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Short Title: State-dependent alterations in CSF Abeta42

Authors: Nunzio Pomara, M.D.,[1,2,3] Davide Bruno, Ph.D.,[4] Ricardo S. Osorio, M.D.,[6] Chelsea Reichert, M.S.,[1,5] Jay Nierenberg, M.D., Ph.D.,[1,2] Antero S. Sarreal, M.D.,[1] Raymundo T. Hernando, M.D.,[1] Charles R. Marmar, M.D.,[2,3] Thomas Wisniewski, M.D.,[2,7] Henrik Zetterberg, M.D., Ph.D., [8,9,10] and Kaj Blennow, M.D., Ph.D. [8,9]

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Correspondence:
Nunzio Pomara, MD
Nathan S. Kline Institute
140 Old Orangeburg Rd., Orangeburg, NY 10962
Pomara@nki.rfmh.org

Statement of Conflicts: Dr. Pomara has a potential conflict of interest related to this work. Dr. Pomara has a joint patent application with the NYU Langone Medical Center related to some of the material described in this report.

Affiliations:
1. Nathan S. Kline Institute, Geriatric Psychiatry Division, Orangeburg, NY, USA
2. Department of Psychiatry, NYU Langone Medical Center, New York, NY, USA
3. Steve and Alexandra Cohen Veterans Center, Department of Psychiatry, NYU Langone Medical Center, New York, NY, USA
4. Liverpool John Moores University, Department of Psychology, Liverpool, UK
5. Program in Behavioral and Cognitive Neuroscience, The Graduate Center of the City University of New York, New York City, NY
6. Center for Brain Health, NYU Langone Medical Center, New York, NY, USA
7. Departments of Neurology, Pathology and Psychiatry, NYU Langone Medical Center, New York, NY, USA
8. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
9. Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden.
10. Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK

Abstract

Depression has been linked to Alzheimer's disease (AD) as either an increased risk factor for its development or as a prodromal symptom. The neurobiological basis for such association, however, remains poorly understood. Numerous studies have examined whether changes in amyloid beta (Aβ) metabolism, which are implicated in AD pathogenesis, are also found in depression. In this paper, we investigated the relationship between depressive symptoms and cerebrospinal fluid (CSF) Aβ indices, in healthy cognitively normal elderly with late-life major depression (LLMD) and controls, by using a longitudinal approach, which is a novel contribution to the literature. Significantly lower levels of CSF Aβ42 were observed in the LLMD group at baseline and were associated with more severe depressive symptoms. During longitudinal follow up, the depressed group remained cognitively unchanged, but was significantly less depressed than at baseline. A greater improvement in depressive symptoms was associated with increases in CSF Aβ42 levels in both groups. Increases in CSF Aβ42 and Aβ40 were also associated with increased CSF total tau levels. Our results suggest that LLMD may be associated with state-dependent effects of CSF Aβ42 levels. Future studies should determine if the association reflects state-dependent changes in neuronal activity and/or brain amyloid burden in depression.

Introduction

Several lines of evidence from epidemiological, case-control and longitudinal studies provide support for an association between depression or depressive symptoms, and an increased risk for dementia and Alzheimer's disease (AD), or for depression as a prodromal state of[1,2]. This relationship has been described not only for late onset depression, but also for depression starting earlier in life [3]. In a longitudinal study conducted by Wilson and colleagues [4] in cognitively normal elderly, a higher number of depressive symptoms at baseline were associated with a 19% increased risk of AD, on average, during a 7-year longitudinal follow-up period. Yet, puzzlingly there have also been results that do not support such an association [5,6], thereby highlighting the possible etiological heterogeneity of depression with respect to its association with AD, and the need for further study.

Although the neurobiological mechanisms underlying the association between AD and depression are not yet clear, it is possible that there may be a common disturbance in amyloid-β (Aβ) metabolism [7] in both conditions. Studies conducted by our group and others [8,9] have highlighted abnormalities in Aβ40 or Aβ42 levels or their ratios, in plasma or serum, in individuals with depression. Analogously, a relatively smaller number of investigations have also reported changes in cerebrospinal fluid (CSF) Aβ concentration or brain amyloid burden using PET imaging in individuals with depression or depressive symptoms, albeit with conflicting results [e.g. 10-13,9].

Methodological differences, however, may be at the root of these differences in results, including heterogeneity in the studied populations, such as inclusion of individuals with mild cognitive impairment (MCI) in the cohorts [14-16,2]. A separate issue pertains to the use of different approaches for detecting depression, with most relying on patients' self-ratings, which may lack diagnostic specificity, and only a few studies employing structured interviews based on DSM diagnostic criteria. Finally, and critically, standardized pre-analytical and laboratory procedures for quantifying Aβ across centers were not

employed (Abbasowa & Heegard, 2014[14]. All of the existing studies have been limited to cross

sectional comparisons based on a single Aβ determination; thus, it is not known if these abnormalities

persist over time.

To address these limitations, we conducted a longitudinal prospective study in depressed elderly

and age-matched controls, all of whom were cognitively normal at baseline. All subjects were diagnosed

using a structured interview as per DSM-4 criteria, and all samples were analyzed at the same lab using

the same immunoassay method with demonstrated sensitivity and reliability for Aβ determination (see

Methods). Our goal was to determine first whether LLMD and time (baseline to follow-up) had an effect

on the Aβ levels; and second to determine whether any time-related change in Aβ was associated with

changes in the severity of depressive symptoms. Additionally, analogous analyses were also carried out

on CSF total-tau and phosphorylated tau (p-tau) to gauge the possible emergence of neurodegeneration

and tau pathology, respectively, in the course of the longitudinal study.

Methods

This study was conducted in accordance with the Declaration of Helsinki. Approval for this study was received

from the Nathan S. Kline Institute/Rockland Psychiatry Center Institutional Review Board (NKI/RPC IRB)

and the NYU Langone Medical Center Institutional Review Board. All participants provided written informed

consent before their participation. Ninety-one participants, aged 60 years and older, with an MMSE score of at

least 28, completed a 3-year longitudinal study. At baseline, 51 of these individuals agreed to an optional

lumbar puncture (LP). Three of these individuals were excluded for MRI findings, and an additional individual

was excluded for an MMSE score below 28 (*Table 1*).CSF was obtained from 47 individuals (see *Table 2*),

with late-life major depression group (LLMD; N=28) and age- and gender-matched control group (N=19), and

again at the 3-year follow-up visit (LLMD group, N=19; control group, N=17). The analyses are limited to the

follow-up group. CSF levels of Aβ42, Aβ40, total-tau (t-Tau) and p-tau were measured using previously

established methods by board-certified laboratory technicians who were blinded to clinical data[9]. Participants

underwent a comprehensive neuropsychological evaluation as well as a clinical evaluation that included the

Hamilton Depression scale (HAM-D), at baseline and at follow-up. No participants were considered to be

suffering from Alzheimer's disease or other neurodegenerative conditions including Lewy Body Disease,

as determined both via interview by a geriatric psychiatrist, and by examination of neuropsychological indices,

either at baseline or follow-up. Pearson's correlations were computed between Aβ indices and HAM-D scores.

All statistical analysis was performed using SPSS statistical software package, version 22.0 for Windows

(SPSS, Inc., Chicago).

Results

To evaluate if clinical group (LLMD and control) and time had an effect on the Aβ levels, we

conducted two 2x2 repeated measures ANOVAs (GROUP, between-subjects; and TIME, within-subjects)

on Aβ40 and Aβ42. A main effect of time was detected on Aβ40, p<.001, showing a decline in levels

between baseline (5882.94, SD=2631.67) and follow-up (3866.17, SD=1264.98); no main effect of

LLMD (p=.202) or an interaction were observed (p=.146). When we examined Aβ42, in contrast, we

found a significant interaction (p=.050), suggesting that although depressed individuals had lower levels

at baseline, this difference was not present at follow-up (see *Figure 1*). To evaluate whether changes in

Aβ were linked with changes in the severity of depressive symptoms, we carried out Pearson's bivariate

correlations between Aβ and Ham-D levels, using change in Ham-D scores and change in CSF Aβ

concentration (follow-up – baseline). The reductions in depressive symptoms observed over time were

significantly correlated with increases in CSF Aβ42 levels, both in the entire cohort (*r*= -.451, *p*=.006)

and within the LLMD group (*r*=-.547, *p*=.015), specifically, but not in the control group (p=.809). The

same relationship was not significant with Aβ40 (p's > .200).

To examine whether changes in Aβ42 were related to t-tau and p-tau, Pearson's bivariate

correlations were conducted between change scores in the LLMD group, as referenced above.

Comparisons of the follow-up to baseline levels, revealed a significant correlation between CSF Aβ42

levels and T-Tau (*r*=.557, *p*=.016). A significant correlation was found between CSF Aβ40 and t-tau

levels as well (*r*=.586, *p*=.011). Thus, increases t-tau in the LLMD group, over time, were associated with

increases in both CSF Aβ42 and CSF Aβ40. The same significant correlations were not found between p-tau and CSF Aβ42 or CSF Aβ40 (p's >.700).

Discussion

This is the first prospective longitudinal study to have examined the relationship between different phases of depression and CSF Aβ indices in cognitively intact elderly. Participants were examined at baseline who either had LLMD or were controls, and CSF Aβ42 and Aβ40 levels were found to be lower in this depressed group compared to controls [9]. Over the 3-year longitudinal study, we observed that the depressed group became significantly less depressed than at baseline and concomitantly, we also noted that levels of Aβ42 increased. CSF Aβ42 has been shown consistently to correlate inversely with brain amyloid due to the tendency of its soluble forms to form fibrils and plaques. This pattern of results, therefore, suggests that there may be a state-dependent association between CSF Aβ42 and depressive symptoms, whereby as depressive symptoms become more severe, brain amyloid deposition intensifies, and vice versa. Critically, this would indicate that the metabolic disturbances leading to Aβ abnormalities in LLMD individuals may be reversible rather than fixed, and thus possibly treatable.

Unlike Aβ42, CSF Aβ40 was not found to change as a function of LLMD, but only to decline with age. CSF Aβ40 levels do not tend to correlate with brain amyloid burden, have been reported to show inconsistent changes during longitudinal follow up, and are not used as AD biomarkers. In addition, amyloid deposits in cerebral blood vessels are known to have a greater proportion of Aβ40 than Aβ42. It is therefore possible that the significant longitudinal reductions in CSF Aβ40 may be due to age-related increases in blood vessel deposition. Relatedly, our findings do not point to a strong role of Aβ40 in relationship with LLMD and depressive symptoms.

We also found that increases in CSF Aβ42 and Aβ40 from baseline during the 3-year longitudinal follow-up were associated with increases in t-tau. Increases in tau have been associated with progressive cognitive decline and AD, and have been ascribed to increase neuronal and axonal degeneration. However, the correlations with tau in this study were not associated with progressive cognitive decline or

the emergence of AD and the increases remained within the normal range of CSF t-tau concentrations. This raises the possibility that other factors may have contributed to this relationship. Several lines of evidence from preclinical studies suggest that increased neuronal activity can result in increased release of Aβ peptides as well as tau [17]. Thus, these results are consistent with the hypothesis that state-dependent changes in neuronal activity may underlie the aforementioned association.

Results from recent investigations of resting fMRI connectivity in depression suggest a complex pattern of neuronal activity in LLMD with reductions in brain functional connectivity in the cognitive network as well as increases in the default mode network (DMN) [18]. However, resting fMRI connectivity studies in individuals with late-life depression, which are most pertinent to this report, have consistently described reductions in the default mode network connectivity[19,20]. Human studies using CBF and FDG-PET report reductions in cortical neuronal activity in the depressive phase of unipolar depression and improvement with remission [21]. These results are consistent with our hypothesis that state-dependent effects on neuronal activity may underlie the changes in CSF Aβ42 across different phases of depression.

However, sole reliance on changes in neuronal activity is not consistent with the observation that CSF Aβ40 declined longitudinally in both groups. If increased neuronal activity were the basis for the correlation between increases in CSF Aβ42 and reductions in depressive symptoms in the MDD group, then CSF Aβ40 should similarly be expected to increase, not decrease. Therefore, alternative hypotheses should also be considered, including the possibility of state-dependent changes in oligomeric forms of Aβ in depression. These forms might have escaped detection by the electrochemiluminescence technology assay that we employed, as was previously reported for the ELISA method [22,23], and they may have also masked epitopes of Aβ42 and Aβ40, resulting in their low levels. Thus increases in oligomeric forms of Aβ might have contributed to the low levels of CSF plasma Aβ42 and Aβ40 observed at baseline and to their association with more depressive symptoms. Conversely, their reduction during the longitudinal period was associated with higher CSF Aβ42 levels and reduced depression.Thus future studies should also examine oligomeric forms of CSF Aβ in elderly depressives. Additionally, since none of the existing

investigations simultaneously determined brain amyloid burden by PET or CSF Aβ and tau levels, future studies should therefore also examine the relationship between these AD biomarkers and measures of neuronal and functional connectivity in elderly depressives, both in the depressive phase of the illness and following remission.

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Table 1. Baseline demographics of cognitively intact individuals with LLMD and aged-matched control subjects.

	Baseline (Mean(*SD*))		Statistical Analysis		
	Control Group (N =19)	**LLMD Group (N=28)**	**t**	**df**	**p**
Age	68.1 (*7.3*)	66.5 (*5.4*)	0.84	45	0.41
Education	16.7 (*2.7*)	16.5 (*2.7*)	0.27	44	0.79
HAM-D Score	1.2 (*1.9*)	14.9 (*8.8*)	8.02	45	<.0001*
MMSE Score	29.5 (*0.5*)	29.8 (*0.6*)	1.56	45	0.13

Table 2. HAM-D and CSF levels of Aβ42, Aβ40, total-tau (t-Tau) and p-tau at baseline and follow-up.

	LLMD		Controls	
	Baseline Mean (*SD*)	**Follow-Up** Mean (*SD*)	**Baseline** Mean (*SD*)	**Follow-up** Mean (*SD*)
HAM-D	14.9 (*8.8*)	8.74 (*8.1*)	1.2 (*1.9*)	2.24 (*6.01*)
CSF Aâ42	231.42 (*117.64*)	261.05 (*148.01*)	335.94 (*187.71*)	279.29 (*118.17*)
CSF Aâ40	5285.84 (*2408.60*)	3728.47 (*1379.17*)	6550.29 (*2799.71*)	4020.06 (*1145.78*)
T-tau	254.33 (*122.39*)	277.33 (*111.98*)	343.59 (*152.59*)	365.71 (*136.17*)
P-tau	48.68 (*30.76*)	49.63 (*34.86*)	48.93 (*25.87*)	51.12 (*18.12*)

Figure 1. Three year follow-up of cognitively intact individuals with LLMD and control subjects. a) HAM-D scores in the LLMD group and control subjects at baseline and 3-year follow-up. There was a significant decrease in HAM-D score in the LLMD group at the 3-year follow-up as previously reported in Hashimoto et al. (2011). b) CSF Aβ42 levels in the LLMD group and control subjects at baseline and 3-year follow-up. There was a significant interaction between Aβ42 levels and time.