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Association of C-reactive protein with mild cognitive impairment

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Abstract

Background—Inflammation is suggested 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 (TNF α), and adiponectin were measured at baseline.

Results—Among 313 subjects with MCI and 1,570 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 non-amnesic MCI (na-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 amnesic MCI (a-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 na-MCI in elderly, non-demented persons in the population-based setting. These findings suggest an involvement of inflammation in the pathogenesis of MCI.

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Disclosure statement for authors

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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) [1–4]. Inflammatory cytokines such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF α) have been associated with AD pathology and with dementia [4,5]. Adiponectin is an anti-diabetic and anti-inflammatory hormone [6–8], and low levels have been associated with vascular disease. The role of inflammation in dementia may be due to an acute phase response to damaged tissue [9], a response to amyloid β , or to inflammation associated with cerebral atherosclerosis [10].

Recent studies suggest that inflammation is associated with mild cognitive impairment (MCI), a transitional stage between normal cognitive aging and dementia [11] or with cognitive decline [12]. MCI is a heterogeneous condition with amnesic (a-MCI) and non-amnesic (na-MCI) subtypes; consequently, there may be etiological differences for the subtypes [13,14]. A-MCI has been hypothesized to progress to AD and therefore, may have a primarily neurodegenerative etiology; na-MCI is thought to progress to non-degenerative or vascular dementias [15]. However, there is limited information on the pathogenesis of MCI subtypes. Because of the association of inflammation with cerebrovascular disease, we hypothesized that inflammation may be associated with na-MCI, but not with a-MCI. In this study, 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 [16]. 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 [17]. We used a random, stratified sampling scheme with equal allocation by age and sex to identify 5,233 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 4,398 eligible subjects, 2,719 (61.9% response rate) agreed to participate in the study by telephone ($n = 669$) or in person ($n = 2,050$), and 1,679 declined to participate. Of the 2,050 subjects who participated in person through the face-to-face evaluation, 1,969 were non-demented (67 were demented and 14 did not complete the evaluation). This cross-sectional study is based on the 1,969 non-demented 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 domains [18]. 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, or participant; cognitive decline or impairment in one or more of the four cognitive domains; essentially normal functional activities; and absence of dementia [19]. 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* [20]. All subjects who did not receive a diagnosis of MCI or dementia were characterized as cognitively normal according to published criteria [18,19].

2.3. Measurement of inflammatory biomarkers

Inflammatory markers were measured from thawed samples of frozen plasma and serum from the blood draw performed at baseline. High sensitivity CRP was measured on a Hitachi 912 chemistry analyzer by a polystyrene particle enhanced immunoturbidimetric assay (DiaSorin, Stillwater, MN 55082) with intra-assay C.V.s of 8.8%, 1.1%, and 0.4% at 0.028, 0.20, and 1.15 mg/dL respectively, and inter-assay C.V.s of 8.0%, 2.0%, and 1.0% at 0.05, 0.30, and 1.86 mg/dL respectively. High sensitivity IL-6 was measured by a quantitative two-site enzyme immunoassay (R & D Systems, Minneapolis, MN 55413) with intra-assay C.V.s of 8.0%, 6.2%, and 4.6% at 0.61, 1.02, and 2.83 pg/mL respectively, and inter-assay C.V.s of 16.0%, 16.5%, and 9.9% at 0.56, 3.58, and 8.16 pg/mL respectively. High sensitivity TNF α was measured by a quantitative two-site enzyme immunoassay (R & D Systems, Minneapolis, MN 55413) with intra-assay C.V.s of 8.8%, 5.9%, and 5.3% at 2.6, 7.2, and 14.0 pg/mL respectively, and inter-assay C.V.s of 16.7%, 12.6%, and 10.8% at 2.4, 6.7, and 13.5 pg/mL respectively. Adiponectin was measured by the Human Adiponectin Double Antibody Radioimmunoassay kit (Linco Research, Inc., St. Louis, MO 63304) with intra-assay C.V.s of 17%, 4.7%, and 7.3% at 5.1, 29.9, and 119 ng/mL respectively.

2.4. Covariates

Date of birth, sex, educational status, current medications, and a history of diabetes (self report of a physician's diagnosis of diabetes or treatment for diabetes), hypertension (self-report of a physician's diagnosis of hypertension or anti-hypertensive therapy), coronary heart disease (CHD; history of myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, angina or treatment for angina), and stroke were assessed by interview [16]. The medical comorbidities were confirmed from the records-linkage system [17]. Current symptoms of depression were assessed by administering the Neuropsychiatric Inventory Questionnaire to a spouse or an informant [21]. Weight was measured using an electronic balance, height was measured using a stadiometer, and body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure was measured in duplicate using a sphygmomanometer. Apolipoprotein E (ApoE) genotyping was performed for each participant using standard methods [22].

2.5. Statistical analyses

We compared the characteristics of subjects with and without MCI using a Wilcoxon rank sum test for continuous measures and a chi-squared test for categorical variables. We used logistic regression models to examine the association of inflammatory markers with MCI and reported odds ratios (OR) and 95% confidence intervals (CI). We examined the effects of the biomarkers as a continuous variable. Since the data were highly skewed, we performed a logarithmic transformation of each inflammatory marker measurement by taking the log of the variable

and dividing by the log of 2; this transformation provided a better interpretation of the data than a simple log transformation. Thus, the estimated ORs are associated with a two-fold increase in the measurement. We also examined the effect of the inflammatory markers as quartiles based on the distribution of the variables in cases with MCI and controls combined. We repeated the analyses for a-MCI and na-MCI.

In multivariable models, we adjusted for sex, age, and years of education (as continuous measures). In the fully adjusted multivariable models, we also adjusted for established risk factors for dementia or cognitive impairment: diabetes, hypertension, CHD, stroke, current depression, and ApoE genotype [$\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$ vs $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 3/\epsilon 3$]). Subjects with ApoE $\epsilon 2/\epsilon 4$ (2.2%) were not included because the $\epsilon 2$ allele is considered protective whereas the $\epsilon 4$ allele increases risk of cognitive impairment.

We also investigated the associations of inflammatory markers (as continuous variables) with the four cognitive domain and global cognitive domain scores (as continuous variables). Each cognitive domain score was calculated first by scaling the raw scores on each test using the mean and standard deviation for the entire sample. Second, the scaled scores in each domain were summed and scaled to obtain a domain score. The domain scores were then summed and scaled to obtain a global score for cognitive function with a mean = 0, standard deviation = 1. All analyses were performed using SAS[®] version 8.0 software (SAS[®] Institute, Cary, NC).

3. Results

Of the 1,969 participants, CRP was measured in 1,883 participants; IL-6, TNF α , and adiponectin were measured in 890 subjects only, due to budgetary constraints. The 890 subjects were essentially representative of the population; they did not differ from the total sample in regard to the distribution of demographic variables (median age = 80 years and median years of education = 13 years in both groups; 59% of the 890 vs 61% of the total cohort were married), clinical variables (frequency of diabetes, hypertension, coronary heart disease, and depression were essentially the same in both groups), ApoE genotype, and the frequency of MCI diagnosis ($P = .49$; Table 1). However, there was a slightly lower proportion of men among the 890 (46.0%) compared to the total sample of 1,969 study participants (50.9%; $P < 0.001$). MCI was significantly associated with age, years of education, CHD, and ApoE genotype, and marginally associated with sex and depression in unadjusted analyses. There were no significant differences between cases with MCI and controls in the distribution of levels of inflammatory markers (Table 1).

3.1. Correlations

Spearman partial correlation coefficients (adjusted for age and sex) were 0.33 ($P < .001$) between CRP and IL-6; -0.10 ($P = .002$) between CRP and adiponectin; 0.42 ($P < .001$) between IL-6 and TNF α ; and -0.09 ($P = .007$) between IL-6 and adiponectin.

3.2. Associations with MCI

A two-fold increase in CRP was associated with a 9% increased OR for any MCI ($P = .03$; Table 2). In the fully adjusted multivariable model, these estimates remained significant and were unchanged. The highest CRP quartile was associated with a 42% increased OR for MCI after adjusting for age, sex, and years of education (Table 2). No associations were observed between any MCI and the remaining inflammatory markers (data not presented).

The associations of biomarkers with MCI varied with MCI subtype. We observed no significant associations of any of the inflammatory markers with a-MCI; however, we observed an association between CRP and na-MCI. A two-fold increase in CRP (as a continuous variable)

was associated with a 21% increase in the OR of na-MCI ($P = .004$) after adjusting for age, sex, and years of education (Table 2). The OR for na-MCI was significantly increased (OR, 2.05) for the highest quartile of CRP compared to the lowest quartile (P for trend = .01). We observed no significant associations with the remaining inflammatory markers (data not presented), but the OR of na-MCI was elevated in the lowest quartile of adiponectin compared to the highest quartile (OR, 2.56; 95% CI, 0.85–7.73).

3.3. Associations with cognitive domain and global scores

CRP was associated with the attention/executive function domain z-score (β , -0.041; standard error [SE], 0.013; $P = .001$) after adjusting for age, sex, and years of education, and in the fully adjusted models (β , -0.046; SE, 0.013; $P < .001$). There were no associations with memory, language, visuospatial, or global domain scores.

4. Discussion

In this population-based study, we observed significant associations between CRP and any MCI, na-MCI, and with the attention/executive function domain score. We observed no significant associations with the other inflammatory markers.

The association of CRP with any MCI, na-MCI, and with executive function (a non-memory domain objectively assessed) is consistent with findings in other cross-sectional [23,24] and longitudinal studies [2,12,24,25]. In a recent study, higher levels of CRP were observed in MCI subjects relative to AD patients [11]. The authors hypothesized that this implied an involvement of CRP in the early stages of AD pathology. Other investigators have not observed an association between CRP and cognitive decline [3].

The associations of CRP with na-MCI suggest a potential role of inflammation and vascular disease in the pathogenesis of na-MCI, given the role of CRP as a marker of inflammation and of vascular risk. This association of CRP with na-MCI may be mediated through cerebral small vessel disease. Consistent with this hypothesis, we have reported a significant association between diabetic retinopathy, an indicator of cerebral small vessel disease, and MCI [26]. The potential role of cerebrovascular disease and associated inflammatory effects in the pathogenesis of na-MCI is demonstrated in our cohort. We observed significant associations between MCI and a history of stroke, a measure of large vessel damage or severe cerebrovascular disease. The OR for na-MCI was 2.8 (95% CI, 1.6–5.1) but was only 1.7 (95% CI, 1.1–2.7) for a-MCI [27]. This suggests that cerebrovascular disease may play a greater role in the pathogenesis of na-MCI than in a-MCI.

Our findings are consistent with a study that reported no association between IL-6 and cognitive decline [3], despite the difference in study design. In contrast, other case-control studies [4, 23,24,28] have reported significant associations of IL-6 and TNF α with dementia or cognitive impairment. We may have failed to observe significant associations, in part, because of the cross-sectional design, or because circulating levels of IL-6 and TNF α may not correlate with the degree of inflammation-related pathology in the brain or with the early stages of the cognitive aging process as in MCI.

Consistent with the hypothesis that low levels of adiponectin may increase vascular risk, the OR of na-MCI was 2.5 in the lowest compared to the highest quartile of adiponectin. Adverse effects of low adiponectin on cognition may be mediated through insulin resistance or cerebrovascular disease [29], whereas the potential beneficial effects may occur through anti-inflammatory mechanisms [30,31]. The association may not have reached statistical significance because of the small sample size.

A primary strength of our study is that the population-based design enhances the generalizability of the study findings and reduces the potential for selection bias. Misclassification in the MCI diagnosis was minimized because we prospectively ascertained MCI using published criteria at the time of the evaluation [19]. Furthermore, each participant was evaluated by three study personnel who made an impression of the diagnosis independently, and the final diagnosis of MCI, dementia or normal cognition was made by consensus.

The potential limitations of the study include the cross-sectional case-control design that precludes our ability to make any causal inferences about the associations. Longitudinal follow-up of this cohort will enable us to determine if CRP predicts incident na-MCI. Because of small numbers of cases of na-MCI, we may have had limited power to detect significant associations with IL-6, TNF α , and adiponectin. There is a potential for non-participation bias since we did not measure IL-6, TNF α , and adiponectin in the entire cohort due to the high costs involved. However, subjects who were not included in analyses for IL-6, TNF α , and adiponectin were similar in age (median = 80 years), years of education (median = 13 years) and frequency of MCI (16.7%) and clinical variables, but had a slightly higher proportion of men (55%) compared to those who were included. Thus, any non-participation bias is likely to be minimal.

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Characteristics of study participants

Table 1

Variable	Total sample (n = 1,969) ^a	Biomarker sample (n = 890) ^a	MCI (n = 143) ^a	No MCI (n = 747)	P value ^b
CRP, mg/L ^c	2.0 (1.0, 3.0)	--	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	.095
IL-6, pg/mL ^c	--	4.1 (2.4, 11.0)	4.8 (2.5, 14.0)	4.0 (2.4, 11.0)	.35
TNFα, pg/mL ^c	--	3.5 (1.6, 12.0)	3.2 (1.5, 12.0)	3.6 (1.6, 12.0)	.43
Adiponectin, mg/L ^c	--	14.4 (9.8, 19.6)	14.4 (9.8, 19.6)	14.5 (9.8, 19.6)	.97
MCI ^d	329 (16.7)	143 (16.1)	--	--	
Age, y ^c	80.4 (75.4, 84.0)	80.4 (75.4, 84.0)	82.0 (78.2, 85.7)	79.8 (75.0, 83.7)	<.001
Sex (% men)	1002 (50.9)	409 (46.0)	76 (53.1)	333 (44.6)	.060
Education, y ^c	13 (12, 16)	13 (12, 16)	12 (12, 15)	13 (12, 16)	.003
≤ 12	919 (46.7)	403 (45.3)	80 (55.9)	323 (43.2)	
> 12	1,050 (53.3)	487 (54.7)	63 (44.1)	424 (56.8)	
Married ^d	1208 (61.4)	524 (58.9)	83 (58.0)	441 (59.0)	.82
Current smoking ^d	79 (4.0)	28 (3.1)	5 (3.5)	23 (3.1)	.79
Diabetes ^d	355 (18.0)	161 (18.1)	29 (20.3)	132 (17.7)	.46
Hypertension ^d	1,388 (70.5)	614 (69.0)	102 (71.3)	512 (68.5)	.51
CHD ^d	611 (31.0)	268 (30.1)	56 (39.2)	212 (28.4)	.010
Depression ^d	290 (14.8)	135 (15.2)	29 (20.6)	106 (14.2)	.055
ApoE ε3/ε4, ε4/ε4 ^d	423 (23.1)	205 (24.3)	44 (32.8)	161 (22.7)	.013
Body mass index ^c	27.2 (24.3, 30.2)	27.0 (24.0, 30.1)	26.8 (24.0, 29.6)	27.1 (24.1, 30.2)	.51

^aThe column totals may not add up to 1,969, 890, or 143 because of missing data. Participants with missing data are excluded from the percent calculations. Data for CRP was based on 1,883 participants; 313 (16.6%) had MCI and 1,570 were cognitively normal. IL-6, TNFα, and adiponectin were assayed in 890 subjects; of these, 143 (16.1%) had MCI and 747 did not; 10 were missing information on one or more of the biomarkers.

^bP value for comparison of subjects with MCI and cognitively normal subjects.

^cMedian (25th, 75th percentile).

^dn (%).

Table 2

Associations of any MCI, amnesic MCI and non-amnesic MCI with C-reactive protein

Variable	MCI n (%)	No MCI n (%)	Unadjusted		Adjusted ^a		Adjusted ^b	
			OR (95% CI)	P value ^c	OR (95% CI)	P value ^c	OR (95% CI)	P value ^c
Any MCI								
CRP, mg/L	1,570 (100)	313 (100)	1.08 (1.00, 1.16)	.05	1.09 (1.01, 1.17)	.03	1.09 (1.00, 1.18)	.04
Q ₁ (≤0.74)	397 (25.3)	72 (23.0)	1.00 (reference)	.19	1.00 (reference)	.10	1.00 (reference)	.12
Q ₂ (>0.74–1.56)	392 (25.0)	80 (25.6)	1.13 (0.79, 1.59)		1.12 (0.78, 1.59)		1.19 (0.83, 1.72)	
Q ₃ (>1.56–3.3)	405 (25.8)	70 (22.4)	0.95 (0.67, 1.36)		0.97 (0.67, 1.39)		0.95 (0.65, 1.40)	
Q ₄ (>3.3)	376 (23.9)	91 (29.1)	1.33 (0.95, 1.87)		1.42 (1.00, 2.01)		1.46 (1.01, 2.10)	
Amnesic MCI								
CRP, mg/L	1,570	226	1.03 (0.94, 1.12)	.57	1.04 (0.95, 1.14)	.37	1.04 (0.95, 1.14)	.37
Q ₁ (≤0.74)	397 (25.3)	55 (24.3)	1.00 (reference)	.93	1.00 (reference)	.60	1.00 (reference)	.58
Q ₂ (>0.74–1.56)	392 (25.0)	63 (27.9)	1.16 (0.79, 1.71)		1.17 (0.79, 1.75)		1.27 (0.84, 1.92)	
Q ₃ (>1.56–3.3)	405 (25.8)	50 (22.1)	0.89 (0.59, 1.34)		0.93 (0.61, 1.41)		0.93 (0.60, 1.45)	
Q ₄ (>3.3)	376 (23.9)	58 (25.7)	1.11 (0.75, 1.65)		1.21 (0.81, 1.82)		1.26 (0.82, 1.93)	
Non-amnesic MCI								
CRP, mg/L	1,570	87	1.21 (1.07, 1.38)	.003	1.21 (1.06, 1.37)	.004	1.18 (1.03, 1.35)	.02
Q ₁ (≤0.74)	397 (25.3)	17 (19.5)	1.00 (reference)	.01	1.00 (reference)	.01	1.00 (reference)	.05
Q ₂ (>0.74–1.56)	392 (25.0)	17 (19.5)	1.01 (0.51, 2.01)		0.99 (0.49, 1.98)		1.00 (0.50, 2.01)	
Q ₃ (>1.56–3.3)	405 (25.8)	20 (23.0)	1.15 (0.60, 2.23)		1.09 (0.56, 2.13)		0.96 (0.48, 1.92)	
Q ₄ (>3.3)	376 (23.9)	33 (37.9)	2.05 (1.12, 3.74)		2.05 (1.12, 3.78)		1.88 (1.00, 3.53)	

^a Adjusted for age, sex, and years of education (as continuous variables).^b Adjusted for age, sex, years of education, diabetes, hypertension, CHD, stroke, depression, and ApoE ε4 allele status.^c P value for the test for trend.