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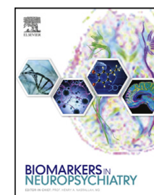

Original Data

Complement component 3 levels in the cerebrospinal fluid of cognitively intact elderly individuals with major depressive disorder

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ABSTRACT

Late-life major depression (LLMD) is a risk factor for the development of mild cognitive impairment and dementia, including Alzheimer's disease (AD) and vascular dementia. Immune dysregulation and changes in innate immune responses in particular, have been implicated in the pathophysiology of both LLMD and AD. Complement system, a key component of the innate immune mechanism, is known to play an important role in synaptic plasticity and cognitive functions. However, its role in LLMD remains unknown. In the present study, we examined the levels of complement component 3 (C3, the convergence point of all complement activation pathways) in the cerebrospinal fluid (CSF) of elderly depressed subjects compared to healthy controls; as well as the relationship of CSF C3 levels with amyloid-beta (Aβ42 and Aβ40), total tau (T-tau) and phosphorylated tau (P-tau) proteins and cognition scores. CSF was obtained from 50 cognitively intact volunteers (major depression group, N = 30; comparison group, N = 20) and analyzed for levels of C3 by ELISA. C3 levels were marginally lower in the major depression group relative to the comparison group. We did not find any significant association of C3 with the AD biomarkers Aβ42 reflecting plaque pathology, P-tau related to tau pathology or the neurodegeneration biomarker T-tau. In contrast, C3 was positively correlated with CSF Aβ40, which may reflect Aβ deposition in cerebral vessel walls. We observed a negative correlation between C3 levels and Total Recall on the Buschke Selective Reminding Test (BSRT) for memory performance in the depressed subjects when controlling for education. This initial evidence on C3 status in LLMD subjects may have implications for our understanding of the pathophysiology of major depression especially in late life.

Introduction

Recent evidence implicates immune dysregulation in the pathophysiology of major depressive disorder (MDD) [1,2]. Although clinical significance has not yet been established, a subset of depressed patients show changes in inflammatory markers and activation of immune cells such as resident brain microglia. Levels of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (Il-6), interleukin-8 (IL-8), and tumor necrosis factor (TNF-α) were found to be increased in the peripheral as well as central nervous systems (CNS) of a subset of depressed subjects (reviewed by [3,4]). The exact mechanism by which these changes relate to depressive phenotypes is currently unclear; in some cases, peripheral pro-inflammatory cytokines have been found to infiltrate into the brain and influence brain function, leading to depressive-like behavior [4]. Once in the CNS, they are thought to activate microglia, which then overproduce glutamate to the point of glutamate neurotoxicity [5]. Some evidence for this hypothesis comes from positron emission tomography (PET) studies using ligands of translocator protein (TSPO) that found greater microglial activation in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) of patients with MDD [6,7]. However, it should be noted that none of the current TSPO ligands are specific tracers of M1 (associated with the release of pro-inflammatory cytokines) or M2 (accompanied by the production of anti-inflammatory molecules) microglia.

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Although a number of therapeutic approaches, such as antidepressant medications and electro-convulsive therapy (ECT), have shown to inhibit inflammatory activity with improvements in depressive symptoms, many patients with baseline high inflammatory activity have been reported to be less responsive to the above approaches [8–13],[14]. Therefore, there is a critical need for studies that elucidate the role of the immune system in MDD in order to identify novel therapeutic targets.

The complement system represents one of the major branches of the innate immune system and consists of cascades of proteins that ultimately activate effector molecules. The cascade can be initiated by three major pathways: the classical pathway, the lectin pathway, and the alternate pathway; all three pathways converge on the cleavage of the major complement component, C3, into its activated subunits. The classical pathway begins when the recognition molecule C1q binds to antigens or antibodies. C1q then activates the associated serine proteases C1r and C1s, leading to cleavage of C2 and C4, which generates the C3 convertase C3b2b. C3b2b in turn cleaves C3 and activates downstream cascade components [15]. Working in parallel to the classical pathway, the lectin pathway is initiated by the molecule mannose-binding lectin (MBL) that recognizes mannose residues. This activates the MBL-associated proteases MBL serine protease 1 (MASP1) and MASP2, which cleave C4 to generate the C4 convertase, C4b2b. The alternative pathway functions primarily as an amplification loop of C3b. Ultimately, all pathways cleave C3 into activated components C3a and C3b. C3a regulates inflammatory signaling via its seven-transmembrane domain receptor, C3aR [16,17].

The complement system plays an important role in synaptic plasticity, and abnormalities in the system may contribute to the development of neurodegenerative diseases such as Alzheimer's disease (AD) [18–20]. Microglia, the innate immune cells that maintain homeostasis in the CNS, use the classical complement pathway to regulate synapse development [15,21], likely through the promotion of synaptic pruning. Aβ plaques have been shown to activate the complement system, which in turn uses activation factors such as C3a and C5a to trigger the activation of phagocytes, including microglia. However, findings on the role of complement system in neurodegeneration have reported conflicting results: some studies indicate that complement proteins promote neurodegeneration whereas others indicate that they provide neuroprotective effects [22–25].

A few studies have previously examined the role of complement proteins in the pathophysiology of depression, but the data remains in need of further investigation. Higher basal plasma levels of C3 (and its breakdown products) and C4 were found in depressed patients compared with healthy subjects in a couple of studies [26,27], while another study found elevated C4 but no significant difference in C3 levels in serum samples of depressed subjects [28]. More recently, our group found a significant increase in C3 expression in the PFCs of depressed suicide subjects [17].

The complement system may potentially link depression and the development of dementia and neurodegenerative disease in the elderly. A number of studies suggest that late-life major depression (LLMD) is a risk factor for the development of mild cognitive impairment and dementia, including AD, and vascular dementia [29–31]. Although the complement system has been implicated in AD and associated with changes in cognitive function, its role in late-life depression remains unknown. In the present study, we examined whether complement system links late-life depression and deterioration of cognitive function. We investigated the levels of C3 in the cerebrospinal fluid (CSF) of elderly depressed subjects compared to healthy controls; as well as the relationship of CSF C3 levels with AD-relevant CSF biomarkers and cognition scores.

Materials and methods

Participants

This study was approved by the institutional review boards of the Nathan Kline Institute for Psychiatric Research and the New York University School of Medicine. All methods were performed in accordance with the guidelines and regulation of the National Institutes of Health, USA. Participants were volunteers who responded to advertisements in local newspapers and flyers or were recruited from the Memory Education and Research Initiative Program [32]. All participants provided informed consent prior to examination and received up to $450.00 in compensation. A total of 133 participants completed the baseline evaluation, and 51 of these took part in the optional lumbar puncture procedure. Of these 51participants, one individual was excluded because of lack of C3 data. Of the 50 remaining participants, 30 were diagnosed with MDD by a board-certified psychiatrist, leaving 20 comparison subjects. The structural interview for DSM-IV disorders (SCID) was administered by a psychiatrist to establish an MDD diagnosis. Of the 30 patients with MDD, 21 (70 %) had recurrent episodes. Table 1 summarizes the demographic and clinical characteristics of the study participants at baseline.

Procedure

The study was conducted over four visits, usually one week apart. The first three visits were conducted at the Nathan Kline Institute for Psychiatric Research and the Clinical and Translational Science Institute, New York University Langone Medical Center. During the first visit, for the purpose of obtaining informed consent, the study procedures were explained and participants were informed of their rights. Participants' medical and psychiatric histories, including any family history of AD, were also obtained, and their vital signs were measured. Participants then underwent a psychiatric evaluation, and their global cognitive status was assessed using the MMSE. Additionally, the Hamilton Depression Rating Scale (HAM-D) was administered to rate the severity of current depressive symptoms. Subjects who met the criteria for past MDD but were not currently depressed (i.e., HAM-D score below 16) were included as MDD subjects. Subjects underwent a comprehensive neuropsychological assessment, including the Buschke Selective Reminding Test [46], the Trail-Making Test, parts A and B [47], and the category fluency test [48] during the third visit.

CSF collection. A lumbar puncture was performed during the fourth visit by a neuroradiologist under guided fluoroscopy in a subset of participants. Prior to the procedure, which was performed between 9:00 a.m. and 10:00 a.m., participants were asked to fast overnight. A total of 15 ml of clear CSF was collected in three polypropylene tubes labeled "A" (first 5 ml), "B" (second 5 ml), and "C" (third 5 ml). The tubes were immediately placed on ice for a maximum of 1 h until the samples were centrifuged at 4 °C (at 1500 rpm) for 10 min. Then, aliquots of 0.25 ml were placed into 1.00-ml polypropylene cryogenic vials and put into Nunc eight-cell storage boxes (Nalge Nunc International, Rochester, N.Y.) at −80 °C. All amyloid-β, tau, and C3 determinations were performed from tube "C".

Table 1
Demographic and Memory Characteristics of Study Participants by MDD diagnosis; Data are the mean ± standard deviation.

Characteristic	Comparison Group (N = 20)	MDD Group (N = 30)	p values (t tests)
Age (years)	68.4 ± 7.2	66.9 ± 5.3	0.39
Education (years)	16.6 ± 2.6	16.4 ± 2.7	0.7
21-item HAM-D	1.2 ± 1.9	14.9 ± 8.8	<**0.001**
17-item HAM-D	1.2 ± 1.8	15.5 ± 8.7	<**0.001**
MMSE	29.5 ± 0.5	29.7 ± 0.8	0.47
Total recall rating	64.5 ± 12.0	62.8 ± 14.9	0.68
Delayed recall rating	8.4 ± 2.7	9.2 ± 2.7	0.33
			p values (χ^2)
Females (n)	12 (60%)	10 (35%)	0.15

21-item HAM-D: 21-item Hamilton Depression Rating Scale, MMSE: Mini-Mental State Examination.

Amyloid Beta and tau protein determination. CSF levels of amyloid beta (Aβ40 and Aβ42) were analyzed with electrochemiluminescence technology using the MS6000 Human Ab Ultra-Sensitive Kit (Meso Scale Discovery, Gaithersburg, Md.). Total tau concentration in CSF was determined using a sandwich enzyme-linked immunosorbent assay (ELISA) (INNOTEST hTAU-Ag, Fujirebio, Ghent, Belgium) specifically constructed to measure all tau isoforms, irrespective of phosphorylation status. Tau protein phosphorylated at threonine 181 was measured using a sandwich ELISA method (INNOTEST Phospho-Tau [181 P], Fujirebio).

C3 ELISA. Complement C3 was quantified by a Complement C3 Human ELISA kit (cat #ab108823; abcam, Cambridge, MA, USA). Briefly, 96-well plates were incubated with C3 standard or sample for two hours at RT. After washing, wells were subsequently incubated with biotinylated C3 antibody for 1 h at RT. Following washing, peroxidase-labelled streptavidin conjugate was added to each well and incubated for 30 min. After washing, chromogen substrate was added and incubated for 10 min. After the reaction had been stopped with a stop solution, the amount of reacted substrate was measured at OD 450 nm. A standard curve was made using serial dilutions of the standard. The amount of C3 in samples was determined from the standard curve. Values were expressed as ng/mL.

Statistical analysis

All statistical analyses were carried out using the IBM SPSS statistical software package, version 24.0 for Windows (IBM Corp., Armonk, New York, USA). Distributions of data for demographic variables and variables of interest were evaluated using z-tests for skewness and kurtosis and were judged to be non-normal when a z value corresponded to alpha level 0.01. In those cases, nonparametric tests were used, as indicated in the Results section. A two-way (2 × 2) ANOVA was conducted to examine the effects of MDD status and sex on CSF C3 levels. Distributions of CSF C3 levels were non-normal across depression and sex subgroups and a square root transformation proved to be the best transformation method. Spearman correlations were used to test associations between untransformed C3 and AD biomarker variables (Aβ and tau). Partial (Pearson) correlations were used to test associations between transformed C3 values and cognitive scores to control for variation in years of education.

Results

Table 1 shows the demographic details of study subjects. For depression subgroups, there are no significant deviations from normality for age distribution, though it was positively skewed. For sex subgroups, the distribution of age deviated significantly from normality. Using z-tests for skew and kurtosis, education distributions did not deviate from normality in either depression of sex subgroups (N = 50). Neither mean age nor education differed by MDD status: Age: t(48) = 0.77, p = 0.45; Education t(48) = 0.35, p = 0.73. In addition, sex groups did not differ by age on Mann-Whitney U test: U = 216, p = 0.072. LLMD subjects showed significant differences in the depression/anxiety scores in 17-item Ham-D and 21-item Ham-D. Cognitive scores measured for MMSE (Mini-Mental State Examination memory), Buschke Selective Reminding Test (Total and Delayed Recall) showed no significant group differences between controls and LLMD subjects.

Effect of depression status on CSF C3 levels

We observed marginally lower mean CSF C3 levels in LLMD than controls (LLMD, 87.19 ± 25.07 (N = 30) vs Control, 102.51 ± 34.93 (N = 20); t(48) = 1.81, p = 0.077). Within the LLMD group, mean CSF C3 levels in subjects taking antidepressant medications (81.71 ± 27.41 (N = 16)) were not statistically different from mean C3 levels in subjects not taking antidepressants (93.45 ± 21.34 (N = 14); t(28) = 1.295, p = 0.206)). We found a significant sex effect on CSF C3 levels (Male, 102.31 ± 24.84 (N = 28) vs Female, 81.87 ± 32.58 (N = 22); t (48) = 2.514, p = 0.015). We found a significant association between CSF C3 and education in LLMD group (r = 0.395, p = 0.031, N = 30). Further, 2 × 2 GLM to test for the interaction of LLMD and sex while controlling for education (*i.e.*, factorial ANOVA) showed no interaction, but main effects of both MDD (p = 0.011) and sex (p = 0.008) on C3 levels (Table 2).

Correlation of CSF C3 with amyloid-beta (Aβ40) levels in LLMD subjects

We found a significant positive association between C3 and Aβ40 in CSF samples of LLMD subjects (r = 0.411; p = 0.024), but not in control subjects (r = 0.259; p = 0.271). We did not find any significant association between CSF levels of C3 and Aβ42 in controls (r = 0.229; p = 0.332) and LLMD subjects (r = 0.303; p = 0.104). Similarly, we did not find any significant association between CSF levels of C3 and Aβ42/40 in controls (r = 0.123; p = 0.605) and LLMD subjects (r = 0.243; p = 0.195). Furthermore, no significant correlations were observed between C3 and tau (controls, r = -0.114; p = 0.631, LLMD, r = 0.162; p = 0.393) or phosphoTau levels (controls, r = -0.117; p = 0.624, LLMD, r = 0.176; p = 0.352).

Correlations between CSF C3 levels and depression scores or cognitive domain scores

Among the different possible correlations between CSF C3 and depression scores or cognitive domain scores analyzed, we observed a negative correlation between C3 levels and Total Recall on the Buschke in the Depressed subjects when controlling for education (r = -0.380, p = 0.046). Although mean HAM-D scores were significantly lower in those taking antidepressants (21.4 vs 13.8; p = 0.03), CSF C3 levels did not significantly correlate with HAM-D scores with (r = -0.153, p = 0.421) or without (r = .047, p = 0.806) controlling for medication status.

Discussion

In CSF samples of LLMD subjects, C3 levels were marginally reduced compared to healthy controls; and lower C3 levels correlated with lower

Table 2
Effect of both Depression status and sex on CSF C3 levels.

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	11553.290[a]	4	2888.323	3.978	0.008	0.261
Intercept	5739.346	1	5739.346	7.904	0.007	0.149
LLMD	5087.734	1	5087.734	7.007	0.011	0.135
sex	5506.151	1	5506.151	7.583	0.008	0.144
LLMD * sex	312.977	1	312.977	0.431	0.515	0.009
Edu	535.725	1	535.725	0.738	0.395	0.016
Error	32675.116	45	726.114			
Total	479652.577	50				
Corrected Total	44228.406	49				

[a] R Squared = 0.261 (Adjusted R Squared = 0.196).

Aβ40 levels. We observed a negative correlation between C3 levels and Total Recall on the BSRT in the depressed subjects. These findings provide the first evidence of altered C3 levels in CSF of depressed subjects as compared to healthy controls, as well as evidence that it may be associated with cognitive impairment.

There exist two possible sources of complement in the brain: those produced in the periphery that enter the CNS, or those produced in the CNS itself. Unlike cytokines, which can enter the brain through transporters on the brain endothelium, peripherally-derived complement components can only enter the brain through a compromised blood-brain barrier [33]. Centrally-derived complement components are likely produced by glial cells such as microglia and astrocytes which have been shown to synthesize most components of at least the classical and alternative pathways, leading to a functional complement system in the CNS modulated by pro-inflammatory cytokines such as IL-1B and TNF-alpha [34–36]. In addition, neurons themselves are also able to produce both classical and alternative pathway components [37]. These studies suggest that CNS is capable of producing complement proteins independent of peripheral complement system, if needed.

While the studies directly linking depression and complement in the CNS are limited, given the known effects of complement, it was hypothesized that complement is abnormally activated or upregulated in depressed patients. However, we observed a reduction in CSF C3 levels in LLMD subjects. The decrease in C3 levels may reflect a decrease in C3 production in LLMD subjects relative to non-depressed controls. It is also possible that the reduction in C3 is a result of increased cleavage of C3 into C3a and C3b, and thus actually reflecting increased downstream complement signaling mediated by proteins such as C5. Further analyses of C3a and C3b levels are necessary to determine the underlying mechanism for the observed reduction in C3 in LLMD subjects.

C3 levels were positively correlated with Aβ40 in CSF samples of LLMD subjects; lower C3 levels reflected lower Aβ40 levels, a finding in line with previous studies. An earlier study from our group has reported decreases in Aβ42 and Aβ40 in CSF samples of LLMD subjects [32], possibly due to increased deposition in formation of brain amyloid beta plaques in the case of Aβ42 or decreased soluble amyloid beta production. A reduction in CSF Aβ40, is also consistent with its preferential deposition in cerebral blood vessels as in cerebral amyloid angiopathy [38,39]. The latter has also been linked to distal complement activation [38] and taken together, they would be consistent with the reductions in both CSF C3 and Aβ40 that we observed and their positive correlation. These results if confirmed might provide a possible mechanism for the increased cerebrovascular pathology which has been reported in depression especially LLMD [40,41]. As previously stated, further data are needed to clarify the relationship between complement activity and the development of AD. C1q deficiency in the Tg2576 mouse model of AD resulted in reduction in microgliosis and rescue of neuronal integrity as compared to Tg2576 mice [22], indicating that complement activity may promote neuronal degeneration. In a recent study using mouse models of amyloidosis (PS2APP) and more extensively tauopathy (TauP301S) [24], showed that C3 is increased in glial cells in the above mice and deleting C3 rescues plaque-associated synapse loss in PS2APP mice and ameliorates neuron loss and brain atrophy in TauP301S mice. Further, they found increased levels of C3 protein in brain and CSF samples of AD patients and C3 levels were correlated with tau [24]. Contradictory to the above studies, a few complement proteins have been shown to provide protective effects such as decreasing neuropathology in rodent models of AD [23,25] or limiting neurodegeneration in injury models [42–44]. Together, these studies suggest that although C3 can be protective in the clearance of Aβ deposits, it could accelerate neuronal dysfunction in response to tau pathology.

Although our findings provide the initial evidence on the status of C3 in the CSF of LLMD subjects, our study has a number of limitations. First, most of the LLMD subjects in our study were medicated and the observed decrease in C3 levels could be a result of medication effects. Second, most of the studies conducted to date have examined inflammatory status in early stage depressed subjects. The LLMD subjects in our study were chronically depressed and may have inflammatory profiles different from patients with less sustained symptoms. It is possible that CSF levels of pro-inflammatory as well as anti-inflammatory markers change over time or with age in depressed subjects. Finally, our study was conducted in a relatively small number of subjects and therefore, additional studies with a larger cohort of samples are warranted.

In future studies, it will be important to determine whether changes in CSF C3 levels correlate with microglial activation in depressed subjects, as we may be able to identify a physiological mechanism behind the observed reduction in CSF C3 levels in LLMD subjects in our study. Also, there might be subtypes of MDD, with microglial decline and suppression (rather than microglial activation), which could occur due to aging or chronic stress conditions [45]. Microglial activation, as determined by TSPO V_T, was found greater in patients with chronologically advanced major depressive disorder with long periods of no antidepressant treatment than in patients with major depressive disorder with short periods of no antidepressant treatment, suggesting a differential microglial activation status between these illness stages [7]. However, the TPSO-based PET has limitations due to the lack of specificity for M1 vs M2 microglial phenotype. Recently, some subtypes of purinergic receptors such as P2 × 7R and P2Y12R, have been validated as promising PET imaging targets for microglia phenotypes in preclinical studies. These tracers will be important for microglial activation studies in depression, given that microglial phenotypes vary according to disease stage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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