American Journal of Alzheimer's Disease & Other Dementias®
2014, Vol. 29(8) 712-717

DOI: 10.1177/1533317514534758
aja.sagepub.com
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Cognitive Impairment Among Elderly Individuals in Shanghai Suburb, China: Association of C-Reactive Protein and its Interactions With Other Relevant Factors

Jin-Mei Chen, PhD[1,2], Guo-Hong Cui, PhD[1,2], Guo-Xin Jiang, PhD[2,3], Rui-Fang Xu, MA[4], Hui-Dong Tang, MD[1], Gang Wang, PhD[1], Sheng-Di Chen, PhD[1], and Qi Cheng, PhD[2,1]

Abstract

Objectives: To investigate the association between serum C-reactive protein (CRP) concentration and cognitive impairment as well as interactions between CRP and other relevant factors. **Methods:** Patients with cognitive impairment and 1 to 2 age- and sex-matched controls nested from a population-based study among residents aged 60 years and older in Shanghai suburb. The associations of serum CRP concentration and other relevant factors were examined with logistic regression analysis. **Results:** The mean CRP in patients with cognitive impairment was higher than that in controls ($P < .001$). The highest quartile of CRP (>4.77 mg/L), abdomen obesity, hypertriglyceridemia, and hyperglycemia was associated with cognitive impairment. Significant interactions were found between increased CRP and hypertriglyceridemia as well as between increased CRP and hyperglycemia on cognitive impairment; and the attributable proportion due to interaction was 82% ($P < .0001$) and 37% ($P = .007$), respectively. **Conclusions:** Increased CRP was associated with cognitive impairment, and additive effects of increased CRP with hypertriglyceridemia and hyperglycemia on cognitive impairment were observed among elderly individuals.

Keywords

cognitive impairment, C-reactive protein, interaction, risk factor

Introduction

Cognitive impairment is an important part of the diagnostic criteria for dementia, and the etiology and pathogenesis are still not fully understood. Recently, inflammatory mechanisms have been suggested to be involved in the process of development for cognitive impairment and dementia.[1,2] C-reactive protein (CRP), a sensitive marker of systemic inflammation, has been implicated as a risk factor for cognitive decline and dementia by epidemiological studies and detected in and around β-amyloid plaques in the brains of patients with dementia.[3-5] The cultured rat microglia could produce CRP, suggesting that microglial cells might be the source of CRP in the central nervous system.[6] A clinical study found a positive correlation of CRP levels between the cerebrospinal fluid and plasma, providing important evidence that certain inflammatory markers in the blood mirror inflammation in the central nervous system.[7] Vascular risk factors are also related to the decline in cognitive function, such as history of hypertension, obesity, and diabetes.[8,9] Therefore, both CRP and vascular risk factors are associated with cognitive impairment. However, most of the studies are limited to examine the association between CRP and cognitive impairment,[3,10-12] and there is a dearth of research examining the interactions between CRP and other risk factors on cognitive impairment. The current study sought to investigate the association between CRP concentration and cognitive impairment as well as its interactions

[1] Department of Neurology, Ruijin Hospital affiliated with the School of Medicine, Shanghai Jiao Tong University, China
[2] School of Public Health, Shanghai Jiao Tong University, China
[3] Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden
[4] Center for Disease Control and Prevention of Qingpu District, Shanghai, China

Corresponding Authors:
Qi Cheng, PhD, School of Public Health, Shanghai Jiao Tong University, 227 Chong Qing Nan Road, Shanghai, 200025, China.
Email: qicheng@shsmu.edu.cn

Sheng-Di Chen, PhD, Department of Neurology, Ruijin Hospital affiliated with the School of Medicine, Shanghai Jiao Tong University, 227 Chong Qing Nan Road, Shanghai, 200025, China.
Email: chen_sd@medmail.com.cn

between CRP and other relevant factors on cognitive impairment among elderly individuals in Shanghai suburb, China.

Methods

Participants

Data are obtained from a research project investigating the common mechanism of dementia and diabetes, a population-based cohort study conducted in 2005. Participants were residents aged 60 years and older in the study area. Details of the sampling frame and recruitment were previously described elsewhere.[13] In that study, 2809 individuals completed the interview, and the Chinese version of the Mini-Mental State Examination (C-MMSE) was used to screen patients with cognitive impairment.[14,15] Cognitive impairment was defined as patients with a C-MMSE score, adjusted for education level, below the cutoff points[13]: 17 of 18 for participants without formal education, 20 of 21 for those with 1 to 6 years of education (primary school), and 24 of 25 for those with >6 years of education (middle school or higher). The sensitivity and specificity of the cutoff scores of the C-MMSE were reported to be 85.2% and 92.7% from a study.[15] Finally, 198 patients with cognitive impairment were screened.

Among a total of 198 patients with cognitive impairment, 109 individuals with measured CRP were included into our case group. Compared to the other 89 patients with cognitive impairment but without measured CRP, there were no significant differences in gender and age distribution for the 109 patients (P value > .05). Each patient with cognitive impairment was matched with 2 controls for sex and age ($\pm$ 5 years), who were from the same study population and without cognitive impairment. When there were more than 2 candidates for the controls, the ones with the closest age to the patient would be chosen. The study was approved by Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University. Informed consent was obtained from each participant.

Data Collection

Data on demographic characteristics and putative risk factors of cognitive impairment were obtained using a standard questionnaire administered by trained staff. Body weight, height, waist, and hip circumference were measured. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. We evaluated overweight and abdomen obesity according to BMI and waist-to-hip ratio (WHR), respectively. Overweight was defined as BMI $\geq$ 24 kg/m^2, and abdomen obesity[16] defined as WHR $\geq$ 0.9 for men and WHR $\geq$ 0.85 for women. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were analyzed enzymatically on a Beckman Synchron CX5 Delta Clinical System (Beckman Coulter, Inc, Fullerton, California) using commercial reagents. Concentration of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald's equation. Hyperlipemia was defined as TC $\geq$ 5.72 mmol/L and/or TG $\geq$ 1.69 mmol/L and/or HDL-C < 0.91mmol/L and/or LDL-C $\geq$ 3.64mmol/L. C-Reactive protein was determined with immunoturbidimetry on a Beckman Synchron CX5 Delta Clinical System using commercial reagents, and increased CRP was defined as CRP > 4.77 mg/L (the highest quartile). Fasting plasma glucose (FPG) was examined by a glucose analyzer (Roche, Basel, Switzerland), and hyperglycemia[17] was defined as FPG $\geq$ 6.1 mmol/L. Radio immunoassay was used to examine serum insulin concentration. Insulin resistance (IR) was defined as homeostasis model assessment-estimated IR (HOMA-IR) >2.82 (HOMA-IR = value of FPG $\times$ value of insulin/22.5). Smoking was defined as smoke daily, and alcohol drinking was defined as alcohol consumption at least once per week.

Statistical Analysis

The data are presented as mean (standard deviation) or percentages for both patients and controls. The 2-sample independent t test was used for continuous variables and the Pearson chi-square test was used to compare characteristics between patients and controls. Univariate logistic regression analysis was performed to estimate the association between putatively related factors and cognitive impairment. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Variables with statistical significance from univariate analyses were entered in the model by means of a forward stepwise logistic regression procedure until all variables in the final model made a significant contribution (P < .05). The participants in the case and control groups were also divided into even quartiles according to their CRP values, and dose–response relationship between CRP concentrations and cognitive impairment was analyzed with logistic models: unadjusted or adjusted for a few variables with statistical significance from univariate analysis. Effects of interaction between increased CRP and other risk factors on cognitive impairment were evaluated by relative excess risk due to interaction (RERI) and attributable proportion (AP) due to interaction, which were calculated using Excel spreadsheet set by Andersson et al[18] after multivariate adjustment. Statistical analyses were conducted using SPSS statistical software (version 20.0). All P values were based on 2-sided tests with a significance level of .05.

Results

A total of 327 participants (109 cases and 218 controls) were included in the current study and were aged from 60 to 88 years. Characteristics of patients and controls were compared (Table 1). The mean CRP in patients with cognitive impairment was significantly higher than that in controls (P < .001), while the mean C-MMSE score was significantly lower than that in controls (P < .001). The proportion of patients with alcohol drinking was smaller than that in controls (P = .040). The proportions of patients with abdomen obesity, hypertriglyceridemia (TG $\geq$ 1.70 mmol/L), and hyperglycemia (FPG $\geq$ 6.1

Table 1. Comparisons of Characteristics Between Patients With Cognitive Impairment and Controls.

Characteristic	Patients	Controls	*P* Value
Number of participants	109	218	
Age, years, mean (SD)	74.1 (6.0)	73.5 (5.3)	.389
Education, n (%)			.877
Without formal education (<1 year)	96 (88.1)	192 (88.1)	
Primary school (1-6 years)	12 (11.0)	25 (11.5)	
Middle school or higher (>6 years)	1 (0.9)	1 (0.5)	
SBP, mm Hg, mean (SD)	135.1 (19.8)	131.1 (17.1)	.078
DBP, mm Hg, mean (SD)	77.9 (9.9)	76.6 (9.3)	.231
C-MMSE score, mean (SD)	15.2 (2.7)	23.8 (2.8)	<.001
Smoking, n (%)	14 (12.8)	31 (14.2)	.733
Alcohol drinking, n (%)	6 (5.5)	28 (12.8)	.040
Overweight (BMI $\geq$ 24.0), n (%)	29 (26.6)	61 (28.0)	.793
Abdomen obesity (WHR), n (%)	85 (78.0)	103 (47.2)	<.001
Triglycerides (TG) $\geq$1.70 mmol/L, n (%)	68 (62.4)	38 (17.4)	<.001
Total cholesterol (TC) $\geq$5.72 mmol/L, n (%)	23 (21.1)	44 (20.2)	.846
LDL-C $\geq$ 3.64 mmol/L, n (%)	16 (14.7)	35 (16.1)	.746
C-reactive protein (CRP), mg/L, mean (SD)	6.3 (3.8)	1.6 (2.1)	<.001
Hyperglycemia (FPG $\geq$ 6.1 mmol/L), n (%)	61 (56.0)	50 (22.9)	<.001
Insulin resistance (HOMA-IR $\geq$ 2.82), n (%)	32 (29.4)	50 (22.9)	.207
Physical activity ($\geq$60 min/d), n (%)	18 (16.8)	53 (24.5)	.115
History of head injury, n (%)	8 (7.3)	18 (8.3)	.773

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist-to-hip ratio; LDL-C, low-density lipoprotein-cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-estimated insulin resistance, value of FPG $\times$ value of insulin/22; C-MMSE, Chinese version of the Mini-Mental State Examination; SD, standard deviation.

Table 2. Results of Multivariate Logistic Regression Analysis for Variables Associated With Cognitive Impairment.

Variable	β	SE	Wald χ^2	*P* Value	OR (95% CI)
Abdomen obesity (WHR $\geq$ 0.85/0.9)	0.906	0.320	8.009	.005	2.475 (1.321-4.636)
Hypertriglyceridemia (TG $\geq$ 1.70 mmol/L)	2.038	0. 303	45.241	<.0001	7.677 (4.239-13.903)
Increased CRP (CRP $\geq$ 4.78mmol/L)	1.287	0.345	13.939	<.0001	3.621 (1.843-7.114)
Hyperglycemia (FPG $\geq$ 6.1 mmol/L)	1.116	0.292	14.592	<.0001	3.053 (1.722-5.413)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; FPG, fasting plasma glucose; OR, odds ratio; SE, standard error; TG, triglyceride; WHR, waist-to-hip ratio.

mmol/L) were significantly higher than that in controls. There were no significant differences in age, blood pressure, the proportions of patients with cigarette smoking, different levels of education, hypercholesterolemia (TC $\geq$ 5.72 mmol/L), IR (HOMA-IR $\geq$ 2.82), high level of LDL-C ($\geq$3.64 mmol/L), overweight, physical activity, and history of head injury between patients and controls.

Univariate logistic regression analysis examined a number of variables that are putatively relevant to cognitive impairment, including cigarette smoking, alcohol drinking, different levels of education, abdomen obesity, hypertriglyceridemia, hyperglycemia, hypercholesterolemia, IR, high level of LDL-C ($\geq$3.64 mmol/L), overweight, physical activity, increased CRP, and history of head injury; the results (data not shown) for a few variables, abdomen obesity, hypertriglyceridemia, hyperglycemia, and increased CRP, were statistically significant. Results of the final model of multivariate logistic regression analysis indicated that variables of abdomen obesity, hypertriglyceridemia, hyperglycemia, and increased CRP were significantly associated with the risk of cognitive impairment (Table 2).

Results of logistic regression analysis on cognitive impairment with quartiles of CRP concentrations are presented in Table 3. The highest quartile of CRP (fourth) was found to be associated with a significantly higher risk of cognitive impairment, when compared with the lowest quartile (first) from both unadjusted analysis and analysis adjusted for variables of abdomen obesity, hypertriglyceridemia, hyperglycemia, and alcohol drinking.

Results of RERI and AP due to interactions between increased CRP and other risk factors are presented in Table 4. A significant interaction was observed between increased CRP and hypertriglyceridemia as well as between increased CRP and hyperglycemia on cognitive impairment, and the corresponding RERI (AP) was 11.621 (82%) and 1.675 (37%), respectively.

Discussion

In the recent years, many interesting studies have been focusing on the relationship between inflammation and cognitive

Table 3. Results of Logistic Regression Analysis on Cognitive Impairment With Quartiles of C-Reactive Protein Concentration.

			Unadjusted		Adjusted[a]	
Quartile of CRP Concentration, mg/L	Cases, n (%)	Controls, n (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
First quartile (<0.60)	22 (20.2)	55 (25.2)	1.00		1.00	
Second quartile (0.60-1.51)	23 (21.1)	60 (27.5)	0.958 (0.481-1.910)	.904	0.995 (0.421-2.354)	.995
Third quartile (1.52-4.77)	25 (22.9)	70 (32.1)	0.89 (0.455-1.750)	.741	0.809 (0.354-1.852)	.616
Fourth quartile (>4.77)	39 (35.8)	33 (15.1)	2.955 (1.500-5.819)	.002	4.197 (1.797-9.801)	.001

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for variables of abdomen obesity, hypertriglyceridemia , hyperglycemia.

Table 4. Relative Excess Risk Because of Interaction and AP Due to Interaction Associated With Interaction Between Increased CRP and Other Risk Factors.

Interaction item	RERI	AP (%)	*P* value
Smoking + CRP	0.954	46.28	.295
Alcohol drinking + CRP	1.338	50.52	.493
BMI + CRP	0.897	85.84	.422
WHR + CRP	1.999	64.15	.100
Hypertriglyceride + CRP	11.621	82.11	<.0001
Hyperglycemia + CRP	1.675	37.35	.007
Insulin resistance + CRP	0.822	87.44	.692

Abbreviations: AP, attributable proportion; RERI, relative excess risk due to interaction; CRP, C-reactive protein; BMI, body mass index; WHR, waist-to-hip ratio; TG, triglyceride; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-estimated insulin resistance.
[a] Hypertriglyceridemia, TG $\geq$ 1.70 mmol/L; hyperglycemia, FPG $\geq$ 6.1 mmol/L; insulin resistance, HOMA-IR $\geq$ 2.82.

impairment.[3,11,12,19,20] In the study, there were 2809 patients aged 60 years and older, and 198 people had cognitive impairment, with a prevalence of 7.0%.[13] C-Reactive protein is a marker of inflammation and vascular diseases and can also be associated with a high risk of dementia. In our results, the mean CRP in patients with cognitive impairment was significantly higher than that in controls ($P < .001$). The highest quartile of CRP (>4.77mg/L) was significantly associated with cognitive impairment, when compared to the lowest quartile (CRP < 0.60 mg/L) from both unadjusted and adjusted logistic regression analyses. Our results were consistent with that from a few other population-based studies.[3,11,21] Wersching and colleagues[11] examined 447 community-dwelling and stroke-free individuals (mean age: 63 years) from the Systematic Evaluation and Alteration of Risk Factors for Cognitive Health (SEARCH-Health) Study and used the California Verbal Learning Test and high-field magnetic resonance imaging as tools to measure the verbal episodic memory and medial temporal brain volume, respectively. They found that individuals with detectable CRP demonstrated lower performance on a measure of recognition memory and smaller left medial temporal lobe volumes when compared to those with undetectable CRP. Laurin and colleagues[21] made a study on the association of midlife high-sensitivity CRP (hs-CRP) concentrations with late life longitudinal trends in cognitive function. The data were from the Honolulu-Asia Aging Study (HAAS), a longitudinal community-based study of Japanese American men. Finally, 691 dementia-free patients in 1991 were followed up for more than 30 years, and their cognitive function was tested with the 100-point Cognitive Abilities Screening Instrument. They showed that a modestly significant difference in cognitive decline between those in the lowest quartile of hs-CRP and the highest quartile. These findings may underscore a potential role for inflammation in cognitive aging. However, there were incompatible results. Ravaglia and colleages[22] analyzed 744 Italian community dwellers aged $\geq$ 65 years and suggested that visuoconstructional ability was inversely associated with the CRP concentration. No association was observed between the levels of hs-CRP and cognitive decline in some other studies.[23,24] These results were heterogeneous and the explanation for that might be due to differences in methodology, for example, differences in study design, participants, and measurements.

Our results indicated that abdomen obesity and hypertriglyceridemia were associated with a high risk of cognitive impairment. Farr et al[25] made a systematic study with obese mice and found that cognitive impairments could be produced with diet-induced obesity, reversed pharmacologically by lowering TG, and induced by direct injection of TG into the brain. Triglyceride impaired the N-methyl-d-aspartate (NMDA)-mediated maintenance of hippocampal long-term synaptic potentiation. Lowering TG levels in diet-induced obese mice decreased oxidative stress in the central nervous system. Therefore, a high level of TG might cause cognitive impairment through impairing NMDA-mediated long-term potentiation. It was reported that obesity could impair brain function through the pathway of reactive oxygen species.[26]

Numerous studies had suggested that diabetes was associated with an increased risk of cognitive impairment.[27-29] Our results also indicated hyperglycemia was significantly associated with the risk of cognitive impairment (OR = 3.053; 95% CI = 1.722-5.413). Hyperglycemia has the theoretical potential to affect cognition in several ways. Advanced glycosylation end products were found in the senile plaques and neurofibrillary tangles which were the hallmarks of Alzheimer's dementia, and it was plausible that chronic hyperglycemia might enhance that process. Similarly, microvascular disease, the hallmark of hyperglycemia in diabetes, could cause neuronal ischemia and dysfunction if it occurred in the brain.[30,31]

In our study, significant interactions between increased CRP and hypertriglyceridemia as well as between increased

CRP and hyperglycemia on cognitive impairment were observed. It is well known that both hypertriglyceridemia and hyperglycemia are important components of metabolic syndrome (MetS), and MetS may play an important role in inflammation mechanism in cognitive impairment and dementia. Recently, Ishikawa et al[32] studied the relationship between CRP and MetS in a Japanese population, and their results showed that geometric mean and median of CRP in the MetS group were higher than that in the non-MetS group, and the proportion of patients with MetS increased with CRP when the patients were divided into tertiles of CRP. Roberts and colleages[33] conducted a population-based study and found that MetS was not significantly associated with mild cognitive impairment (MCI). However, the combination of high CRP and MetS was significantly associated with nonamnestic MCI. Consistent with our finding, it was suggested that the increased CRP could play a synergistic interaction with hyperlipmia and/or hyperglycemia in the development and presence of cognitive impairment.

The proportion of patients with alcohol drinking was significantly smaller than that in controls in the univariate analysis, suggesting that alcohol drinking might be a protective factor against cognitive impairment. However, alcohol drinking was not included in the final model of multivariate logistic regression analysis. At present, there seems no indication that light to moderate alcohol drinking would be harmful to cognition,[34,35] but it would be difficult to define the beneficial levels of alcohol intake for cognitive performance.

Although BMI and IR are also key components of metabolic syndrome, no significant interactions were observed with increased CRP from our study. The inconsistency may be, in part, due to certain reasons. High BMI in elderly persons may reflect well-being, consistent with the hypothesis that some forms of obesity may not be associated with IR and therefore may not increase the risk of cognitive impairment.[36] It is also possible that the perceived beneficial effects of MetS or its components on cognition in the elderly individuals may be due to survival bias wherein patients with MetS or its components, who are at a greater risk for cognitive impairment, have a higher mortality and do not survive to an older age.

Regarding TC, there was no significant association between high TC and cognitive impairment from our results. Mielke et al[37] made an investigation with a study population aged 70 years and older in the United States and reported that high cholesterol in late life was associated with a decreased risk of dementia. However, there were inconsistent results. Many large epidemiological studies had showed that midlife serum TC was associated with an increased risk of later cognitive impairment.[38,39] The inconsistent results may be explained in part by the different timing of the cholesterol measurement in relationship with the age of study patients and the clinical onset of cognitive impairment.

There are some limitations in our study. For example, a case–control study could not finally make a conclusion regarding the causal relationship between increased CRP and cognitive impairment. C-Reactive protein is a nonspecific marker of inflammation and other inflammatory markers such as different interleukins may have their impacts. In addition, age and gender were matched for patients and controls so that the roles of age and gender were preexcluded in our analysis. It was the same situation for the educational level because the diagnostic criteria of cognitive impairment in our study were adjusted by educational level. There were 88.1% of patients in our study without formal education, indicating our results from a low-education population. Therefore, the generalization of our finding should be cautious. Unfortunately, in this study, we did not make further investigations for the diagnosis of dementia as well as its subtypes like Alzheimer's disease or vascular dementia due to the feasibility and other conditions so we are not able to provide more information regarding those aspects.

In summary, our results indicate that increased CRP was significantly associated with cognitive impairment, and there were positive interactions between increased CRP and hypertriglyceridemia as well as between increased CRP and hyperglycemia on cognitive impairment among elderly individuals.

Authors' Note

Jin-Mei Chen and Guo-Hong Cui contributed equally to this work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by funds from Natural Science Foundation of China (81070958 & 81371218) and Shanghai Municipal Health Bureau Key disciplines (12GWZX0101) and Shanghai Science and Technology Commission (07DJ14005).

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