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Association of C-reactive protein with mild cognitive impairment

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Abstract

Background: Inflammation is proposed to play a role in the development of Alzheimer's disease, and may also be involved in the pathogenesis of mild cognitive impairment (MCI). This study examined the association of inflammatory markers in serum or plasma with prevalent MCI and MCI subtypes in a population-based sample.

Methods: Olmsted County, MN, residents aged 70–89 years on October 1, 2004, were evaluated using the Clinical Dementia Rating Scale, a neurological evaluation, and neuropsychological testing. Information ascertained for each participant was reviewed by an expert panel of neuropsychologists, physicians, and nurses, and a diagnosis of normal cognition, MCI, or dementia was made by consensus. C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis alpha (TNFα), and adiponectin were measured at baseline.

Results: Among 313 subjects with MCI and 1570 cognitively normal subjects, a CRP level in the upper quartile (>3.3 mg/L) was significantly associated with MCI (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.00–2.01) and with nonamnestic MCI (OR, 2.05; 95% CI, 1.12–3.78) after adjusting for age, sex, and years of education. However, there was no association with amnestic MCI (OR, 1.21; 95% CI, 0.81–1.82). No association was observed with the other inflammatory markers.

Conclusions: Plasma CRP is associated with prevalent MCI and with nonamnestic MCI in elderly, nondemented persons in a population-based setting. These findings suggest the involvement of inflammation in the pathogenesis of MCI.

Keywords: C-reactive protein; Interleukin-6; Adiponectin; Inflammation; Cytokines; Mild cognitive impairment; Cross-sectional; Population-based

1. Introduction

Several studies have suggested that inflammation may play a role in dementia, including Alzheimer's disease (AD) [1–5]. Inflammatory markers have been demonstrated in the AD brain [1,2,6,7]. Recent studies suggest that inflammation is also associated with cognitive decline [8,9] and with mild cognitive impairment (MCI), a transitional stage between normal cognitive aging and dementia [10]. The precise role of inflammation, however, is uncertain and several questions remain. Is inflammation the cause or a consequence of the disease process? Is inflammation simply a marker for some

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other etiologic process? When does inflammation become evident in the pathologic process of the development of cognitive impairment? What is the association of inflammation with amyloid β, neurofibrillary tangles, and neurodegeneration? Most relevant to the present study, does degree of inflammation in the brain correlate with cognitive impairment and with circulating levels of markers of inflammation?

The role of inflammation in dementia may be mediated by several mechanisms including an acute phase response to damaged tissue [11] or a response to amyloid β. Several markers of inflammation including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFα) have been implicated in the pathogenesis of AD and other dementias [4,12]. These markers of inflammation are also associated with vascular disease [13]. Low levels of adiponectin, an anti-diabetic and anti-inflammatory hormone [14–16], have been associated with vascular disease, and thereby may be associated with cognition.

Several investigators have assessed the association of inflammation with cognitive function, yet varied criteria have been used to assess cognition [3,9]. Relatively few studies have assessed the association with mild cognitive impairment as defined using previously published criteria [10], and studies typically have not distinguished between the affected cognitive domains or the MCI subtypes: amnestic (a-MCI) and nonamnestic (na-MCI) MCI. It is important to understand the associations of inflammation with MCI subtypes because of potential etiological differences [17,18]. It is suggested that the *Apolipoprotein E* (*APOE*) ε4 allele may modify the association between inflammation and cognitive decline; specifically, the association between baseline inflammation and cognitive decline was stronger in subjects with the *APOE* ε4 allele than in noncarriers [9]. Other cross-sectional studies have suggested that *APOE* ε4 is associated with lower levels of inflammation [19,20]. Our previous investigations in the present study sample have shown significant associations between *APOE* ε4 allele status and a-MCI as well as specific impairment in the memory domain [21]; this is consistent with the hypothesis that a-MCI has a primarily neurodegenerative etiology, and progresses to AD [22]. In contrast, *APOE* ε4 allele status was not associated with na-MCI, but vascular diseases were significantly associated with na-MCI and with nonmemory cognitive domains [21,23], consistent with the hypothesis that na-MCI progresses to nondegenerative or vascular dementias [22]. Given these previous findings, we hypothesized that we would observe either no association or only a weak cross-sectional association of inflammation with a-MCI at this phase of the AD disease spectrum. On the other hand, because the association of inflammation with cognitive impairment may be mediated by vascular disease [8,24], we hypothesized that inflammation would be associated with na-MCI. Thus, we investigated the associations of inflammatory markers with MCI and MCI subtypes in a population-based sample of subjects who have been characterized for MCI, normal cognition, and dementia using specified published criteria at the time of the evaluation.

2. Methods

The details of the study design and participant selection have been previously published [25]. Briefly, we enumerated all Olmsted County, MN, residents aged 70–89 years old on October 1, 2004, through the medical records-linkage system of the Rochester Epidemiology Project [26]. We used a random, stratified sampling scheme with equal allocation by age and sex to identify 5233 potential participants. We excluded subjects who died before their initial contact (n = 263), subjects who were terminally ill and in hospice (n = 56), subjects who could not be located (n = 114), and subjects who had previously been diagnosed with dementia (n = 402). Among 4398 eligible subjects, 2719 (61.9% response rate) agreed to participate in the study by telephone (n = 669) or in person (n = 2050), and 1679 declined to participate. Of the 2050 subjects who participated in person through the face-to-face evaluation, 1969 were nondemented (67 were demented and 14 did not complete the evaluation). This cross-sectional study is based on the 1969 nondemented subjects who completed the face-to-face evaluation. All study protocols were approved by the Institutional Review Board of the Mayo Clinic and of Olmsted Medical Center.

2.1. Participant evaluation

Each participant provided informed, written consent prior to participation, and underwent a blood draw and a face-to-face evaluation. This included a risk factors assessment, administration of the Clinical Dementia Rating Scale to the participant and to an informant, a neurological evaluation, and a neuropsychological evaluation using nine cognitive tests to assess four domains of cognition: memory, executive function, language, and visuospatial skills [27]. All the data for each participant were reviewed by an expert panel of physicians, neuropsychologists, and nurses, and a diagnosis was made by consensus.

2.2. Characterization of MCI, dementia, or normal cognition

A diagnosis of MCI was made according to published criteria: cognitive concern by physician, nurse, informant, or participant; cognitive decline or impairment in one or more of the four cognitive domains; essentially normal functional activities; and absence of dementia [28]. Subjects were characterized as having a-MCI if there was impairment in memory or na-MCI if there was no memory impairment. A diagnosis of dementia was made according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* [29]. All subjects who did not receive a diagnosis of MCI or dementia were characterized as cognitively normal according to published criteria [27,28].

2.3. Measurement of inflammatory biomarkers

Inflammatory markers were measured from thawed samples of frozen plasma and serum from the blood draw