Neuroscience Letters 694 (2019) 41–45

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Association of CSF CD40 levels and synaptic degeneration across the Alzheimer's disease spectrum

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ARTICLE INFO

Keywords:
CD40
Alzheimer's disease
Neuroinflammation
Synaptic degeneration

ABSTRACT

The CD40 pathway has been implicated in microglial activation, which is considered as a key factor in the pathogenesis of Alzheimer's disease (AD). However, the association of CSF CD40 and synaptic degeneration in living human is not clear. A total of 294 subjects with different severities of cognitive impairments were included in this study: 84 participants with normal cognition, 143 patients with mild cognitive impairment (MCI) and 67 patients with mild AD. Levels of CD40 in CSF were compared among the three groups. Further, several linear regression models were conducted to explore the associations of CSF CD40 and neurogranin levels (reflecting synaptic degeneration) when controlling for age, gender, educational attainment, APOE4 genotype, clinical diagnosis, CSF Aβ42 and tau proteins. We found that CSF CD40 levels were significantly decreased in patients with mild AD compared with healthy controls and MCI patients (control vs. AD, $p = 0.0026$; MCI vs. AD, $p = 0.0268$). However, there were no significant differences in CSF CD40 levels between controls and patients with MCI ($p = 0.37$). In addition, CSF CD40 levels were associated with neurogranin in the pooled sample when controlling for age, gender, educational attainment, APOE4 genotype and diagnosis. In summary, our findings support the notion that the CD40 pathway may contribute to an important mechanism underlying synaptic degeneration in AD.

1. Introduction

Synapses play crucial roles in long-term potentiation (LTP), decline early in normal aging [20] and Alzheimer's disease (AD), and are more strongly associated with impairments in cognitive function than β-amyloid or tau protein [2,29]. Neurogranin (NG), a postsynaptic protein, is involved in memory consolidation and LTP signaling [17,31]. It has been reported that CSF NG levels were significantly increased in patients with mild cognitive impairment (MCI) and AD, suggesting that NG may be a useful biomarker reflecting synaptic degeneration [16,17].

A growing body of reports have suggested that microglia-mediated neuroinflammation may be involved in the pathogenesis of AD [13,24]. CD40, a transmembrane receptor, is a member of tumor necrosis receptor super-family [4]. It has been implicated in microglial phenotypic transformation from a resting, to an activated morphology [23]. In addition, Aβ-induced microglial activation is substantially elevated by stimulation of the CD40 pathway [28]. In contrast, Laporte and colleagues reported that blockage of CD40 signaling in AD mice leads to markedly less tau hyperphosphorylation and microgliosis [28]. Clinical studies found levels of soluble CD40 and its cognate CD40 ligand (CD40 L) in blood were increased in patients with MCI and AD compared with cognitively normal older adults [1,3,8,19,30]. However, it remains unclear whether levels of CD40 in CSF are altered in patients with MCI and AD, and whether CSF CD40 levels are associated with synaptic degeneration in living human.

To examine the association of clinical diagnosis with CD40, CSF CD40 levels were investigated in subjects with normal cognition, patients with MCI and AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Further, Pearson correlation test was conducted to examine the correlation between CSF levels of CD40 and neurogranin in the whole sample. Finally, we investigated the associations of CD40 with neurogranin by controlling for age, gender,

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

https://doi.org/10.1016/j.neulet.2018.11.019
Received 27 August 2018; Received in revised form 1 November 2018; Accepted 13 November 2018
Available online 15 November 2018

educational attainment, APOE4 genotype, clinical diagnosis, amyloid and tau proteins.

2. Methods

2.1. Alzheimer's disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were downloaded on 15 May 2018 from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2004 as a public-private partnership with the primary goal of testing whether demographics, neuropsychological assessments, serial MRI, PET and other biological markers can be combined to measure the progression of MCI and early AD. Institutional review board approval was obtained at each ADNI center, and all participants provided informed consents at initial visit. In this analysis, there were 84 subjects with normal cognition, 143 patients with MCI and 67 patients with mild AD. For up-to-date information, visit (www.adni-info.org)

2.2. CSF biomarker analyses

2.2.1. Quantification of CD40 antigen in CSF

CD40 antigen levels in CSF was measured as part of a CSF multiplex proteomic processing stream using an xMAP multiplex panel (MyriadRBM) [18], details of which can be found at the ADNI website (www.adni-info.org). The values of CD40 were log-transformed to better approximate a normal distribution.

2.2.2. Quantification of CSF Aβ42 and t-tau

Levels of Aβ42 and t-tau in CSF were measured as described previously [26]. CSF data were downloaded from the ADNI website and obtained for all included subjects. Values are given in pg/ml for both Aβ42 and t-tau.

2.2.3. Quantification of CSF neurogranin

Neurogranin levels in CSF were determined by electrochemiluminescence technology (Meso Scale Discovery, Gaithersburg, Maryland, USA) using Ng 7 as a coating antibody and polyclonal Ng anti-rabbit (ab 23,570, Upstate) as a detector antibody [17]. Values are given in pg/mL. Further information can be found at the ADNI website (www.adni-info.org).

2.3. Statistical analysis

The F test and Pearson x^2 were used to investigate differences in demographics and clinical variables across the three diagnostic groups. To explore the relationship between CSF levels of CD40 and neurogranin, Pearson correlation test was performed. In addition, several linear regression models were used to examine the associations between CSF levels of CD40 and neurogranin: model 1 was unadjusted; model 2 was adjusted for age, gender, educational attainment, APOE4 genotype, clinical diagnosis; model 3 was additionally adjusted for Aβ42 and t-tau levels in CSF. All statistical work was performed with R (version 3.3.3). The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographics and clinical variables

The one-way analysis of variance (ANOVA) and Pearson x^2 were used to examine differences in demographics and clinical variables. Table 1 summarizes the demographic and clinical data: 84 participants with normal cognition, 143 patients with MCI and 67 patients with AD. There were no significant differences in age or educational attainment across the three diagnostic groups. Compared with subjects with normal cognition, subjects with MCI were more likely to be male. As expected, there were significant differences in MMSE scores, CSF NG, Aβ42 and t-tau across the three groups (Table 1). Consistent with the previous findings, more than half of the patients with MCI and mild AD were APOE4 carriers [10].

Table 1
Demographic and clinical variables.

Characteristics	NC (n = 84)	MCI (n = 143)	AD (n = 67)	P value
Age, year	75.7 (5.5)	74.7 (7.3)	75 (7.6)	0.5
Female/Male, n	43/41	47/96 [a]	30/37	0.02
Education, year	15.7 (2.98)	15.9 (2.94)	15.1 (3)	0.27
APOE4 noncarrier vs carrier, n	64/20	66/77 [a]	20/47 [b,c]	< 0.001
MMSE	29.1 (0.9)	26.9 (1.8) [a]	23.5 (1.87) [b,c]	< 0.001
CSF NG, pg/ml	366 (209)	506 (304) [a]	558 (312) [b,c]	< 0.001
CSF Aβ42, pg/ml	207 (53.8)	160 (49.6) [a]	35.5 (124) [b,c]	< 0.001
CSF t-tau, pg/ml	71.5 (25.9)	105 (49.3) [a]	124 (58.3) [b,c]	< 0.001

Abbreviations: NC: normal control; MCI: mild cognitive impairment; AD: Alzheimer's disease; MMSE: mini-mental state examination; NG: neurogranin; Aβ42: β-amyloid; t-tau: total tau.
Comparison between NC group and MCI group is marked behind "MCI group"
[a] $p < 0.05$.
Comparison between MCI group and AD group is marked behind "AD group"
[b] $p < 0.05$.
Comparison between NC group and AD group is marked behind "AD group"
[c] $p < 0.05$.

3.2. Decreased levels of CSF CD40 in patients with AD

The ANCOVA model suggested that CSF CD40 significantly differed across the three diagnostic groups after adjusting for age, gender, educational attainment, APOE4 genotype ($p = 0.003$, Fig. 1). Further, Tukey's post hoc tests found that levels of CD40 in CSF were significantly decreased in AD patients compared with normal controls and MCI patients (control vs. AD, $p = 0.0026$; MCI vs. AD, $p = 0.0268$). However, there were no significant differences in CSF CD40 levels between controls and patients with MCI ($p = 0.37$). As shown in Fig. 1, the means of CSF CD40 levels in the healthy controls, MCI patients and AD patients were 0.551 (sd: 0.07), 0.536 (sd: 0.07) and 0.514 (sd: 0.06), respectively. The y axis of Fig. 1 represents the mean of CSF CD40 levels with their 95% confidence interval.

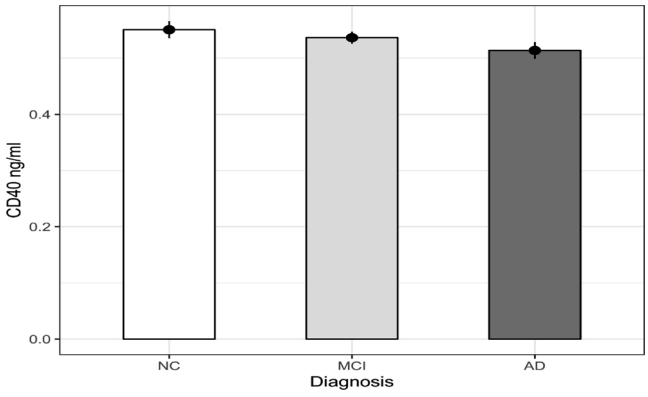

Fig. 1. CSF CD40 levels in three diagnostic groups.
Abbreviations NC normal control; MCI mild cognitive impairment; AD Alzheimer's disease.
Note: The error bars represent 95% confidence interval.

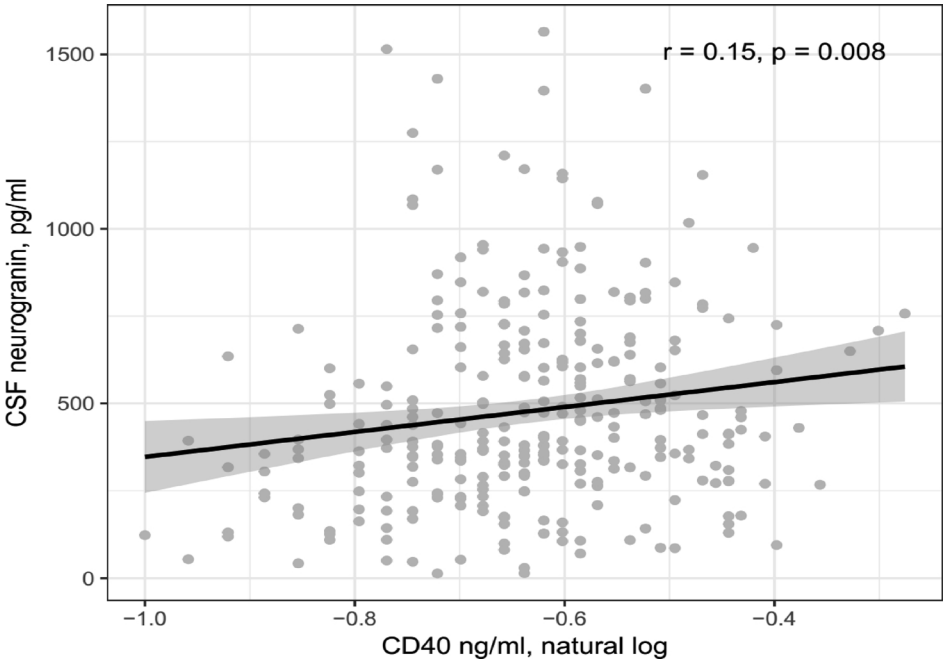

Fig. 2. Associations of CSF levels of CD40 with neurogranin.

3.3. Correlation of CD40 with neurogranin

Pearson correlation test was applied to examine the relationship between CSF levels of CD40 and neurogranin. A positive correlation between CSF CD40 and neurogranin was observed (r = 0.15, p = 0.008, Fig. 2). However, the effect size of the correlation (r = 0.15) is small according to Cohen [6].

3.4. Association of CD40 with neurogranin

To examine the association of CD40 and neurogranin, several linear regression models were used (Table 2). The model 1 suggested that CSF CD40 was significantly associated with neurogranin (standardized beta = 0.15 (0.06), p = 0.008). A significant association between CSF CD40 and neurogranin was observed when controlling for age, gender, educational attainment, APOE4 genotype and clinical diagnosis (standardized beta = 0.3 (0.06), p < 0.001, model 2). Finally, after the additional adjustment of CSF Aβ42 and tau, the association of CSF CD40 with neurogranin was no longer present (standardized beta = 0.02 (0.05), p = 0.69, model 3).

4. Discussion

In this study, CSF CD40 levels were significantly lower in AD patients compared with healthy controls and MCI subjects. However, there were no significant differences in CD40 levels between healthy controls and MCI subjects. In addition, CSF CD40 levels were significantly associated with neurogranin independent of age, gender, education, APOE4 genotype and clinical diagnosis.

In this study, we found that CSF CD40 levels were lower in AD patients compared with healthy controls and MCI patients. To our knowledge, this is the first report of significantly decreased CSF CD40 levels in AD patients, which appears to be inconsistent with previous findings. For example, previous studies reported that levels of soluble CD40 and CD40 L in the blood are markedly increased in patients with AD as well as in subjects with MCI [1,3,8,19,30]. One possible explanation is that the severity of cognitive deficits of AD patients from the ADNI cohort is relatively mild. Evidence from preclinical studies suggested that microglial activation may be involved in phagocytosis and Aβ clearance in early stages of the disease. On the contrary, in later stages, proinflammatory microglia would rather promote synapse loss and tau pathology [15,24]. Further, neuroimaging studies reported that microglial activation was positively associated with cognitive function

Table 2
Modeling of potential association of CSF CD40 with neurogranin controlling for age, gender, educational attainment, APOE4 genotype, clinical diagnosis, CSF Aβ and tau proteins.

	Model 1 Beta (se)	p	Model 2 Beta (se)	p	Model 3 Beta (se)	p
CD40	0.15 (0.06)	0.008	0.3 (0.06)	< 0.001	0.02 (0.05)	0.69
Age, y			−0.18 (0.06)	0.001	−0.08 (0.04)	0.06
Female vs. male			0.2 (0.05)	< 0.001	0.09 (0.04)	0.02
Education, y			0.02 (0.05)	0.71	−0.02 (0.04)	0.66
APOE4 noncarrier vs. carrier			0.22 (0.06)	< 0.001	0.07 (0.05)	0.14
MCI vs. control			0.23 (0.06)	< 0.001	0 (0.05)	0.99
AD vs. control			0.27 (0.07)	< 0.001	−0.05 (0.05)	0.31
Aβ42					0.03 (0.05)	0.51
T-tau					0.74 (0.05)	< 0.001

Abbreviations: MCI: mild cognitive impairment; AD: Alzheimer's disease; Aβ42: β-amyloid; t-tau: total tau; Beta: standardized beta; se: standard error.
Annotations: Model 1 was unadjusted; model 2 was adjusted for age, gender, educational attainment, APOE 4 genotype and clinical diagnosis; model 3 was additionally adjusted for CSF Aβ42 and tau levels.

and gray matter volume in patients with MCI, suggesting that microglial activation may be neuroprotective in early stages of AD [12]. However, in AD patients, microglia activation negatively correlated with glucose metabolism [9], indicating a link between microglial activation and synaptic dysfunction in later stages of AD. Importantly, the CD40 pathway plays an important role in microglia phenotypic transformation [23] and promotes release of inflammatory cytokines [7]. Thus, due to the dual role of microglia in AD pathogenesis, we speculate that CSF CD40 levels may be increased in patients with moderate to severe AD. However, this statement needs to be further clarified in patients with moderate to severe AD.

Regarding microglia and synaptic function, animal studies have suggested that microglia is critical for the synaptic and neuronal function in the healthy brain. Paolicelli et al. found that microglial cells actively engulf synaptic material and play an important role in synaptic pruning during brain development [22]. It has been reported that prolonged microglial activation may result in physical disconnections between presynaptic and postsynaptic components of inhibitory synapses [5]. Furthermore, previous work using 11C-(R)-PK11195 PET found that microglial activation is associated with cerebral glucose hypometabolism in patients with AD [9]. Importantly, the CD40 pathway is essential to microglial activation in pathological conditions [11]. Consistent with previous findings, we found that CSF CD40 levels are associated with synaptic dysfunction in subjects with different severities of cognitive impairments. However, the association of CD40 with neurogranin was no long present when CSF Aβ42 and t-tau levels were controlled for in the analysis (Table 2), suggesting that β-amyloid and tau pathologies may play a critical role in synaptic degeneration. A growing body of evidence have shown that β-amyloid-induced synaptic dysfunction is relying on NMDA receptor-mediated pathways, contributing to dendritic spine loss [21,25]. More specifically, our linear models suggested that the association found between CD40 and neurogranin is actually because of tau pathology. It has been reported that tau pathology contributes more to synaptic dysfunction and cognitive decline [14,27]. We believe that the interaction among neuroinflammation, amyloid, tau protein may contribute to a crucial mechanism underlying synaptic degeneration in AD. Further studies are needed to better understand the relationship between CD40, amyloid and tau.

Our study was limited by the cross-sectional design. Longitudinal studies are needed to examine how levels of CD40 correlates with synaptic degeneration over time. Second, the ADNI cohort is a convenience sample. Thus, the ability to generalize our findings to other populations may be limited. Finally, in the present study, the severity of cognitive deficits of AD patients was relatively mild. To further examine the role of CD40 in the pathogenesis of AD, it would be important to include patients with moderate to severe AD in future studies.

In conclusion, we found that CSF CD40 levels were significantly decreased in patients with mild AD compared with subjects with normal cognition and patients with MCI. Further, levels of CD40 in CSF were associated with synaptic degeneration, suggesting that neuroinflammation may contribute to an important mechanism underlying synaptic degeneration in AD.

Disclosure of conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgements

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

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