Full Title: State-dependent alterations in CSF Abeta42 levels in cognitively-intact elderly with late life major depression

Short Title: State-dependent alterations in CSF Abeta42

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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 has been implicated in AD, 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 depressive symptoms. During the 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. 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 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 AD (Jorm, 2001; Osorio, Gumb, & Pomara, 2014). This relationship has been described not only for late onset depression, but also for depression starting earlier in life (Byers & Yaffe, 2011). In a longitudinal study conducted by Wilson and colleagues (2002) in cognitively normal elderly, increases in the 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 (Beck et al., 2009; Richard et al., 2013), 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 Beta (Aβ) metabolism (Pomara and Doraiswamy, 2003) in both conditions. Studies conducted by our group and others (Pomara et al., 2006; 2012) 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. Dinniz, Teizeira, Machado-Vieira, Talib, Radanovic, Gattaz, & Forlenza, 2014; Gudmundsson, Skoog, Waern, Blennow, Palsson, Rosengren, & Gustafson, 2007; Madsen et al., 2012; Pomara et al., 2012; Yasuno et al., 2016).

Methodological differences , however, may be at the root of these differences in results, including heterogeneity in the studied populations, including sometimes presence of individuals with

MCI(Abbasowa & Heegaard, 2014; do Nascimento, Silva, Malloy-Diniz, Butters, & Diniz, 2015; Harrington, Lim, Gould, & Maruff, 2015; Osorio, Gumb, & Pomara, 2014). 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). 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 andage-matched controls, all of whom were cognitively normal at baseline. All subjects were diagnosed using a structured interview as per DSM-4 criteria, and the same lab and immunoassay method with demonstrated sensitivity and reliability for Aβ determination was employed (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 p-tau to gauge the possible emergence of neurodegeneration and neurofibrillary 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*).

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

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 (Pomara et al. 2012). 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. 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).

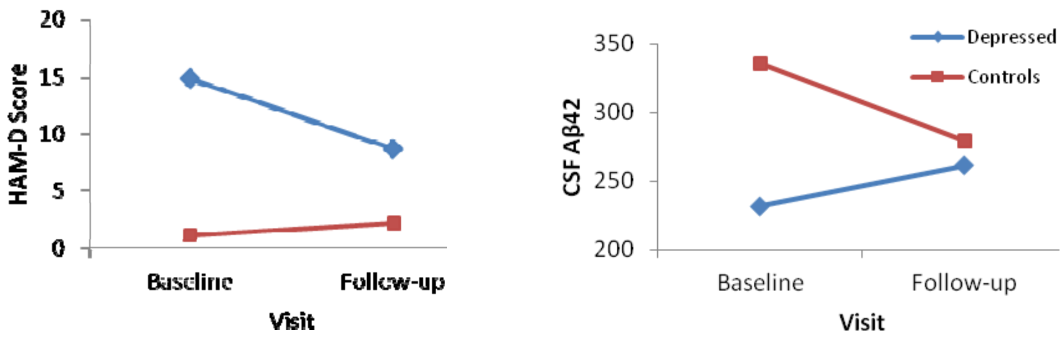
Table 2. HAM-D and CSF levels of Aβ42, Aβ40, total-tau (t-Tau) and p-tau at baseline and follow-up.

	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*)

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*).

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.



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 with CSF Aβ40 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 (Pomara et al., 2012). Over the 3-year longitudinal study, we observed that the depressed group became significantly less depressed than at baseline. At the same time, we also noted that the difference in CSF Aβ levels between groups was no longer significant. Consistently with this finding, we observed that the degree of change in the severity of depression in all participants over the life of the study was correlated with change in Aβ42. All in all, these findings suggest the possibility of a state-dependent association between CSF Aβ levels, especially Aβ42, and depressive symptoms. This would indicate that the metabolic disturbances leading to Aβ abnormalities in LLMD individuals are reversible rather than fixed, and possibly treatable.

Additionally, the possibility that the numerical increase in soluble CSF Aβ42 level, which we observed in the MDD group, emerged in the presence of increased brain amyloid burden cannot be excluded since CSF Aβ42 levels in the depressed group were still numerically lower than in controls at year three.

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 (Yamanda et al., 2014). 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) (Kenny, O'Brien, Cousins, Richardson, Thomas, Firbank, & Blamire, 2010). 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 (Wu et al. 2011, Alexopoulos et al. 2012). Human studies using CBF and FDG-PET report reductions in cortical neuronal activity in the depressive phase of unipolar depression and improvement with remission (Nikolaus, Larisch, Vosberg, & Muller-Gartner, 2000). 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, alternative hypotheses should be considered for the association between CSF Aβ42 and depressive symptoms 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 (Englund et al., 2009; Stehn et al., 2005), 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.

There is also emerging evidence that changes in the quality of sleep and its architecture, which are commonly disrupted in depression, can result in increased brain amyloid burden through effects in neuronal activity and glymphatic clearance. However, so far none of these studies have been conducted in depression. Thus it will important for future studies to determine if these factors contribute to altered Aβ dynamics in elderly depressives.

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