

Differences in C-reactive Protein Level in Patients with Alzheimer's Disease and Mild Cognitive Impairment

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Abstract

Background: Numerous studies are supporting the hypothesis that neuroinflammation may play an important role in the pathogenesis of Alzheimer's disease (AD). Reports on increased serum C-reactive protein (CRP) concentration as a risk factor for AD are conflicting. We examined the differences in the serum CRP levels in patients with AD and mild cognitive impairment (MCI) and normal controls.

Methods: We enrolled 56 subjects with AD, 29 subjects with MCI, and 24 healthy control subjects in the study. A total of 109 subjects agreed to blood sampling to evaluate serum CRP levels. A dementia screening test was performed using the Korean version of the Mini-Mental Status Examination. Inclusion criteria for MCI used the Petersen guidelines

Results: Among AD, MCI, and control groups, there were no significant differences in serum CRP levels. There was no association between CRP levels and MMSE scores in AD and MCI groups. Also CRP level did not significantly correlated with age or level of education.

Conclusion: We observed no significant association between serum CRP values and the diagnosis of MCI and AD. Further longitudinal studies involving larger study population are needed to clarify possible role of CRP in the pathogenesis of this disease.

Keywords: Alzheimer's disease; Mild cognitive impairment; C-reactive protein

Introduction

Alzheimer's disease (AD) is a progressive and most common type of dementia. Main symptoms of AD are cognitive decline, memory loss, altered behavior and language deficit [1]. As they progress in time, these symptoms lead to severe impairment in daily functioning and in later stages AD patients require total care [2]. This disease is neuropathologically characterized by presence of β amyloid and neurofibrillary tangle.

Mild cognitive impairment (MCI) is used when cognitive changes are more frequent or exceed what's expected for an individual at a particular age. It can be thought of as a stage between normal forgetfulness due to age and the development of dementia. In MCI, memory problems may be minimal to mild, and hardly noticeable to the individual. Some MCI can be the sign of the dementia, early detection, diagnosis and management is considerably important.

MCI and AD is multifactorial but its etiology and pathophysiology are still not fully understood. Recent studies suggest that inflammation is also associated with cognitive decline and with MCI [3]. The role of inflammation in dementia may be mediated by several mechanisms including an acute phase response to damaged tissue or a response to amyloid β [4]. There have been several studies linking CRP specifically to AD. C-reactive protein, composed of five 23kDa subunits, is a hepatically derived pentraxin that has a crucial role in the human

immune system [5], and has been widely considered as a sensitive biomarker for systemic inflammation [6]. It is transcriptionally regulated by IL-6 as well as by interleukin-1 beta (IL-1 β), and measures of serum CRP levels are used clinically as a biomarker of inflammation [7]. High serum concentration of CRP has been associated with increased risk for adverse cardiovascular events and cognitive impairment and dementia [8,9]. CRP has been detected in the senile plaques and neurofibrillary tangles of patients with Alzheimer's disease. However, the predictive value of CRP for cognitive outcomes is unclear in patients with mild cognitive impairment (MCI), a prodrome for dementia.

Studies of brain tissues from patients with AD consistently show evidence of inflammation, as indicated by the presence of activated microglia, activated complement factors, cytokines, and other inflammatory proteins [4]. Elevated levels of inflammatory proteins have also been found outside of the brain in patients with AD [10]. CRP has ability to activate complement system in an antibody-independent manner; CRP is thought to be an important part of innate immune system [11].

Previous studies reported inconsistent findings regarding the relationship between CRP and AD. Histopathological studies of AD brain tissue demonstrate widespread CRP immunoreactivity in areas with AD pathology. Mid-life elevations in serum CRP have been reported as a risk factor for the development of AD in the Honolulu-Asia Aging Study (1991-1996) [12]. Paradoxically, however, recent cross-sectional studies by Nilsson et al. [13] and O'Bryant et al. [14]

found that serum CRP levels are reduced in patients with established AD. Though the significant decrease in CRP among AD cases has now been cross-validated across multiple cohorts, the impact of ethnicity on the CRP-AD link has not been investigated [15]. Prior work has shown that CRP levels vary according to ethnicity and ancestry with CRP levels being higher among Hispanics when compared to non-Hispanic whites [16].

Identifying the factors that potentially affect the cognitive function in patients with MCI is of crucial importance since a large portion of MCI patients could develop dementia in a few years after the diagnosis. If efficacious intervention is initiated promptly at the early stage, dementia could be delayed or even prevented in these patients. The purpose of the present study was to further investigate the association between the level of serum CRP and AD and MCI in the Korean elderly.

Methods

Subjects

We enrolled 56 subjects with AD, 29 subjects with MCI, and the 24 healthy control subjects in the current study. Patients in all three groups underwent physical, neurological, and psychiatric examinations. All subjects provided informed consent prior to participation. The study protocol was also approved by the Institutional Review Board (IRB) of Ilsanpaik hospital.

A dementia screening test was performed using the Korean version of the Mini-Mental Status Examination (MMSE-K) and for the final diagnosis of AD, the diagnostic standard of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) was used. Inclusion criteria for MCI used the Petersen guidelines [17]: i) complaint of defective memory only (amnestic MCI) or memory plus another cognitive domain (multidomain MCI), ii) normal activities of daily living, iii) normal general cognitive function, iv) abnormal memory function of age, and v) absence of dementia.

Patients with a history or the current presence of major physical illness such as uncontrolled diabetes, obstructive pulmonary disease, cardiovascular disease, comorbidity of primary psychiatric or neurologic disorder, and alcohol or substance abuse were excluded from the study. A total of 109 subjects agreed to blood sampling to evaluate serum CRP levels.

Measurement of CRP serum concentration

Non-fasting samples were collected with 10mL serum-separating vacutainers tubes at the time of interview. Samples were allowed to clot at room temperature for 30 minutes in a vertical position before being centrifuged at 1300× g for 15 minutes. A enzyme-linked immunosorbent assay (ELISA) kit was used to determine CRP concentration.

Statistical analyses

Chi-square tests and/or analyses of variance (ANOVAs) were conducted to assess the demographic and clinical data. Comparisons among the experimental groups on continuous variables were performed using univariate ANOVAs followed, when appropriate, by post-hoc testing. The level of statistical significance was set at $p < 0.05$. Potentially confounding variables were incorporated into

subsequent regression analyses. Regression analysis was used to determine the relationship between CRP levels and MMSE score in AD and MCI; age and education were entered as covariates.

Results

Demographic and clinical data

Clinical and demographic data of the AD, MCI, and control groups are shown in Table 1. A chi-square analysis revealed that there was no significant difference in gender distribution among the groups ($\chi^2=4.052$, $df=2$, $p=0.132$). As compared to the control group, subjects in the AD group were significantly older ($p < 0.01$) but there were no significant age differences between either the AD group ($p > 0.05$) or the control group ($p > 0.05$) and the MCI group. Educational level was significantly higher in the control group than in the AD group ($p < 0.05$) and the MCI group ($p < 0.05$).

The mean MMSE-K score of the AD group was significantly lower than that for the other groups ($p < 0.01$), but there was no significant difference in MMSE-K scores between the MCI group and the control group ($p > 0.05$). In addition, the mean Clinical Dementia Rating (CDR) score of the AD group was significantly higher than that for the other groups ($p < 0.05$), but there was no significant difference in CDR scores between the MCI group and the control group ($p = 0.051$).

CRP serum levels in AD, MCI, and control groups

CRP serum levels in the AD, MCI, and control groups are shown in Figure 1. Among these groups, there was no significant difference in serum CRP levels ($df=2$, $F=1.260$, $p=0.288$). Post-hoc comparisons revealed that there were no significant differences between AD, MCI and control group.

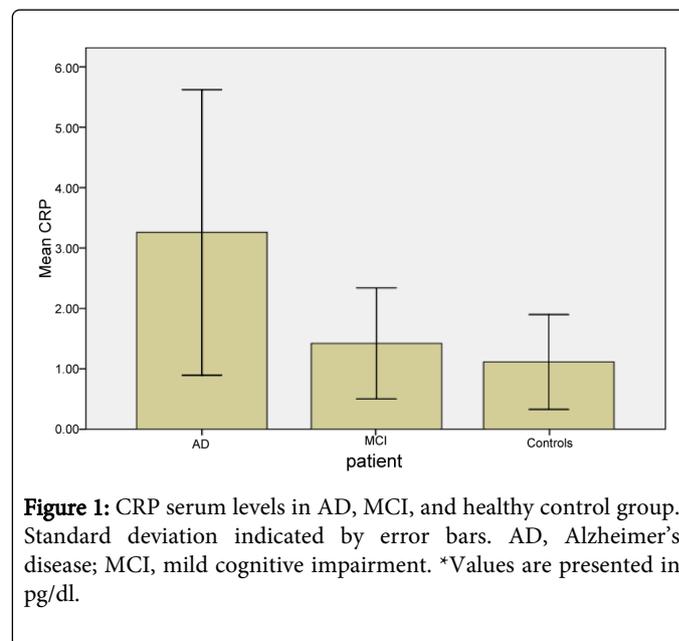


Figure 1: CRP serum levels in AD, MCI, and healthy control group. Standard deviation indicated by error bars. AD, Alzheimer's disease; MCI, mild cognitive impairment. *Values are presented in pg/dl.

The Mini-Mental State Examination score and serum CRP concentration

There was no association between CRP levels and MMSE scores in AD ($B = -0.69$, $SE = 0.08$, $p = 0.394$) and MCI groups ($B = -0.39$, $SE = 0.167$,

p=0.816). Also CRP level did not significantly correlated with age or level of education.

Discussion

Numerous studies are supporting the hypothesis that neuroinflammation may play an important role in the pathogenesis of AD [11,18-20]. However, the impact of inflammation on AD development is less clear. Reports on increased serum CRP concentration as a risk factor for AD are conflicting. We observed no significant association between serum CRP values and the diagnosis of MCI and AD. These results are consistent with the previous studies by Dik et al. [21]. Two other cross-sectional studies found the significant association between CRP and AD [10,22]. However, there were many articles suggesting increased CRP in Alzheimer's disease. Results of Honolulu-Asia Aging study have shown that men with elevated baseline levels of CRP had 3-fold significantly increased risk for all types of dementias [23]. Dimopoulos et al. [24] reported significantly higher serum concentration of adhesion molecules and CRP in patients with dementia compared to controls. Elevated serum levels of adhesion molecules and CRP are suggesting that low-grade chronic inflammation may lead to cognitive impairment and can also predispose elderly for the development of dementia. Gupta et al. [25] who found elevated serum CRP levels in patients with AD. In present study, although there was no statistically significant difference, we found some tendency showing higher CRP levels in Alzheimer's disease than in normal control. This suggests that Alzheimer's disease might be associated with inflammation process.

On contrary, the studies by Karin Nilsson et al. [13] and O'Bryant et al. [14] have observed decreased serum CRP levels in patients with AD compared to non-AD controls or other diagnostic groups of elderly patients with mental illness [13,14,26]. However, the study of Karin Nilsson et al. [13] that elevated CRP in patients with AD was associated with lower cognitive function, shorter survival time, despite the overall lower CRP level as compared to other patients with mental illness, suggest the presence of inflammatory activity in a subgroup of patients with AD.

One of the possible explanations for increased level of CRP in patients with probable Alzheimer's disease might be the presence of accelerated atherosclerosis and chronic low-grade inflammation in these patients. It has previously been reported that elevated serum CRP concentration is associated with atherosclerosis and increased cardiovascular risk [27]. Cerebral atherosclerotic changes may interrupt the integrity of the frontal-subcortical circuit and thus result in cognitive impairment. Increased CRP concentrations and chronic inflammation have been proposed as an underlying mechanism associated with dementing illness [28,29] and depression [30,31]. CRP has been detected in the senile plaque and neurofibrillary tangles of patients with AD [9,32]. Also, Strandberg et al. [33] have proposed as the most likely explanation for increased serum CRP concentration in patients with dementia their proneness to minor trauma and infections that leads to systemic acute-phase response.

Also, Gelinx et al. [34] study demonstrated that serum CRP levels were associated with cognitive function and development of dementia in MCI patients. Patients with high levels of serum CRP had significantly increased rate of cognitive decline, and increased risk for dementia in MCI during the two-year follow-up. Recent studies suggest that inflammation is also associated with cognitive decline [11,35] and with MCI [36]. However, the precise role of inflammation

is uncertain and several questions remain. Especially it is important to understand the associations of inflammation with MCI subtypes because of potential etiological differences [37,38]. In our study, there was no association between CRP levels and MMSE scores in AD and MCI groups. Also, this study has a limitation in that we didn't categorize the subtypes of MCI.

There are still many unanswered questions related to underlying impact of inflammatory processes on cognitive decline. It is possible that discordant results on serum CRP concentration in patients with AD are reflection of numerous confounding factors such as heterogeneous patient's population, different protocols in serum collection, small sample size or presence of other inflammatory disease. This study also has its limitations. Since studies on serum CRP concentration in patients with AD have provided conflicting results, further longitudinal studies involving larger study population are needed to clarify possible role of CRP in the pathogenesis of this disease.

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