Neuroscience Letters 738 (2020) 135392

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

TNF receptors are associated with tau pathology and conversion to Alzheimer's dementia in subjects with mild cognitive impairment

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ARTICLE INFO

Keywords:
Tumor necrosis factor
Alzheimer's disease
Mild cognitive impairment
Tumor necrosis factor receptor
MCI-to-AD conversion

ABSTRACT

Background: Tumor necrosis factor-a (TNF-α) signaling pathway plays a significant role in Alzheimer's disease (AD). This study aimed to explore the relationship between TNF-α related inflammatory proteins and pathological markers of AD, and examine their possibility as a predictor of the conversion of mild cognitive impairment (MCI) to AD.

Methods: This study included both cross-sectional and longitudinal designs. The levels of TNF-α related inflammatory proteins, $A\beta_{1\text{-}42}$, total-tau(t-tau), phosphorylated tau (p-tau) from cerebrospinal fluid (CSF) were analyzed in healthy controls (HC, n = 90), MCI (n = 116), and AD participants (n = 75) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Kaplan-Meier analyses were used to evaluate the predictive value of the examined putative AD markers after follow-up visits.

Results: In the cross-sectional cohort, we observed higher CSF levels of TNF-α related inflammatory proteins in the MCI and AD patients with positive tau pathology. TNF receptors (TNFR) were more closely associated with t-tau and p-tau than $A\beta_{1\text{-}42}$, in HC, MCI and AD subjects. In the longitudinal cohort with a mean follow-up of 30.2 months, MCI patients with high levels of CSF TNFR1 ($p = 0.001$) and low levels of TNFR2 ($p < 0.001$) were more likely to develop into AD.

Conclusion: TNFR-signaling might be involved in the early pathogenesis of AD and TNF receptors may serve as potential predictive biomarkers for MCI.

1. Introduction

Extensive evidence supports that neuroinflammation plays a significant role in the neurodegeneration of Alzheimer's disease (AD) [9,23,31]. Tumor necrosis factor-a (TNF-α) is one of the important inflammatory cytokines in mediating neuron loss of AD [33]. TNF-α functions through binding two receptors (TNFR1 and TNFR2) to regulate two downstream TNF-α effectors: intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) [6]. Several studies confirmed that disease-state-dependent changes of TNF-α levels, especially increased cerebrospinal fluid (CSF) TNF-α in patients with severe AD [1,15]. Higher levels of both soluble TNFR1 and TNFR2 in the CSF of patients with AD and mild cognitive decline(MCI) [16]. Meanwhile, higher levels of CSF ICAM-1 and VCAM-1 increased risk of progression into AD dementia in patients without cognitive impairment [14]. Hence, TNF-α related inflammatory proteins were significantly associated with the development and progression of AD.

The formation and accumulation of insoluble beta-amyloid (Aβ) and hyper-phosphorylated tau (p-tau) was assessed as hallmarks of initial and coursing neuropathological events in AD [18]. Anti-TNF-α therapy modulated the amyloid phenotype and tau phosphorylation by regulating immune cell trafficking in the mouse brain [29]. Inhibition of soluble TNF signaling in AD model prevents pre-plaque amyloid-associated neuropathology [20]. However, it has not been systematically evaluated that the association of TNF-α related inflammatory proteins and Aβ/tau pathology within the patients to further explain the pathophysiological changes in AD. Here, we first investigated the levels of TNF-α related inflammatory proteins in total 281 participants enrolled

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https://doi.org/10.1016/j.neulet.2020.135392
Received 2 April 2020; Received in revised form 23 June 2020; Accepted 13 September 2020
Available online 15 September 2020

in in the Alzheimer's Disease Neuroimaging Initiative (ADNI) under the new A/T/N classification [32]. Moreover, we examined the relationship between Aβ/tau levels and TNF-α related inflammatory proteins. Finally, we investigated whether CSF TNF-α related inflammatory proteins could predict the cognitive decline in patients with mild cognitive impairment (MCI) or MCI subgroups.

2. Materials and Method

2.1. Study design

A total of 90 healthy controls, 116 MCI patients and 75 AD patients in the ADNI database from 2010 to 2019 were included into this study. Diagnosis of AD was based on the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) criteria [5], while MCI patients were diagnosed according to the Mayo Clinic criteria [30]. Neuropsychological tests, including Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale cognitive subscale (ADAS13), and functional activities questionnaire (FAQ), were performed every six months to evaluate the cognitive ability. The death outcome was excluded in in the AD progression-free survival outcome. To fully evaluate the AD-related patterns of neurodegeneration, we applied the recently published A/T/N classification framework of AD which proposes 3 binary biomarker groups [13]: (1) aggregated Aβ (A+/A-), (2) aggregated tau (T+/T-) and (3) neurodegeneration (N+/N-). Each individual was rated as either positive (+) or negative (-) on each biomarker. Given that CSF total-tau (t-tau) and CSF phospho-tau (p-tau) were highly correlated, the tau(T) and neurodegeneration (N) groups can be merged into "TN" group [36]. 'TN- "profile was defined as both CSF P-tau and T-tau within the normal range, whereas 'TN+' was defined as abnormal levels of CSF P-tau or T-tau.

2.2. Measurement of TNF-α related inflammatory proteins in the CSF

A detailed description of CSF t-tau, p-tau and $A\beta_{1-42}$ data, as well as the original results, can be downloaded from the LONI Image and Data Archive (https://ida.loni.usc.edu). The measurement of CSF $A\beta_{1-42}$, t-tau and p-tau was performed by the ADNI Biomarker Core team at the University of Pennsylvania, using the electrochemiluminescence immunoassays Elecsys and a fully automated Elecsys Cobas e 601 instruments (provided in UPENNBIOMK9.csv file available in the ADNI databank). TNF-α related inflammatory proteins were measured by William Hu's lab of Emory University with ELISA kits. All samples were run in duplicate along with six CSF standards on each plate. Samples were normalized across plates using CSF standard values (the results can be found under the name "ADNI Data Hu Lab.csv" in the ADNI database).

2.3. Statistical analysis

Statistical analysis was mainly performed with SPSS (version 19.1; IBM Corp., Armonk, NY). The significance level was set at 0.05. Continuous variables were expressed as mean (standard deviation) in the tables. We used the chi-squared and split chi-squared tests to identify differences in dichotomous variables, such as sex and ApoE ε4 carrier status. One-way ANOVA with least significant difference (LSD) post-hoc tests were used to compare differences of TNF-α related inflammatory proteins between the HC, MCI, and AD in different A/TN groups. Pearson correlation test was used to determine the association between the TNF-α related inflammatory proteins, t-tau, p-tau and $A\beta_{1-42}$. False Discovery Rate (FDR) was used to adjust after multiple testing. Spearman's rank-order correlation were performed using JMP software, version 9.0 (SAS Institute Inc., Cary, NC, USA). The threshold values of CSF TNFR1, TNFR2, t-tau, p-tau and $A\beta_{1-42}$ were determined by the mean value from all participants. The rate of progression-free survival was estimated by using the Kaplan-Meier method to analyze the relationship between TNFR1, TNFR2 and disease risk.

3. Results

3.1. Demographic and clinical characteristics of participants at baseline

Demographic and clinical features of healthy controls (HC) and patients with AD and MCI are listed in Table 1. No significant differences were observed in age, gender or education. For the genotype, there were more subjects with ApoEε4 positive (ApoE ε4 carriers) in AD and MCI patients than in the control group ($p < 0.001$, Table 1). Differences in cognitive function, assessed by MMSE and ADAS13 questionnaires, were compared among groups, and both AD ($p < 0.001$) and MCI ($p < 0.001$) patients exhibited different score compared to HC subjects. Furthermore, MCI and AD patients showed lower CSF $A\beta_{1-42}$ concentration compared to the HC group (both $p < 0.001$, Table 1). As for tau pathology, MCI and AD patients showed higher CSF total tau levels and p-tau levels than HC group ($p < 0.001$, Table 1).

3.2. Evaluation of CSF TNF-α related inflammatory proteins within the A/T/N classification of AD

Considering the impact of Aβ deposition or tau pathology, we compared four different biomarker profiles within each clinical stage, namely: (1) A-/TN-, (2) A+/TN-, (3) A-/TN + and (4)A+/TN + . Within the HC group, significant different levels of TNFR1 and VCAM-1 between the four biomarker profiles ($p < 0.001$, **Supplementary** Table1). A Bonferroni post hoc test revealed that the A-/TN- and A+/TN- profile had significant lower TNFR1 and VCAM-1 compared to A-/TN + groups. For the MCI group, there was also a significant difference of the four biomarker profiles: patients with A+/TN- profile presented with a lower concentration of TNFR1, TNFR2 and VCAM-1 compared to the A-/TN + group (**Supplementary** Table1). While for the AD group, there were significant difference between the four biomarker profiles in all five TNF-α related inflammatory proteins. Subjects in A-/TN + group showed the highest levels of the proteins above compared to the other profiles (**Supplementary** Table1).

Table 1
Demographics and clinical characteristics of the participants.

	HC (N = 90)	MCI (N = 116)	AD (N = 75)	*P*
Age	75.32(5.34)	74.21(7.41)	74.74(8.17)	0.532
Gender				
Female	42	45	36	0.364
Male	48	71	39	
Education	15.72(3.03)	15.73(3.16)	17.97(3.02)	0.186
ApoE ε4 carrier				
(+)	22	63	52	0.000[a,b,c]
(-)	68	53	23	
MMSE	28.97(1.16)	26.82(1.75)	23.57(1.90)	0.000[a,b,c]
FAQ	0.14(0.70)	4.26(4.79)	12.81(6.76)	0.000[a,b,c]
ADAS13	9.81(4.27)	18.86(5.98)	29.03(7.98)	0.000[a,b,c]
CSF $A\beta_{1-42}$ (pg/ml)	1082.87 (379.11)	761.12 (341.33)	605.29 (241.45)	0.000[a,b,c]
CSF t-tau(pg/ml)	236.62 (307.56)	307.57 (112.33)	364.16 (136.14)	0.000[a,b,c]
CSF p-tau(pg/ml)	21.69(7.62)	30.22(12.98)	36.98(16.06)	0.000[a,b,c]

$P < 0.05$: "a": HC vs MCI; "b" :HC vs AD; "c" MCI vs AD

3.3. Association between CSF TNF-α related inflammatory proteins and AD pathological markers

We further analyzed the relationship between these TNF-α related inflammatory proteins and AD pathological markers. Firstly, we investigated the association between CSF TNF-α related inflammatory proteins and total tau levels. Significant correlation between TNFR1, TNFR2 and t-tau among three groups were shown (FDR < 0.05, Table 2). Moreover, both ICAM-1 and VCAM-1 were positively associated with t-tau levels in three groups as well (FDR < 0.05, Table 2). Subsequently, we analyzed the correlation between p-tau and TNF-α related inflammatory proteins. The result also showed that TNFR1 and TNFR2 were significantly associated with CSF p-tau level, among all the subjects in the three groups (FDR < 0.001, Table 2). On the other hand, we also analyzed the relationship between these markers and $A\beta_{1\text{-}42}$ levels, however, significant association was solely found in AD and HC groups (**Supplementary** Table 2). The same results were also validated using Spearman rank correlation (**Supplementary Table 3**).

3.4. Predictive evaluation of the MCI-to-AD conversion with TNF-α related inflammatory proteins

Since TNF-α related inflammatory proteins was associated with tau pathology, as we showed above, and therefore could be predictive markers during disease progression. Thus, we further evaluated their predictive value in a longitudinal study. Of 116 MCI patients followed-up until 2019, 64 (55.2 %) developed defined AD after a mean of 30.2 months. Kaplan-Meier analysis indicated mean progression-free survival time of 36.0 months in subjects with higher CSF TNFR1 levels (TNFR1+), and of 60.0 months in the remaining population ($p = 0.001$; Fig. 1A).In contrast, patients with high levels of CSF TNFR2 (TNFR2+) at baseline showed a mean AD-free survival time of 60.0 months, whereas the remaining MCI patients exhibited a mean AD-free survival time of 24.0 months ($p < 0.001$; Fig. 1B). Among patients with lower tau pathology levels (TN-), subjects with lower CSF TNFR1 (TNFR1-) showed a mean AD-free survival time of 48.0 months, while, in the others, the mean AD-free survival time was 36.0 months ($p = 0.001$; Fig. 1C). Similarly, in TN- MCI groups, patients with higher CSF TNFR2 (TNFR2+) revealed a mean AD-free survival times of 60.0 months, and of 48.0 months in the other group ($p = 0.039$; Fig. 1E). No significant differences in mean AD-free survival time were observed in MCI TN + patients with different levels of CSF TNFR1 and TNFR2 (**Figure 4D&Figure 4F**). However, TNF-α, ICAM-1 and VCAM-1 failed to predict the cognitive decline in MCI (data not shown).

4. Discussion

In this study, we applied the A/T/N classification to assess TNF-α related inflammatory proteins in different stages of AD. The higher CSF levels of TNF-α related inflammatory proteins in the A-/TN + groups confirm that CSF TNF-α related signaling rises with neurodegeneration without Aβ pathology. Hence, during Alzheimer's *continuum*, we can conclude that increased CSF TNF-α related inflammatory proteins, especially TNFR1 and TNFR2, are more closely associated with the pathological processes of both tau pathology and neurodegeneration, than the $A\beta_{1\text{-}42}$ levels. The use of this classification system enabled us to unravel the effect of tau pathology and its downstream processes on TNF-α related inflammatory proteins. Interestingly, TNFR1 and TNFR2 can differentially predict the MCI-to-AD conversion. MCI patients with lower CSF TNFR1 levels or higher CSF TNFR2 levels showed slower cognitive decline to AD. Our results indicated that TNFR1 and TNFR2 associated with tau pathology could serve as a potential predictive biomarker for MCI-to-AD conversion.

Extensive evidence supported that the excessive TNF-α played a central role in AD [37]. TNF-α conducted its function by binding to TNFR1 and TNFR2 which are a super-family of transmembrane receptors that are defined by a similar cysteine-rich extracellular domain [2]. Considering that TNFR1 exerts inflammatory and pro-apoptotic functions, whereas TNFR2 has a neuroprotective function, it is of utmost importance to define the expression of both receptors in AD [27]. The deletion of TNFR1 resulted in the decreased brain inflammation and blood-brain barrier integrity [35]. A previous study showed higher levels of serum predicted the conversion from MCI to AD [4], which was consistent with our results with CSF TNFR1. On the other hand, TNFR2 mediated inflammatory signal pathways promote survival and proliferation [8]. Ablation of TNFR2 exacerbated AD pathology in a transgenic mouse model of AD [24]. A soluble TNFR2 agonist (TNC-scTNFR2) successfully protected against the neuron loss due to oxidative stress which was proven to be a trigger point for AD [8]. In our study, higher levels of TNR2 in MCI suggested a significant slower conversion to AD which also supported the protective role of TNFR2.

Elevation of soluble TNF was a hallmark of chronic neuroinflammation as well as a number of neurodegenerative conditions including AD, Parkinson's (PD) [22]. Soluble TNF and transmembrane TNF exert different functions under normal and pathological conditions in the CNS. Soluble TNF signals elicit its biological effects primarily though TNFR1 [11], and transmembrane TNF signals primarily function though TNFR2 [10]. Soluble TNFR1 binding of TNF receptor associated death domain (TRADD) initiated cytokine production and caspase-dependent apoptosis [12,17]. Signaling through TNFR2 activates inflammatory and pro-survival signaling pathways through the activation of NF-κB pathway to promote neuron survival [19]. In triple (3xTgAD) transgenic mice lacking soluble TNFR1, exposure to chronic systemic inflammation did not result in intraneuronal accumulation of amyloid immunoreactivity, suggesting that soluble TNFR1 signaling may be an important regulator of APP processing and that pathological elevation of soluble TNFR1 may contribute to pre-plaque pathology and acceleration of cognitive deficits [21].

Table 2
Correlation between TNF-α related inflammatory proteins and tau pathology.

t-tau	HC			MCI			AD		
	r	*P*	FDR	r	*P*	FDR	r	*P*	FDR
TNFR1	**0.637**	**0.000**	**0.000**	**0.652**	**0.000**	**0.000**	**0.632**	**0.000**	**0.000**
TNFR2	**0.259**	**0.014**	**0.042**	**0.616**	**0.000**	**0.000**	**0.674**	**0.000**	**0.000**
TNF-α	0.135	0.203	0.305	0.128	0.171	0.257	**0.315**	**0.006**	**0.011**
ICAM-1	**0.318**	**0.002**	**0.008**	**0.295**	**0.001**	**0.003**	**0.314**	**0.006**	**0.013**
VCAM-1	**0.421**	**0.000**	**0.000**	**0.540**	**0.000**	**0.000**	**0.646**	**0.000**	**0.000**
p-tau	HC			MCI			AD		
	r	*P*	FDR	r	*P*	FDR	r	*P*	FDR
TNFR1	**0.454**	**0.000**	**0.000**	**0.426**	**0.000**	**0.000**	**0.520**	**0.000**	**0.000**
TNFR2	**0.279**	**0.000**	**0.000**	**0.341**	**0.000**	**0.000**	**0.581**	**0.000**	**0.000**
TNF-α	0.012	0.856	0.988	−0.034	0.717	0.896	**0.321**	**0.006**	**0.023**
ICAM-1	**0.245**	**0.000**	**0.000**	**0.352**	**0.000**	**0.000**	0.175	0.143	0.268
VCAM-1	**0.272**	**0.000**	**0.000**	0.175	0.063	0.135	**0.307**	**0.009**	**0.027**

*all results were adjusted for age, education and sex.

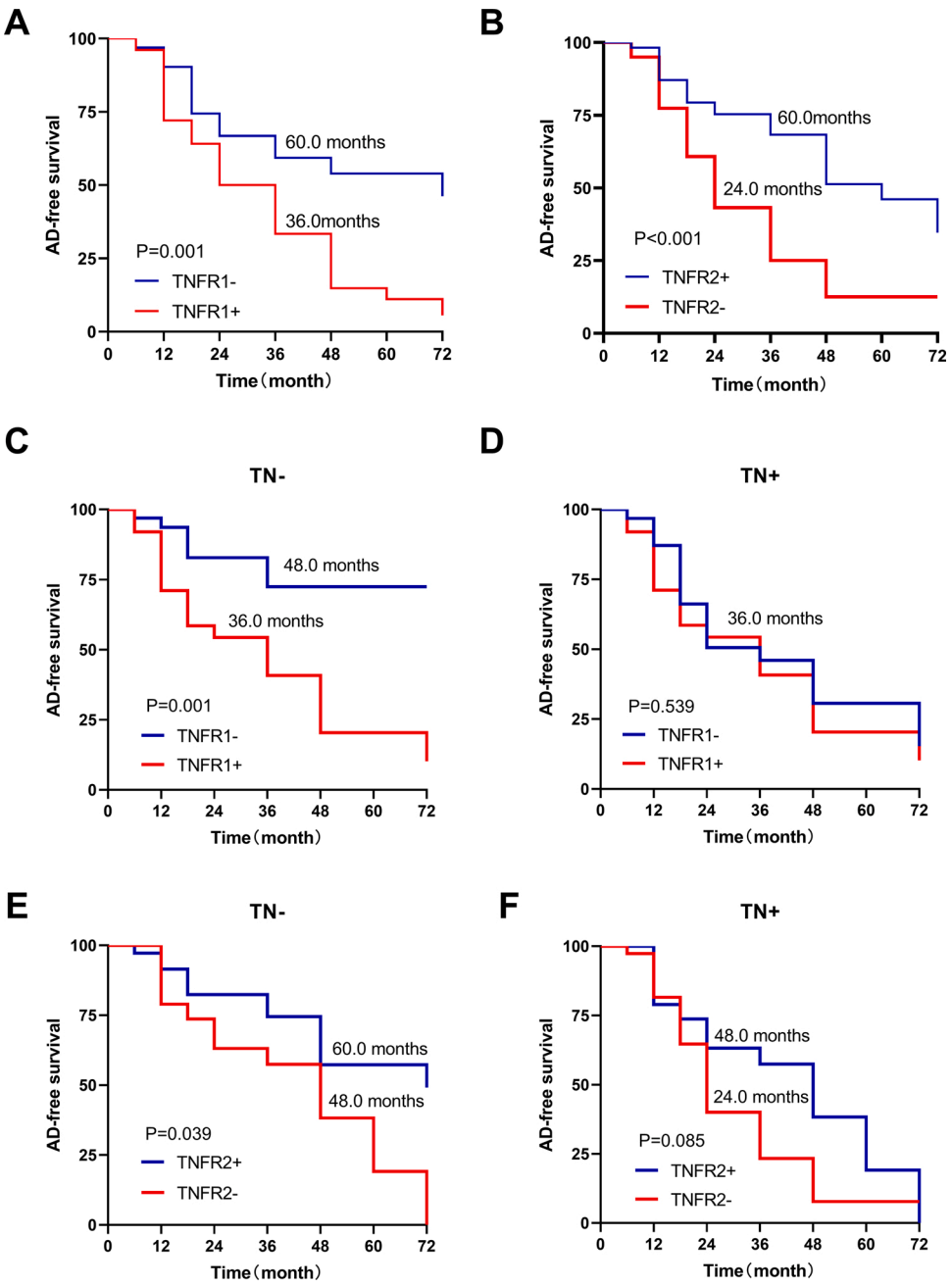

Fig. 1. Kaplan-Meier plot of AD-free survival in MCI patients with different TNFR1 and TNFR2 levels.
A TNFR1 levels related to MCI-to-AD conversion in total MCI patients
B TNFR2 levels related to MCI-to-AD conversion in total MCI patients
C TNFR1 levels related to MCI-to-AD conversion in TN- group of MCI patients
D TNFR1 levels failed to predict MCI-to-AD conversion in TN + group of MCI patients
E TNFR2 levels related to MCI-to-AD conversion in TN- group of MCI patients
F TNFR2 levels failed to predict MCI-to-AD conversion in TN + group of MCI patients
MCI: mild cognitive impairment; N: neurodegeneration biomarker status; T: tau pathology biomarker status.

Our results showed that the TNF-α related inflammatory proteins were more closely associated with tau pathology than Aβ pathology. Considering that CSF t-tau may not necessarily reflect neurodegeneration but could result from physiological production of tau [32], the combination of "T" and "N" groups ensured the exclusion of other cause of neural injuries. One previous study showed that soluble TNF receptors in CSF and serum were associated with t-tau and $A\beta_{1\text{-}40}$ conducted on MCI patients without any research on p-tau and $A\beta_{1\text{-}42}$, which were more representative biomarkers for neurodegeneration [2]. The discordant outcomes from previous studies may also result from due to the different number of participants in the preclinical stage of late-onset AD and the application of the A/T/N classification. Previous research found that patients with AD have significantly lower serum BDNF levels compared to healthy controls [26]. Future research is required to modulate the endogenous production of BDNF and the microglia activation to modulate TNF-α-containing microglia.

The mechanism of how TNF signaling related to tau protein remained to be explained. In AD, the inhibition of TNF-α can revert the effect of tau accumulation in neurites through high affinity binding to TNFR1 [28]. Intracerebroventricular injection of infliximab which was a neutralizing antibody reduced tau phosphorylation, TNF levels and improved visual recognition memory in AD mouse models [34]. However, Long-term global inhibition of TNFR1 and TNFR2 signaling without cell or stage specificity in triple-transgenic AD mice exacerbates tau accumulation and neurofibrillary tangle pathology [25]. Hence, the different roles of TNF receptors might affect AD pathology in complex ways at various stages of disease.

Yet, this study has some limitations. Although the ADNI coohort is a convenient population, our findings still needed other populations to be validated. Second, the supplementary biomarkers and neuroimaging data are in principle applicable for the A/T/N classification of CSF biomarker and further studies based on the biomarkers are needed to confirm our study. Thirdly, the strong correlation with tauopathy might indicate the underlying relationship with the biologically

defined subtypes of AD which required including more MRI and PET data to explore the possible mechanism [7]. At last, the role of TNF receptors has been extensively studied and some contradictory data about the alteration of TNFR1 and TNFR2 also existed [3]. Hence, it is necessary to validate the result for a larger cohort in a long-term follow-up study.

In conclusion, the present study attempted to study CSF TNF-α related inflammatory proteins based on the A/T/N classification framework. We demonstrated in the ADNI cohort that the TNF-α related inflammatory proteins were associated with tau pathology and neurodegeneration. What's more, TNFR1 and TNFR2 can be potential biomarkers for the prediction of MCI-to-AD conversion.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Aonan Zhao: Software, Visualization, Investigation, Writing - original draft. **Yuanyuan Li:** Methodology, Software, Writing - review & editing. **Yulei Deng:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Acknowledgements

We would like to thank all the researchers and participants in the ADNI initiative. 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

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neulet.2020.135392.

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