Aß42 and T-tau levels in cerebrospinal fluid associate with survival in an 85-year old population-based cohort followed until death.

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Running head: CSF Aß42 and Tau levels are associated with mortality in octogenarians.

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1. Abstract

Background: Dementia of Alzheimer's type (AD) is related to decreased survival. It is not clear whether also biological markers of AD are related to mortality. Low levels of amyloid beta-42 (Aβ42) and high levels of total tau (T-tau) in cerebrospinal fluid (CSF) are established biomarkers for AD. **Objective:** Our aim was to investigate if levels of Aβ42 and T-tau are associated with survival among octogenarians independent of dementia status. **Methods:** Sixty-five 85-year-olds underwent lumbar puncture and were followed with repeated neuropsychiatric examinations until death. **Results:** Lower CSF Aβ42 (p=0.010) and higher CSF T-tau (p=0.005) at age 85 was associated with lower survival independent of dementia status at baseline and follow-up. Low CSF-Aβ42 and high CSF-T-tau also related to baseline dementia at age 85 years, and lower CSF Aβ42 with increased dementia incidence during the first three years of follow-up. **Conclusions:** Biological markers of AD are associated with mortality in octogenarians. The reason for this needs further study. Our findings highlight the importance to consider competing risk of death when evaluating biological markers of AD in the very old.

2. Introduction

Alzheimer's disease (AD) is the most common form of dementia. The prevalence of AD increases with age, most cases occurring after age 80 years. Dementia disorders, such as AD, are major causes of death among older people (1-4). We previously reported that dementia accounts for 30.7% of deaths in men and 49.7% of deaths in women among 85-year-olds (1). The explanation for the increased mortality in dementia is not clear. One reason may be that pathological processes in dementia and AD might affect brain control systems, which regulate e.g. cardiac function, blood pressure, electrolytes, appetite, and energy balance (5, 6). These systems may be affected early in the disease process, as it was recently reported that cerebral atrophy in older persons without dementia is related to increased mortality (7). Lower levels of amyloid beta (Aβ) and higher levels of total tau (T-tau) in cerebrospinal fluid (CSF) are even earlier biomarkers for AD changes in these markers are supposed to occur before cerebral atrophy (8). It is suggested that low CSF Aβ42 is the first manifestation of AD, occurring decades before neurodegeneration and clinical symptoms, while increasing CSF T-tau levels occur later, but still before clinical manifestations (9). We have previously reported that CSF Aβ42 is reduced before onset of sporadic dementia in 85-year olds during a three-year follow-up (10). In a younger sample (mean baseline age 72 years), low levels of CSF Aβ42 predicted development of AD nine years later (11).

Two clinical studies in patients with manifest AD showed that higher CSF T-tau were associated with increased mortality during follow-up (12, 13). The impact of early biological markers of AD on mortality among older adults without dementia is unclear. However, in a longitudinal study, participants with preclinical AD had an increased risk of death (14). To our knowledge, no population study has examined CSF Aβ42 and CSF T-tau in relation to mortality among octogenarians with or without dementia with follow-up until death of all individuals. The aim of this study was twofold. First, we aimed to study how CSF levels of Aβ42 and T-tau affected survival in 85-year-olds followed until death. Second, we aimed to examine how levels of CSF Aβ42 and CSF T-tau were related to risk of dementia during 15 years follow-up.

3. Materials and Methods

Study population

A representative sample of 85-year-olds was invited to take part in a health survey. Persons invited were registered as inhabitants in Gothenburg according to the Swedish Population Register, which covers names and addresses of all people living in Sweden. All samples were systematically obtained, based on birth dates. The study included persons living in private households and in institutions. A neuropsychiatric examination was performed on a systematic sample of 494 individuals (response rate 63%), as described previously (15). The first 165 participants were invited to undergo lumbar puncture (LP). Sixty-nine (31 with dementia and 38 without dementia) accepted. Of these, four individuals were excluded due to technical reasons or haemorrhagic spinal taps (>500 erythrocytes/µL), leaving 65 individuals (29 with dementia and 36 without; 43 women, 22 men) for the present study. Among the 29 with dementia at age 85, AD was diagnosed in 13 individuals (nine women, four men), vascular dementia (VaD) in 14 individuals (twelve women, two men) and other types of dementia in two individuals (one woman, one man). All had onset of dementia after age 65 years.

The cohort who underwent LP has been described previously (16). In short, among individuals without dementia, participants who underwent LP were more often married, less often widowed, more often carriers of the apolipoprotein E (*APOE*) ε4 allele and had a higher mean Mini Mental State Examination (MMSE) score than those who did not participate. Among individuals with dementia, participants who underwent LP were more often living in institutions, had more often cancer and had a lower mean MMSE score than those who did not participate. Participants and non-participants were similar regarding sex, frequency of psychiatric disorders, cardiovascular disorders, cerebrovascular disorders, diabetes mellitus, peptic ulcer, mean systolic and diastolic blood pressure and 3-year mortality rate.

Participants were followed until death. Re-examinations were performed at ages 88 (N=37), 90 (N=22), 92 (N=14), 95 (N=7), 97 (N=3), 99 (N=1) and 100 years (N=1). Most losses were due to death. Participants lost to follow-up were traced for dementia by information from the Swedish Hospital Discharge Register. Information on date of death was obtained from the Swedish National Board of Health and Welfare.

The study was approved by the Ethics Committee at the University of Gothenburg. All individuals (or their closest relatives) gave informed consent to participate in the study.

General examinations

The clinical examinations were conducted at an outpatient department or in the participant`s home and included comprehensive social, functional, physical, neuropsychiatric and neuropsychological examinations, as well as close informant interviews (15).

The diagnosis of dementia at each examination was based on the Diagnostic and Statistical Manual of Mental disorders, Third Edition, Revised (DSM-III-R) criteria (17), using information from neuropsychiatric examinations and close informant interviews, as described previously (15). Dementia diagnoses for individuals lost to follow-up were based on the Swedish Hospital Discharge Registry according to the International Classification of Diseases (ICD) Ninth (18) and Tenth (19) Edition and, medical records. Mini-Mental State Examination (MMSE) measured global cognitive function (20). Major depression was diagnosed according to DSM-III-R criteria (17). Medical disorders were diagnosed from physical and laboratory examinations, the Swedish Hospital Discharge Register, self-reports and key informant interviews. Systolic and diastolic blood pressure was registered to the nearest 5 mmHg, and measured in the right arm in the seated position after 5 minutes rest. Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, or taking anti-hypertensives. Myocardial infarction was diagnosed from physical examinations, electrocardiograms or documented history of myocardial infarction. Stroke diagnoses were based on self-reports, key informants and the Swedish Hospital Discharge Register. Information on cancer was from the Swedish Cancer Registry. Diabetes mellitus was defined as fasting blood glucose of $\geq$7.0 mmol/L or being on anti-diabetics. Information about smoking (never versus ever) and education (mandatory 6 years versus more than that) was based on self-reports.

Mortality data

Survival was determined from the time of examination to date of death. Date and cause of death was obtained from the Swedish National Board of Health and Welfare, which is known to be complete regarding mortality on all individuals living in Sweden and Swedish citizens living abroad.

CSF sampling and analysis

Lumbar punctures were performed in the morning, under standardized conditions, through the L3/L4 or L4/L5 interspace. The first 12 ml of CSF was collected in polypropylene tubes and gently mixed to avoid gradient effects. Aβ40, Aβ42 and t-tau were determined by sandwich enzyme-linked immunosorbent assay (21, 22).

Statistical analyses

Differences between groups were tested with t-test, Chi-Square and ANOVA. Time to death was defined as the time from the date of the baseline examination to the date of death. Time to death in relation to levels of CSF Aβ40, CSF Aβ42, CSF T-tau and biomarkers-ratio was examined with Spearman´s rho, and Pearson correlation. Linear mixed-effects models were used to analyse the interaction with dementia. To graphically present the relationship between biological markers and years of survival Kaplan-Meier curves were used. $p<0.05$ (two-tailed) was considered statistically significant.

4. Results

Baseline characteristics

Individuals with or without dementia at baseline were similar regarding *APOE ε4*-allele possession, educational level, prevalence of ischemic heart disease, cancer, diabetes and major depressive syndrome (Table 1).

Those with dementia had lower MMSE score, lower blood pressure, lower CSF Aβ40 and CSF Aβ42, higher T-tau, lower age of death, and higher prevalence of institutionalization and stroke.

All participants were followed until death. Causes of death were cardiovascular in 60.0% (N=39), cancer in 17.0% (N=11), pneumonia in 12.3% (N=8), cerebral events in 9.2% (N=6) and aortic rupture in one case (1.5%).

CSF-biomarkers in relation to survival

Lower levels of CSF Aβ42 and higher levels of CSF T-tau at age 85 years were related to shorter survival (Spearman's rho CSF Aβ42; 0.316; p=0.010 and CSF T-tau; -0.350; p=0.005). Every mean decrease of 25.3 pg/ml in CSF Aβ42 or increase of 6.54 pg/ml in T-tau was associated with one less year of survival (figure 1 and 2). To explore if dementia affected the relation between AD markers (CSF Aβ42 and CSF T-tau) and survival, a linear mixed model was used. There was no significant difference in the slope between participants with dementia at baseline, participants with dementia development and participants without dementia development during follow-up (CSF Aβ42; p=0.11 and CSF T-tau; p=0.31). Furthermore, results did not change after excluding one person who died without dementia at age 100.3 years, and who had a very high CSF Aβ42 level (1453 pg/ml).

We also examined the CSF Aβ42/T-tau-ratio, categorized into tertiles (high, intermediate, low). Participants in the highest tertile survived longer compared to participants in the intermediate- and low ratio groups (figure 3).

CSF Aβ42/40-ratio (p=0.091), and CSF Aβ40 (p=0.132) alone did not significantly relate to mortality.

CSF biomarkers in relation to dementia development

Table 2 shows levels of CSF Aβ42 and CSF T-tau in relation to baseline dementia and dementia development during follow-up. Among those without dementia at baseline (N=36), 13 developed dementia during follow-up (seven between age 85 and 88 years, four between age 88 and 90, one between 91 and 95 years and one after the age of 95 years). Those who developed dementia (N=13)

after age 85 years did not differ significantly in CSF Aβ42 levels from those who did not develop dementia (N=23; 498.2 pg/ml versus 669.8 pg/ml; *p*=0.12). CSF T-tau levels did not differ significantly between those who developed dementia after age 85 years and those who did not (187.8 pg/ml versus 161.0 pg/ml; *p*=0.31). When stratifying between development of dementia during the first three years (N=7), and later development of dementia (N=6), those who developed dementia during the first three years had lower levels of CSF Aβ42 than those who did not develop dementia (415.6 pg/mL versus 669.8 pg/ml; *p*=0.03). There were no differences between the groups in CSF T-tau levels (190.6 pg/ml versus 161.0 pg/ml; *p*=0.45). There were no differences in baseline CSF Aβ42 and CSF T-tau between those who developed dementia after 88 years of age and those who did not (*p*=0.64 and *p*=0.48 respectively).

5. Discussion

Lower levels of CSF Aβ42 and higher levels of CSF T-tau at age 85 related to mortality independent of dementia status at baseline and follow-up in a population followed until death. In addition, lower levels of CSF Aβ42 only related to dementia at baseline and during short-term follow-up (3 years), while CSF T-tau only related to baseline dementia.

The relation between CSF markers of AD and mortality has previously only been studied in patients with AD from clinical samples in younger age groups with mean ages of 68.6 (12) and 75.8 years (13). In these studies, higher levels of CSF T-tau related to shorter survival. CSF T-tau is less specific for AD than CSF Aβ42, reflects multiple degenerative processes, such as advancing age (23) and Lewy Body Disease (24), and relates to rapid cognitive decline and mortality in severe dementia (25). Our study shows that both CSF Aβ42 and CSF T-tau are related to mortality among very old individuals independent of dementia status. For every 25.3 pg/ml decrease in CSF Aβ42 or every 6.54 pg/ml increase in CSF T-tau at age 85 years, life expectancy decreased with one year. Low CSF Aβ42 and high CSF T-tau are markers for incipient and manifest AD (26-28). It is well known that manifest clinical AD is strongly related to mortality (1, 3), although the reason for this is not entirely clear. Some functions in the body of importance for survival are regulated by the brain, such as fluid control, electrolyte homeostasis, blood pressure, temperature, energy balance and cardiac function (5, 6). AD neuropathology might interfere with these neural functions very early in the disease process, long before clinical manifestations of the disease. Support for this possibility is that blood pressure (29-31), and BMI (32) decline several years before dementia onset in individuals who later develop AD. Among persons without dementia, blood pressure is lower in individuals with brain atrophy on computerized tomography (33), and brain atrophy is related to increased mortality in persons without dementia (7). Our new findings extend this latter finding to CSF markers of AD.

CSF Aβ42 only related to dementia in the short-term (3 years), as reported previously (10). Using follow-up data of more than 15 years, we now report that CSF Aβ42 did not predict dementia beyond the first three years of follow-up. This is shorter than the 25 years suggested by Jack *et al.*(9). One reason could be competing risk of death in very old age. Very old individuals with preclinical AD may to a larger extent than in younger age groups die before they manifest clinical symptoms of dementia. It is thus important to consider competing risk of death when evaluating biological markers of preclinical AD in relation to the development of dementia among the very old.

The phase between onset of early Alzheimer pathology and onset of symptoms may also be shorter among very old people. Aβ production gradually shift from soluble to insoluble Aβ-peptides with

increasing age (34), which may shorten the time from occurrence of pathological amyloid metabolism to onset of clinical symptoms. A third reason could be that Aβ is a less important cause of dementia in the oldest-old. In an autopsy study, brain amyloid load of very old people did not have the same association with dementia as in younger individuals (35). With increasing age, people without dementia have increasing amounts of Aβ in the brain (36), and decreasing levels of CSF Aβ42 (27, 35), diminishing the difference between normal old people and individuals with incipient dementia.

Strengths of this study include the population-based sample, the comprehensive examinations performed by psychiatrists, and the long follow-up until death. There are also limitations and methodological issues. First, measures of CSF were performed at one time point only. Longitudinal studies are needed to examine whether changes in CSF markers over time are related to survival. Second, although the sample is drawn from the general population, only 41.8% consented to an LP, which nevertheless is a high response rate for this type of examination. The sample is therefore not representative of the general population at this age. Third, the sample size was too small to examine subtypes of dementia, e.g. Alzheimer's disease and vascular dementia. The small sample size also resulted in low statistical power. Fourth, we did not measure levels of phosphorylated Tau (P-tau). However, several studies report strong correlations between levels of CSF T-tau and CSF P-tau in patients with Alzheimer's disease and in controls (37, 38).

CSF Aβ42 and CSF T-tau associated with mortality independent of dementia status at baseline and follow-up in octogenarians. Our findings highlight the importance to consider competing risk of death when evaluating biological markers of AD in the very old.

6. Statements

6.1. Acknowledgement

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6.2. Statement of Ethics

The study was approved by the Ethics Committee at the University of Gothenburg. All individuals (or their closest relatives) gave informed consent to participate in the study.

6.3. Disclosure Statement

Authors report no disclosures relevant to the manuscript.

Full disclosures:

Mats Ribbe, Silke Kern and associate Professor Svante Östling: Reports no actual or potential conflicts of interest associated with this research.

Anne Börjesson-Hanson: Speakers Bureaus for Jansen Pharmaceuticals, Pfizer, Novartis, Lundbeck. Consultant for Sanofiaventis, Janssen Pharmaceuticals. Investigator in clinical trials for Novartis, Pfizer, ACImmune, Sanofiaventis, Lilly.

Henrik Zetterberg: Co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. Dr. Zetterberg also served at scientific advisory boards for Roche Diagnostics, Wave, Samumed and CogRx.

Kaj Blennow: Served as a consultant or at advisory boards for IBL Internation, Roche Diagnostics, Eli Lilly, Fujirebio Europe, and Novartis, and is a co-founder of Brain Biomarker Solution in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg.

Ingmar Skoog: Speakers Bureaus for Takeda. Consultant for Takeda.

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6.5. Author Contributions

Dr. Mats Ribbe – writing, study concept, design, analysis and interpretation.

Dr. Silke Kern, Dr. Anne Börjesson-Hanson, associate Professor Svante Östling, Professor Henrik Zetterberg, Professor Kaj Blennow and Professor Ingmar Skoog – critical revision of the manuscript for important intellectual content.

Professor Henrik Zetterberg and Professor Kaj Blennow - acquisition of data.

Professor Ingmar Skoog – acquisition of data and study supervision.

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