Original Research Article

Cerebrospinal Fluid Alzheimer Markers in Depressed Elderly Subjects with and without Alzheimer's Disease

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Key Words

Abstract

Background: The aim of this study was to explore the relationship between cerebrospinal fluid Alzheimer's disease (AD) markers and depression in elderly people. **Method:** We included subjects with AD as well as persons with subjective cognitive impairment and normal cognition. Depression was assessed with the Cornell Scale for Depression in Dementia, and a cut-off score of >6 was used to define depression. Cerebrospinal fluid was analyzed using commercially available assays for β-amyloid 1–42, total tau, and phosphorylated tau 181. **Results:** A total of 183 participants (66.7% female) were included (92 with AD and 91 with subjective cognitive impairment), with a mean age (±SD) of 67.6 ± 7.4 years, a Mini-Mental State Examination score of 26.0 ± 4.0, and a median Cornell Scale for Depression in Dementia score of 5 (range 0–19). Depression scores were not associated with higher phosphorylated tau 181 and total tau or reduced β-amyloid 1–42 in AD or non-demented subjects. **Conclusions:** These results suggest that AD pathology does not contribute to depression, indicating that other factors may be more important. Further studies of the aetiology of depression in elderly people with and without AD are warranted.

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Introduction

Depression is one of the most common health problems in the elderly, and non-major depression syndromes such as minor depression occur in 4–13%, dysthymia in 2%, and clinically significant symptoms of depression in 8–16% of patients, with major implications for quality of life, physical health, independent functioning, and costs [1].

There is a complex relationship between late-onset depression and cognitive impairment. Executive dysfunction is common in depressed elderly subjects, and depression is more prevalent among patients with Alzheimer's disease (AD) and other dementias than in non-demented elderly subjects; furthermore, there is emerging evidence that mid-life depression is a risk factor for AD decades later [2]. Finally, in many studies, depression has been found to be a prodromal syndrome of early AD [2, 3].

The aetiology of late-life depression is complex and only partially understood. Psychosocial, genetic as well as brain changes probably contribute, and potential mechanisms include toxic stress, with the activation of the hypothalamic-pituitary-adrenal axis, hypercortisolaemia, inflammation, and hippocampus atrophy, monoaminergic changes, and cerebrovascular disease [4].

There is evidence that AD pathology is a contributing factor to the development of depression in elderly subjects with and without AD, possibly associated with decreased serotonin, which is likely to be related to depression in AD [5] since serotonin influences the shifting in the processing of amyloid precursor protein towards amyloidogenic pathways [6, 7]. MRI studies have reported more hippocampal atrophy in elderly patients with depression [8]. Moreover, clinicopathological studies have reported more AD-type changes in AD patients with a previous history of depression compared to those without a history of depression [9]. The same authors also reported increased tangle pathology in AD patients with comorbid depression compared to those without depression [10]. Recent studies using amyloid PET imaging have, to some extent, been consistent with these autopsy findings [11, 12]. However, autopsy studies of late-life depression without dementia have failed to find significantly more AD pathology in depressed compared to non-depressed elderly persons [13]. Thus, the association between depression and AD pathology is not clear.

In cerebrospinal fluid (CSF), a characteristic pattern of metabolites of amyloid plaques [low β-amyloid 1–42 (Aβ42)] and tau [increased total tau (t-tau) and phosphorylated tau 181 (p-tau)] has been consistently shown in patients with AD [14]. However, the few studies that have explored whether AD-type changes in CSF are associated with depression have not found associations with more severe depression in mild AD [15] or elderly non-demented women [16].

Taken together, there is inconsistent evidence regarding the role of AD-type pathological changes in depression. Understanding the aetiology of depression in the elderly is important for diagnostic purposes as well as background information for the development of novel pharmacological strategies. We administered the Cornell Scale for Depression in Dementia (CSDD) [17] to 183 elderly subjects who had been referred to a memory clinic and diagnosed as having AD or subjective cognitive impairment [SCI; i.e. normal cognitive functioning without a diagnosis of dementia or mild cognitive impairment (MCI)], and measured CSF levels of Aβ42, t-tau, and p-tau. The aim of this study was to test the hypothesis that AD-type changes, i.e. reduced Aβ42 and increased t-tau and p-tau, are associated with depression in elderly subjects with and without AD.

Methods

Subjects

The base population for the study consisted of 1,154 referrals to the Memory Clinic at Karolinska University Hospital in Huddinge, Sweden, between 2007 and 2009. Inclusion criteria for the current project were: (a) age 60 years or older, (b) CSDD administered, (c) lumbar puncture, and (d) diagnosis of AD or normal cognition (i.e. SCI). Excluded were patients with: (a) physical disease significantly affecting cognitive performance, (b) life-threatening disease with expected reduced survival time, (c) MCI, and (d) dementia due to diseases other than AD.

All subjects signed informed consent prior to lumbar puncture, and the study was approved by the Ethical Committee at Karolinska University Hospital in Huddinge (43/03).

Assessment

Participants underwent a medical examination and assessment of depression using the combined patient- and informant-based CSDD, which has excellent psychometric properties in both demented and non-demented people [17, 18]. For this study, a cut-off score of >6 was used to define depressed and non-depressed subjects, based on a validation study performed in Denmark [19]. The CSDD was completed by a licensed geriatrician or psychiatrist, or a research nurse.

For the dementia diagnosis, a standardized informant-based scale of the patients' history of cognitive decline (Informant Questionnaire on Cognitive Decline in the Elderly) [20] was administered, and dementia was staged using Global Deterioration Scales after a clinical medical examination including cognitive screening with the Mini-Mental State Examination (MMSE) [21]. To aid in the diagnostic process, the majority of subjects completed a neuropsychological examination: tests of verbal abilities (similarities and information), visuospatial abilities (block design and Rey-Osterrieth copying), working memory (digit span and Corsi span), episodic memory (learning and retention after 30 min, Rey Auditory Learning Test), and executive functioning (Digit Symbol and Trail Making Test). Patients were diagnosed as having AD using ICD 10 criteria after a consensus meeting with clinicians and neuropsychologists, taking into account all available information.

In addition to the clinical assessment, brain imaging MRI or CT according to a dementia protocol, routine blood tests, and CSF analyses were performed; furthermore, EEG was performed in a large subgroup.

CSF Measurement

CSF was obtained by lumbar puncture between the L3/L4 or L4/L5 intervertebral space using a 25-gauge needle and collected in 12-ml polypropylene tubes. Within 2 h, the CSF samples were centrifuged. A small amount of CSF was used for routine analysis, including total cells (leucocytes and erythrocytes), total protein, and glucose. CSF was aliquoted in polypropylene tubes of 0.5 or 1 ml and stored at –80°C until further analysis. CSF $A\beta42$, t-tau, and p-tau were measured by commercially available sandwich ELISAs (Innogenetics, Ghent, Belgium).

Statistics

We divided the subjects into four groups based on the presence or absence of depression in AD and SCI. Group comparisons were made using parametric or non-parametric tests as appropriate. For the descriptive statistics presented in table 1 a χ^2 test and a pre-planned post hoc analysis have been used. The CSF values were compared using simple logistic regression comparing depressed and non-depressed subjects with and without AD in two separate anal-

Table 1. Characteristics of the study sample

	All (n = 183)	SCI			AD		
		not depressed (n = 51)	depressed (n = 41)	p	not depressed (n = 60)	depressed (n = 31)	p
Age, years	67.6 ± 7.4	65.0 ± 5.6	62.7 ± 3.0	0.02	72.0 ± 8.2	70.1 ± 6.6	0.26
Females	122 (66.7)	32 (62.7)	32 (78.0)	0.11	38 (63.3)	20 (64.5)	0.9
Education, years	11.7 ± 3.7	13.4	12.4	0.19	11.0	11.2	0.8
MMSE score	26.0 ± 4.0	28.9 ± 1.4	28.7 ± 1.5	0.5	23.1 ± 3.6	23.2 ± 3.9	0.9
AD duration, years	3.2 ± 2.3	3.0	3.2	0.6	3.0	3.4	0.5
CSDD score	5.0 (0–19)	3 (0–6)	11 (7–19)	<0.0005	2 (0–6)	9 (7–14)	<0.0005
Antidepressant use	61 (33.3)	10 (19.6)	12 (29.3)	0.28	26 (43.3)	13 (41–9)	0.9

Numbers represent mean ± SD, n (%), or median (range).
Between-group comparisons were made using Mann-Whitney or χ^2 tests as appropriate.

Table 2. CSF markers and depression in subjects with and without AD

	SCI			AD		
	not depressed (n = 51)	depressed (n = 41)	p*	not depressed (n = 60)	depressed (n = 30)	p*
p-tau, pg/l	57.3 (31)	50.1 (23)	0.045	85.5 (42)	79.5 (31)	0.256
t-tau, pg/l	302 (157)	237 (145)	0.023	560.5 (496)	439 (240)	0.027
Aβ42, pg/l	883 (372)	896 (298)	0.897	504 (160)	429 (154)	0.157

Numbers represent median (interquartile range).
* p values are based on logistic regressions with depressed/not depressed as outcome.

yses. In addition, Spearman's correlation analyses were performed between the CSDD score and each of the three CSF measures in the total group and in the AD and SCI groups separately. Ordered logistic regression was used to analyze the association between CSF measures and depression scores using the entire CSDD scale. Two models were used, adjusting for age and sex (Model 1) and age, sex, and MMSE score (Model 2).

Results

The sample included 183 patients. The characteristics of the four groups are shown in table 1. Age, MMSE score, and CSDD score, but not gender, differed significantly between the groups. The pre-planned post hoc analyses showed that in AD and SCI, the only significant difference was in the non-demented group, with a lower age in the depressed compared to the non-depressed subjects (table 1).

CSF Analyses

The median values of the three CSF measures in the four groups are shown in table 2 and figures 1–3. As expected, in the AD groups, t-tau and p-tau were higher and Aβ42 low-
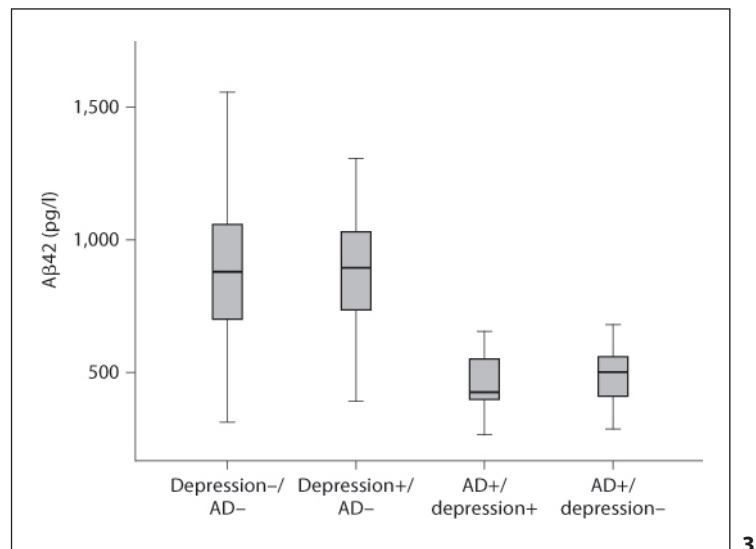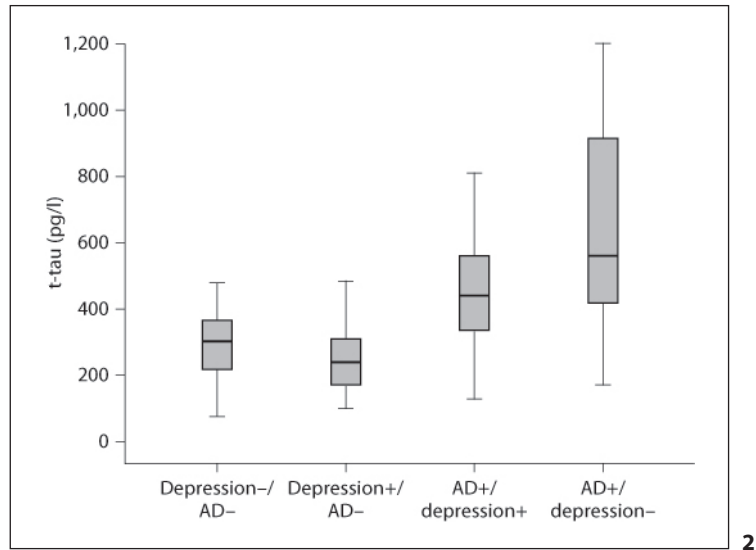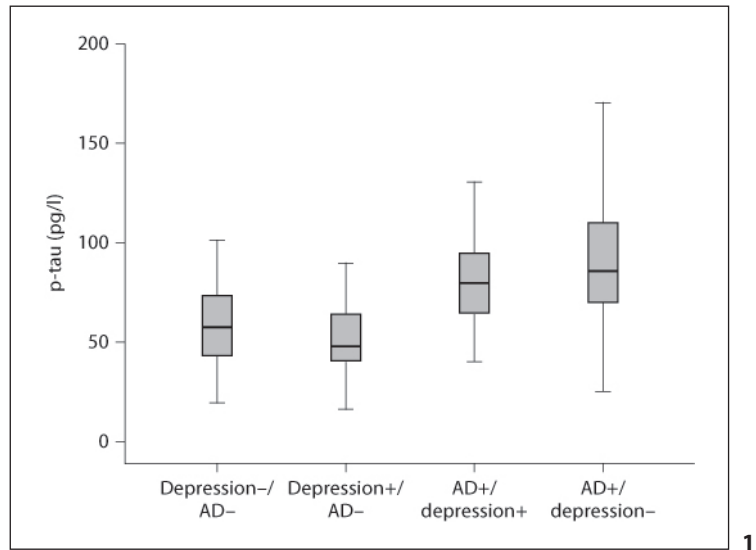
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Fig. 1–3. Box plot of the three CSF markers in depressed and non-depressed patients with and without AD.

Table 3. Associations between CSDD scores and CSF measures

Independent variable:	p-tau/10		t-tau/100		Aβ42/100	
	OR	p value	OR	p value	OR	p value
Model 1	0.92	0.039	0.87	0.005	1.03	0.526
Model 2	0.92	0.071	0.85	0.008	0.98	0.811

Ordered regression analysis. Model 1: adjusting for age and sex. Model 2: adjusting for age, sex, and MMSE score.

er than in the non-AD groups (all p values <0.001). T-tau differed significantly between AD patients with and without depression, with the depressed patients having lower values than the non-depressed AD patients, whereas p-tau and Aβ42 did not differ significantly. In the SCI group, both t-tau and p-tau were significantly lower in the depressed compared to the non-depressed group, whereas Aβ42 did not differ significantly.

The correlation analyses were consistent with the above-mentioned findings. In the total group, bivariate correlations showed a significant negative correlation between the CSDD score and p-tau (Spearman's $\rho = -0.21$, p = 0.004) as well as t-tau ($\rho = -0.25$, p = 0.001), but not with Aβ42 (p = 0.25). In the AD group, there was a trend towards a correlation between the CSDD score and t-tau ($\rho = -0.21$, p = 0.05), whereas no significant correlations between the CSDD score and CSF measures were found in the SCI group. The ordered regression analyses, adjusting for age and sex (Model 1) and for age, sex, and MMSE score (Model 2), showed similar findings (table 3). Interpretations from Model 2 show that for each 10-pg/l increase in p-tau, the odds for having more depressive symptoms decreases by 8%, and for each 100-pg/l increase in t-tau, the odds for having more depressive symptoms decreases by 15% (p = 0.008).

Discussion

In this study, analysis of the three different CSF measures Aβ42, t-tau, and p-tau did not support the hypothesis that more severe AD pathologies such as amyloid plaques or tau pathologies are associated with more severe depression. In contrast, depressed patients tended to have lower p-tau levels and, in particular, lower t-tau levels than those without depression, indicating less tau pathology and neurodegeneration. These findings were found both in patients with a clinical diagnosis of AD and in subjects without dementia, using either continuous data or categories based on cut-off scores for the CSDD and reference norms for CSF values, and also after adjusting for potential confounders.

Few previous studies of CSF AD markers in patients with depression have been reported. One study reported on a population-based sample of 81 elderly women, 11 with major depression [16]. They were without dementia up to 10 years after lumbar puncture. Aβ42 concentrations were higher among those with major depression compared to non-depressed women, whereas t-tau levels did not differ between the groups. p-tau was not measured in that study. In another study of patients with mild AD, apathy was associated with higher p-tau levels, but no associations between CSF Aβ42, t-tau, or p-tau levels and the Neuropsychiatric Inventory depression item were found [15]. Thus, the current findings are consistent

with previous CSF studies suggesting that AD pathology does not contribute to depression in elderly subjects with or without AD.

One previous clinicopathologic study reported more severe tau pathology in AD patients with comorbid depression compared to AD patients without depression [10]. Thus, it is possible that depression later in the disease course is more closely related to the underlying pathology, whereas other factors are more important in the earlier stages. However, the effect of depression on neurofibrillary tangle occurrence was rather small, and the interval between depression diagnosis at study inclusion and death was nearly 10 years [10]. In another autopsy study, 10 patients with late-onset major depression were followed prospectively to death [22]. AD was the most frequent pathology, in particular among the 7 patients who developed dementia, but Lewy body pathology and stroke were also common. Although the study shows that AD and other pathologies probably contribute to dementia in patients with late-onset major depression, whether these pathologies are related to the symptoms of depression was not reported. Finally, in a recent population-based clinicopathologic study of subjects who did not develop dementia during life, no association between AD-type changes and depression could be observed [13].

Amyloid imaging provides another means of exploring the association between depression and AD pathology. In one such study, patients with remitted depression underwent detailed neuropsychological assessment and Pittsburgh compound B (PiB) imaging [11]. Two subjects with normal cognition showed PiB retention in the normal range. In 3 of 6 patients with MCI, the PiB retention fell in the range of AD. However, associations between depression and PiB binding were not reported, and thus it is unclear whether the increased binding was related to cognitive impairment as a prodrome of AD or to the remitted depression [11]. In another PET study of non-demented subjects, a marker of amyloid plaques and neurofibrillary tangles was found to correlate with a self-report measure of depressive symptoms in both cognitively normal and MCI subjects [12].

Methodological limitations of the current study include the cross-sectional design; therefore, assumptions regarding causality cannot be made. The study sample was selected from referrals to a university memory clinic, and thus generalizations to the population are not possible. In particular, the non-AD group consisted of SCI subjects, with an increased proportion having an AD-type CSF profile [23], and hence extrapolation to non-demented depressed elderly persons is difficult. The diagnosis of AD was clinical, and thus there is a possibility of misdiagnosis. However, the lack of association between AD markers and depression was independent of AD diagnosis; therefore, inaccurate diagnosis is an unlikely explanation.

Conclusion

Our CSF analyses did not support the hypothesis that depression is associated with more AD pathology, neither in subjects with AD nor in subjects without AD, suggesting that other factors are more important contributors to depression in the elderly. Future studies should explore the role of potential aetiological factors for depression in the elderly, such as neuroinflammation and cerebrovascular disease as well as psychosocial factors.

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Disclosure Statement

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