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Research article

# Cerebrospinal fluid levels of YKL-40 in prodromal Alzheimer's disease☆

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ABSTRACT

Recently, cerebrospinal fluid (CSF) YKL-40 levels were reported to be a promising candidate biomarker of glial inflammation in Alzheimer's disease (AD). To detect how APOE ε4 affects CSF YKL-40 levels in cognitively normal (CN) states, mild cognitive impairment (MCI) and AD dementia, data from 35 CN subjects, 63 patients with MCI, and 11 patients with AD from a cross-sectional study in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were investigated. The results showed that CSF YKL-40 concentrations were increased in the AD dementia group than in the CN group. CSF YKL-40 levels were higher in APOE ε4 carriers than in noncarriers with MCI. No statistically significant difference was found in CSF YKL-40 levels between APOE ε4 carrier and noncarriers in AD and CN subjects. CSF YKL-40 concentrations were tightly related to CSF tau and p-tau concentrations in the MCI group. Analysis implied that APOE ε4 might affect CSF YKL-40 levels in MCI subjects, suggesting a crucial role of APOE ε4 in neuroinflammation in detecting individuals who might convert to AD from MCI and, thus, as an effective predictive factor.

## 1. Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disease with occult onset [1,2]. CSF levels of Aβ and tau protein are now deemed the two most obvious biomarkers indicating amyloid deposition and the severity of neurodegeneration in the pathophysiological process of AD [3,4]. Meanwhile, neuroinflammation has been treated as a possible pathophysiological event in the occurrence of AD [5,6]. YKL-40, or chitinase-3-like protein 1 (CHI3L1), has been reported as a promising candidate marker of glial inflammation in AD [7–9]. Previous studies have revealed that CSF YKL-40 levels were higher in AD groups than in cognitively normal (CN) groups [7,10,11] or in subjects suffering from mild cognitive impairment (MCI) [10,12–14]. This phenomenon is consistent with the potential role of astrocytosis in early AD pathogenesis [15]. In contrast, some researchers reported that CSF YKL-40 levels were not significantly increased in MCI and AD patients compared with those in CN subjects [16]. Apolipoprotein E (APOE) ε4, which was proven to be linked to up to 50% of AD cases, plays a crucial role in the pathophysiology of AD [17,18]. However, the correlation between APOE ε4 and CSF YKL-40 levels and alterations in other biomarkers is still unknown. Inconsistent results about the CSF YKL-40 levels among AD, MCI and cognitively normal subjects have been reported. Therefore, this inconsistent results drive us to design the current study in order to analyze how APOE ε4 affects CSF YKL-40 concentrations in CN states, MCI and AD using the Alzheimer's Disease Neuroimaging Initiative (ADNI) platform, which is a publicly available database.

## 2. Methods

### 2.1. ADNI

Patients' data were downloaded from the ADNI database (adni.loni.usc.edu). Data management staff were blinded to the subjects' information in the tests. The ADNI was built in 2003 as a public-private partnership organized by Principal Investigator Michael W. Weiner,

☆ Data used in the 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 the data but did not participate in the analysis or writing of this report. A complete list of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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MD. The main purpose of the ADNI was to combine data from serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biomarkers, and clinical and neuropsychological assessments to quantitatively describe the progression of MCI and early-stage AD. It is a global research cooperation of the ADNI to actively assist in investigating and developing treatments that could potentially slow or stop the occurrence of AD. Participants in this database were collected from up to 50 sites throughout Canada and the USA. Further details are available at www.adni-info.org. Each ADNI site has institutional review board approval and has received written informed consent from all subjects or authorized representatives.

### 2.2. Subjects

Based on sharing available baseline CSF YKL-40, Aβ42, total tau, and p-tau level information, CN subjects and those with MCI and AD dementia from ADNI-1 were included in the analysis. Inclusion/exclusion standard details are given at http://www.adni-info.org. The subjects involved in the analysis met the following criteria: (1) being aged between 55 and 90 years; (2) having finished at least 6 years of school education; (3) being fluent in Spanish or English; and (4) being free of serious neurological diseases other than AD. CN subjects were defined as subjects with Mini-Mental State Examination (MMSE) score ≥ 24 and Clinical Dementia Rating (CDR) score of 0. MCI patients were defined as subjects who met all the following criteria, including MMSE score ≥ 24; loss of objective memory, as reflected in the scores of delayed recall in the Wechsler Memory Scale Logical Memory II (> 1 standard deviation (SD) below the normal mean); CDR of 0.5; preserved activities of daily living; and the absence of dementia. AD dementia patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) standard for probable AD and had MMSE score between 20 and 26 and CDR between 0.5 and 1.0 [19]. In total, 109 participants (35 who were CN, 63 with MCI, and 11 with AD) were involved in the current research.

### 2.3. Neuropsychological assessment

Different domains of cognition were assessed in all the participants by a standardized cognitive evaluation that included the following dimensions: (1) the MMSE [20], Alzheimer's Disease Assessment Scale-cognitive subscale 13 (ADAS-13) [21], and Global Clinical Dementia Rating Scale (CDR-SB) [22] to reflect global cognitive function; (2) the Rey Auditory Verbal Learning Test (RAVLT), including 5-minute delayed recall (RAVLT-immediate recall), 30-minute delayed recall (RAVLT-delayed recall), and yes-no recognition (RAVLT-recognition), to reflect memory; (3) the Trail Making Test-A and B (TMT-A/B) [23] to reflect attention/executive function; (4) animal fluency and the 30-item Boston Naming Task (BNT-30) [24] to reflect language function; (5) the Functional Assessment Questionnaire (FAQ) [25] and Neuropsychiatric Inventory (NPI) [26] to reflect psychosocial function.

### 2.4. APOE genotyping

APOE (gene map locus 19q13.2) genotypes of the research participants were obtained from the previously mentioned ADNI database. All participants were divided into two groups: the APOE ε4 carriers group, with the phenotypes ε2/ε4, ε3/ε4, and ε4/ε4, and the APOE ε4 noncarriers group, with ε2/ε2, ε2/ε3, and ε3/ε3 genotypes.

### 2.5. Measurements of YKL-40, Aβ42, tau, and p-tau levels in CSF

CSF YKL-40 levels (Unit: ng/mL) were determined by the MicroVue YKL-40 ELISA assay (Quidel Corp.) at Washington University [7]. CSF Aβ42, total tau, and p-tau quantitation (unit: pg/mL) was performed in the ADNI biomarker core (University of Pennsylvania) through the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) with the INNOBIA AlzBio3 kit (Fujirebio, Ghent, Belgium), which has been described in previous publications [27–29]. More information on how CSF was obtained and on the determination methods and quality control processes of the ADNI is available at www.adni-info.org.

### 2.6. Measurements of the volumes of Hippocampus, entorhinal cortex, fusiform and medial temporal lobe

Detailed information about ADNI neuroimaging standardized steps can be found in previous publications [30]. ADNI MRI data were obtained using 3 T MRI scanners. The FreeSurfer version 5.1 image analysis suite (http://surfer.nmr.mgh.harvard.edu/) [31] was applied to reflect cortical reconstruction and volumetric segmentation, as described in previous reports [32–35]. In this study, entorhinal cortex (EC), hippocampus, and fusiform and medial temporal lobe atrophy (MTA) volumes were assessed. More information about ADNI imaging protocols is available at http://adni.loni.usc.edu/methods/documents/mri-protocols/.

### 2.7. Statistical analysis

Demographic and clinical data were compared among the CN, MCI and AD subjects. Continuous variables using one-way ANOVA were expressed as the mean ± standard deviation (SD). The frequencies of categorical variables were examined using the chi-square test, and skewed distributed variables represented by median (M) and interquartile range (IQR) were tested by the Kruskal-Wallis test. Statistical differences of CSF YKL-40 concentrations between APOE ε4 carriers and APOE ε4 noncarriers were determined using two-tailed Student's *t*-test. The association between CSF YKL-40 levels and other variables in the sample was analyzed using Spearman's correlation test. SPSS software (version 23.0; IBM SPSS) was used to perform the statistics in the study. Statistically significant difference was acknowledged if $P < 0.05$, and all tests were two-sided unless otherwise specifically noted in the research. Figures were obtained from GraphPad Prism 6.

## 3. Results

### 3.1. Demographic features of the subjects

Table 1 summarizes the demographic characteristics and clinical findings of the participants. The results revealed that no statistically significant differences (all $P > 0.05$) existed in the ages or the extent of MTA among these three diagnostic groups (CN, MCI and AD subjects). A relatively higher proportion of females was found in the AD group than in the other two groups ($P = 0.006$). The percentage of APOE ε4 carriers in the AD, MCI and CN groups was 72.7% vs. 54% vs. 22.9%, respectively ($P = 0.002$). Not surprisingly, the results of neuropsychological assessments (including global cognitive function, memory, attention/executive function, and language) were significantly different among these three groups, and the worst results were found in the AD group. In addition, significant differences among CSF Aβ42, total tau, and p-tau levels were detected across the three groups ($P < 0.001$, $P = 0.004$, and $P < 0.001$). There were significantly smaller hippocampus, entorhinal cortex and fusiform lobe volumes in AD patients ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively).

### 3.2. Concentrations of CSF YKL-40 in APOE ε4 carriers

The CSF YKL-40 concentration was significantly increased in AD patients compared with that in CN subjects (mean, AD > MCI > CN, 467.1 vs. 374.2 vs. 335.0 ng/mL, $P = 0.036$, $P = 0.085$, $P = 0.199$, Fig. 1). In addition, to investigate the relationship between the APOE ε4 genotype and CSF YKL-40 concentration, the concentrations of CSF YKL-40 between APOE ε4 carriers and noncarriers in the 3 categories

**Table 1**
Demographic and clinical characteristics of the study subjects.

| Variable | CN (n = 35) | MCI (n = 63) | AD (n = 11) | P value |
|---|---|---|---|---|
| Age, years | 75.9 (5.2) | 73.8 (6.4) | 73.6 (5.6) | 0.214 |
| Education, years | 16 (13–18) | 16 (14–18) | 13 (12–16) | 0.014 |
| Female [n (%)] | 20 (57.1) | 18 (28.6) | 7 (63.6) | 0.006 |
| APOE ε4 carriers [n (%)] | 8 (22.9) | 34 (54) | 8 (72.7) | 0.002 |
| MMSE | 29 (29–30) | 27 (26–28) | 24 (22–25) | < 0.001 |
| ADAS-13 | 8.9 (3.7) | 18.3 (6.4) | 27.9 (7.5) | < 0.001 |
| CDR-SB | 0 (0-0) | 1.5 (1.0–2.0) | 4.0 (3.0–5.5) | < 0.001 |
| RAVLT-immediate recall | 8 (7–10) | 3 (1–6) | 1 (1–2) | < 0.001 |
| RAVLT-delayed recall | 8 (6–10) | 1 (0–4) | 0 (0–3) | < 0.001 |
| RAVLT-recognition | 14 (12–15) | 10 (7–13) | 9 (5–10) | < 0.001 |
| TMT-A | 34 (29–38) | 39 (30–50) | 43 (36–74) | 0.028 |
| TMT-B | 77 (67–103) | 102 (74–130) | 182 (121–300) | < 0.001 |
| BNT-30 | 28 (26–30) | 28 (25–29) | 23 (23–28) | 0.008 |
| Animal fluency | 19.1 (5.5) | 16.0 (4.1) | 12.6 (4.5) | < 0.001 |
| NPI | 0 (0-0) | 0 (0-0) | 0 (0–1) | 0.010 |
| FAQ | 0 (0-0) | 2 (0–5) | 10 (7–20) | < 0.001 |
| CSF Aβ42 (pg/mL) | 1245 (744–1643) | 658 (521–958) | 511 (351–618) | < 0.001 |
| CSF tau (pg/mL) | 239.5 (77.2) | 303.1 (114.9) | 354.7 (147.3) | 0.004 |
| CSF p-tau (pg/mL) | 22.1 (8.1) | 30.1 (13.3) | 36.4 (14.7) | < 0.001 |
| Hippocampus ($mm^3$) | 7219.3 (807.9) | 6285.0 (1045.0) | 5551.5 (1010.9) | < 0.001 |
| Entorhinal cortex ($mm^3$) | 3794.9 (761.7) | 3360.1 (795.7) | 2554.5 (621.3) | < 0.001 |
| Fusiform lobe ($mm^3$) | 16829.5 (2084.4) | 16951.3 (2052.9) | 14223.2 (2008.3) | < 0.001 |
| MTA ($mm^3$) | 19178.5 (2761.1) | 19116.2 (2600.7) | 17344.5 (2979.3) | 0.115 |

CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; APOE: Apolipoprotein E; MMSE: Mini-Mental State Examination; ADAS-13: Alzheimer's Disease Assessment Scale-cognitive subscale 13; CDR-SB: Global Clinical Dementia Rating Scale; RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test; BNT-30: Boston Naming Task; NPI: Neuropsychiatric Inventory; FAQ: Functional Assessment Questionnaire; CSF: cerebrospinal fluid; MTA: Medial temporal lobe atrophy.
Data are presented as the mean ± SD for one-way ANOVA for normally distributed continuous variables and as the median (M) and the interquartile range (IQR) for the Kruskal-Wallis test for skewed distribution variables. For gender and genotype distribution, values are presented as numbers (%) using the chi-square test.

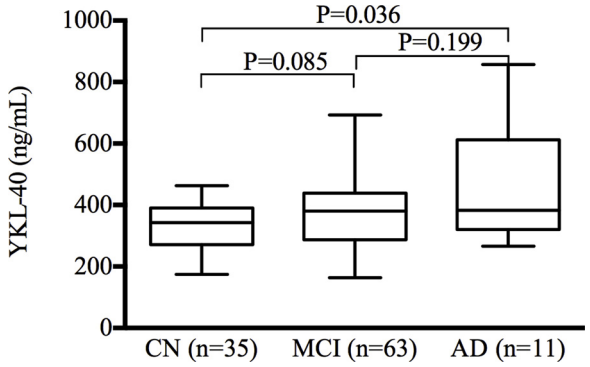


**Fig. 1. Comparison of CSF YKL-40 concentrations in CN, MCI and AD groups.** *P value tested by the Kruskal-Wallis test.*

were compared. As demonstrated in Fig. 2A, the concentrations of CSF YKL-40 in APOE ε4 carriers in the MCI group were significantly higher than those of noncarriers (P = 0.032). However, no statistically significant difference was found in the CN or AD groups (all P > 0.05). To explore how APOE ε4 status affects levels of CSF YKL-40, the relationship between APOE ε4 carrier status and CSF YKL-40 was investigated. Fig. 2B indicates that concentrations of CSF YKL-40 increased in a gene dose-dependent manner.

### 3.3. Correlations between CSF YKL-40 and other variables

With the aim of determining whether the variation in CSF YKL-40 concentrations is associated with Aβ42, tau and p-tau levels in AD, the correlations between CSF YKL-40 and other CSF biological markers were examined in all diagnostic groups (Table 2) using Spearman's correlation analyses. No significant correlations were found between the levels of CSF YKL-40 in the CN group (correlation = 0.144, P = 0.410; correlation = 0.166, P = 0.342; correlation = 0.174, P = 0.318). In the MCI group, it was found that CSF YKL-40 levels were positively related to tau and p-tau levels (correlation = 0.380, P = 0.002; correlation = 0.306, P = 0.015). In the AD group, no significant correlations were found between the concentrations of CSF YKL-40 and Aβ42, tau and p-tau (correlation = 0.509, P = 0.110; correlation = 0.382, P = 0.247; correlation = 0.336, P = 0.312).

## 4. Discussion

Inflammation is thought to contribute to AD pathogenesis [6,36]. In the central nervous system (CNS), astrocytes and microglia, which express YKL-40 to modulate neuroinflammation [7,37], produce most of the APOE.

In the present study, a higher concentration of CSF YKL-40 was detected in the AD dementia group than in the CN group, indicating that elevated CSF YKL-40 levels may be a critical characteristic of AD pathogenesis. Although not statistically significant, our data still demonstrated higher CSF YKL-40 levels in MCI patients than in CN subjects. The results were consistent with previous studies [7,14,38].

Moreover, CSF YKL-40 levels were significantly higher in APOE ε4 carriers than in noncarriers with MCI. However, the level of CSF YKL-40 did not appear to vary significantly between APOE ε4 carriers and APOE ε4 noncarriers in CN and AD subjects. These results were in accordance with findings from prior studies [7,10,14,38] and indicate a role of neuroinflammation in the early stage of AD and even in MCI. To examine how APOE ε4 affects levels of CSF YKL-40, subjects involved in the research were further divided into groups of APOE ε4 (-/-), APOE ε4 (+/-) or APOE ε4 (+/+) individuals. As expected, a statistically significant positive association was observed between CSF YKL-40 concentrations and the number of APOE ε4 genes in a seemingly dose-dependent manner. The existence of APOE ε4 might also be a predictive factor of the progression from MCI to AD. This result suggests that elevated CSF YKL-40 levels in APOE ε4 carriers with MCI might indicate early activity of the AD pathophysiology.

Furthermore, it was found that in MCI subjects, the CSF YKL-40 concentration was strongly correlated with CSF total tau and p-tau concentrations. This relationship strongly supports the assumption that CSF YKL-40 levels could be applied as a biomarker to characterize sensitivity to AD-related biological variations in prodromal AD. Therefore, using these multiple biomarkers could potentially allow us to monitor the pathophysiological phase of the disease, to identify MCI patients who are at higher risk of progressing into AD [39] and to enhance the accuracy of diagnosis [40].

A number of limitations in this research should be addressed. First, it is a simple cross-sectional study. Though correlations were observed between YKL-40, tau and p-tau protein levels, a causal relationship could not be determined between the different biomarkers. Therefore, further longitudinal studies are needed to confirm the interaction between APOE ε4, neuroinflammation and cognitive decline. Second, in the AD group, YKL-40 levels between APOE ε4 carriers and noncarriers demonstrated no statistically significant difference. One possible reason for this result could be the comparatively small sample size of AD subjects. Another possible reason is that a neuroinflammation plateau may have been reached in AD patients.

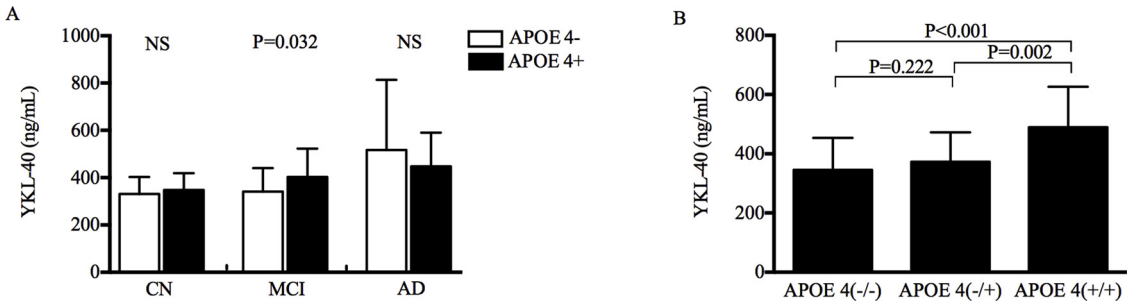


**Fig. 2. Comparison of CSF YKL-40 levels in APOE ε4 carriers and APOE ε4 noncarriers in the CN, MCI and AD groups.** *P value tested by two-tailed Student's t-test* in Fig. 2A; P value tested by one-way ANOVA in Fig. 2*B*.

**Table 2**
Correlations among CSF YKL-40 levels and Aβ42, tau and p-tau across the three groups.

| YKL-40 | Aβ42 | | Tau | | P-tau | |
|---|---|---|---|---|---|---|
| | Correlation | P-value | Correlation | P-value | Correlation | P-value |
| CN | 0.144 | 0.410 | 0.166 | 0.342 | 0.174 | 0.318 |
| MCI | 0.071 | 0.580 | 0.380** | 0.002 | 0.306* | 0.015 |
| AD | 0.509 | 0.110 | 0.382 | 0.247 | 0.336 | 0.312 |

CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease.
Associations were measured by Spearman's correlation analyses.
* $P < 0.05$.
** $P < 0.01$.

## 5. Conclusion

In summary, the CSF YKL-40 concentration was shown to be higher in APOE ε4 carrier MCI patients than in noncarrier MCI patients. Thus, CSF YKL-40 levels could be used as a potential inflammation biomarker to detect individuals who might convert from MCI to AD. Further larger sample studies are needed to determine the correlation between CSF YKL-40 levels and amyloid deposition and neurodegeneration in the prognosis of progression from prodromal MCI to dementia.

## Ethical approval

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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## Declaration of Competing Interest

The authors declared that they had no conflicts of interest.

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