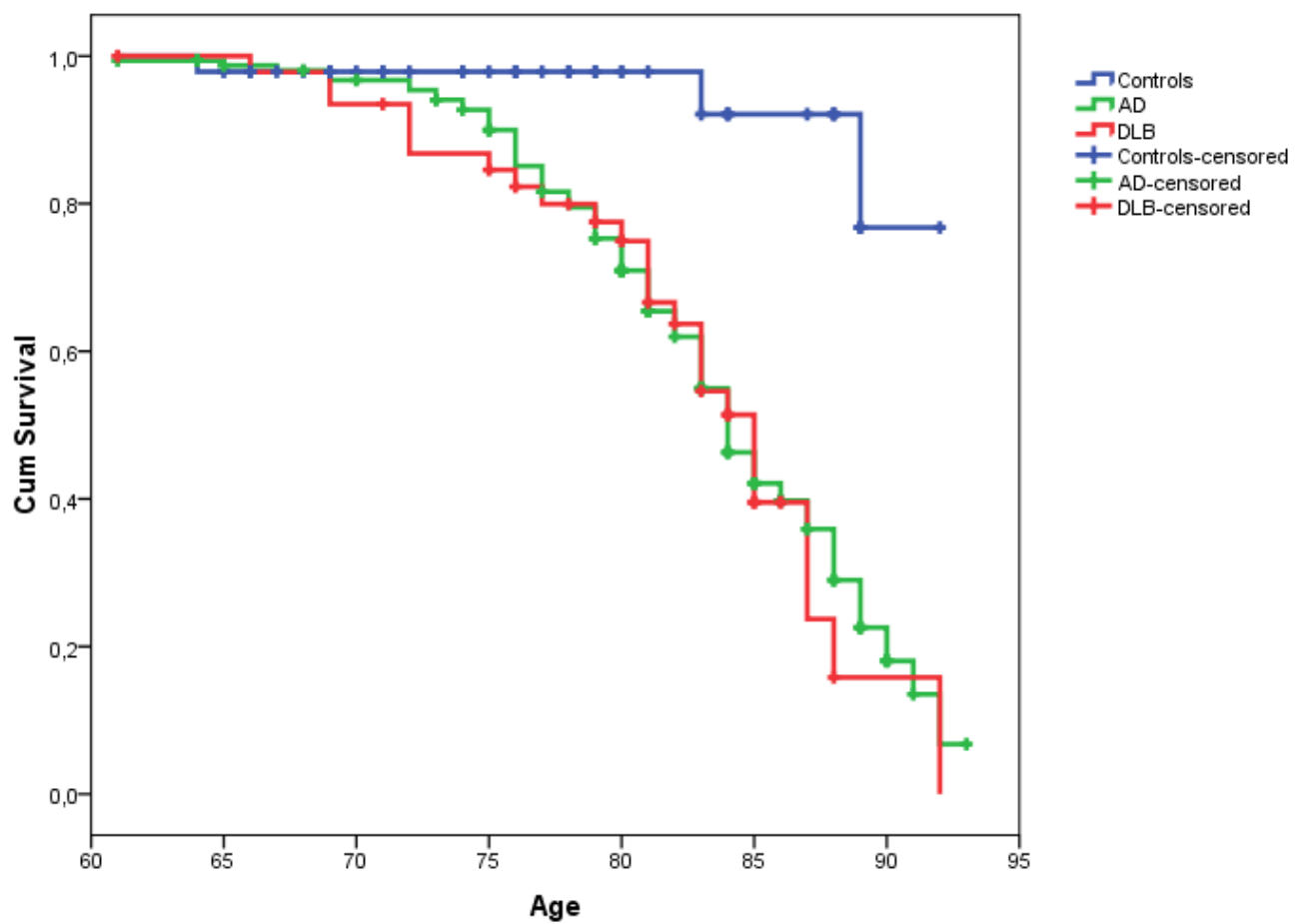


Figure 1. Kaplan Meier Survival curves comparing mortality for DLB and AD. There was no difference in age at death (X^2 0.012, $p=0.92$. Mean age at death was 80 (66-92) yrs in the DLB group and 81 years (61-92) in the AD group. Controls vs other $p<0.001$.

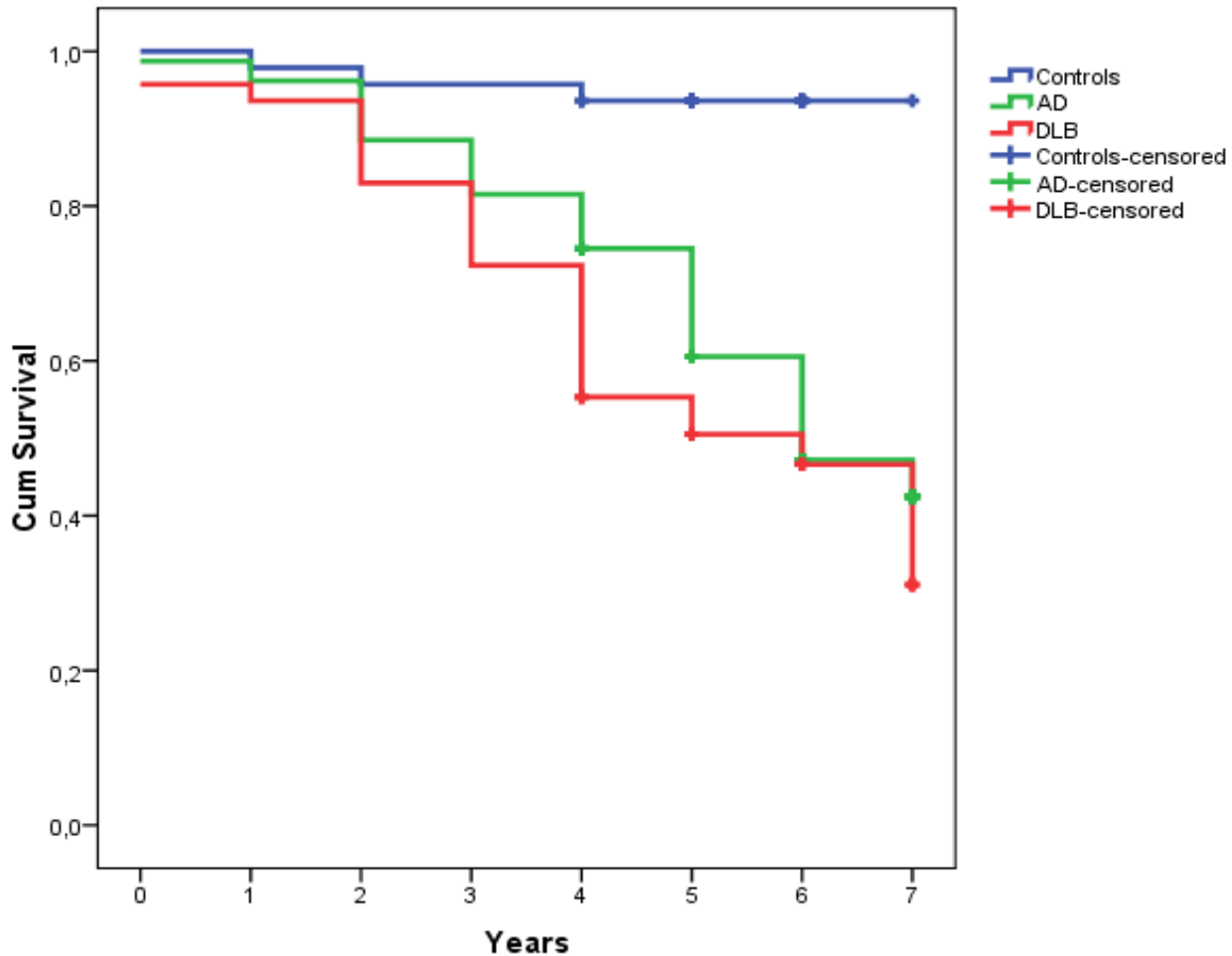


Figure 2. Kaplan-Meier survival curves comparing the survival among DLB and AD patients as well as healthy controls, with a reference point from the first contact with the specialist clinic. Mean survival was 7.02 (6.28-7.76) yrs in the AD group compared to 5.59 (4.71-6.48) yrs in the DLB group ($X^2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