Correlation between High Sensitivity-Crp Level and Executive Function Disorders in Elderly Patients

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Abstract

Background: C-Reactive Protein is a marker of inflammation and vascular disease. The high serum of high-sensitivity C-Reactive Protein (hs-CRP) concentration was associated with interruption the integrity of the frontal-subcortical circuit.

Objective: To determine the correlation between high serum concentration of hs-CRP and executive function disorder in elderly patients.

Method: Thirty six elderly patients was examined by using a case control study. The subjects were enrolled from the out-patient at Neurology Departement Dr. Soetomo General Hospital, Surabaya, Indonesia. The time period was 4 months (April to July 2015). Executive function was measured with the Trail Making Test B (TMT B) and divided into two groups, case and control. Complete blood count and serum hs-CRP concentration were measured from nonfasting blood samples. Chi-square test was used for data analysis.

Results: Eighteen subjects were enrolled in the case group (3 men, 15 women) and the other 18 subjects were enrolled in the control group (4 men, 14 women). Executive function disorder was found in 17 (94,4%) subjects of case group and 11 (61,1%) subjects of control group. High levels of hs-CRP was not associated with executive function, with p = 0,149 and adjusted OR 5,629 (CI 95% 0,538-58,860).

Conclusion: These data suggested that high levels of hs-CRP was not associated with executive function in elderly patients.

Keywords : *High hs-CRP, Executive Function, Elderly Patient*

Introduction

The inflammation plays an important role because it was involved in all stages of atherosclerosis. Atherosclerosis is a chronic inflammatory process that occurs in the arterial endothelium.[1] The CRP has been shown to be a marker and mediator of atherosclerosis. The previous laboratory testing methods were not sensitive enough to measure the CRP levels <10 mg /L. Hs-CRP, that was a quantitative methode of CRP concentration which could measure the levels up to <0.2-0.3 mg/L. It was an acute phase plasma protein, synthesized by hepatocyte cells and the most sensitive marker of systemic infection. Various studies reported that the high serum hs-CRP or CRP will lead to increasing the risk factors for vascular dementia, Alzheimer's disease, cognitive disorder and White Matter Hyperintensities (WMH) [1].

The high levels of CRP in microvascular cerebral might accelerate atherosclerosis. Narrowing of the vascular lumen and cerebral regulatory damage lead to cerebral microangiopathy. The process will affect the integrity of the frontal-subcortical circuitry thus providing a clinical picture of cognitive disorder [2].

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The results of Kirova et al's study using the prospective cohort method showed that the increase in serum CRP was associated with cognitive disorder in individuals with metabolic syndrome. In the elderly population, high levels of CRP and Interleukin 6 (IL-6) will cause worsening of cognitive function. Six 6 meta analysis studies have shown that elevated CRP could be used as a predictor of cognitive and dementia disorders[3].

However, some studies showed that there was no association between hs-CRP and cognitive disorder. Even four cohort studies in Scotland have shown no association of CRP gene variation with cognitive function in old age. Yilmaz et.,al investigated parents aged 64 to 85, and the results suggested that α1-antichymotrypsin was associated with decreased cognitive function, but not for CRP, IL-6, and albumin [4].

The difference results might be due to the measurement of inflammatory markers using the different types, the methods, and the sensitivities. The CRP levels were varied in each population. Then, more importantly, the selection of measuring instruments for assessment of cognitive function was on executive function. There were several studies relying solely on the examination of the Mini Mental State Examination (MMSE). The MMSE instrument was not as diagnostic but as a screening for cognitive disorder. One of the most sensitive and widely applied measures of executive function was TMT B [5].

Additionally, because of the different results and the minimal use of hs-CRP as the most sensitive atherosclerotic marker in the previous studies, it needed to determine the correlation between hs-CRP levels and executive function measured by using TMT-B.

Method

This study used a case-control design in all elderly patients who visited the Neurosurgery Outpatient Unit at Dr. Soetomo General Hospital and fulfilled the inclusion-exclusion criteria during the period April-July 2015. The inclusion criteria were elderly patients aged 45 - 65 years old who able to read and write also willing to participate the study. The case group was determined by value of TMT B >180 seconds, while for the control group has the value of TMT B ≤180 second [6].

The exclusion criteria were cognitive disorder with a definitive cause of structural lesions (cerebral tumor, moderate to severe brain injury, stroke, Parkinson Disease, brain infection); suffering from rheumatoid arthritis, lymphoma, Systemic Lupus Erythematosus, cancer; using corticosteroid drugs; showing a Systemic Inflammation Response Syndrome; hsCRP ≥10 mg/L; and they had has a history of alcoholism, schizophrenia, and depression [7]. The elderly patients who fulfilled the inclusion and the exclusion criteria were given a careful physical examination and neurologic examination. Then they were examined the value of TMT B by Resident in Training of Neurology Department. After that, the subjects were performed complete blood tests and hs-CRP levels by Prodia laboratories [8].

The high hs-CRP levels were defined if the hs-CRP levels in plasma >1.0 mg/L. Plasma were taken from 0.5 ml of venous blood by using the immunometric assay technique method; and hs-CRP was examined by Immulite 2000 hs-CRP and expressed in mg/L units.The executive function disorder was defined if there was an extension of TMT-B time than normal value of ≤180 seconds [9].

Statistical analysis was performed using SPSS 22.0 program. Collected categorical data were tested by Chi Square test and Fisher test, meanwhile Unpaired T test was used for numerical data [10]. The difference in the proportion of executive function in both groups was tested using Chi Square test, then analyzed using logistic regression [11].

Result

The total subjects of the study were 36 subjects then 18 subjects were included in the case group (3 men, 15 women) and the other 18 were included in the control group (4 men, 14 women). The basic characteristics of subjects consisted of demographic and clinical data were shown in table 1.

Table 2 showed the correlation between high hs-CRP levels and executive function in elderly patients. This difference was statistically significant with p = 0.041 and OR=10,818 (95% CI 1.165 – 100.439). Then, we obtained type II error (β error) of 1% in this study.

Logistic regression on the level of education, hypertension and high levels of hs-CRP was analyzed. The analysis obtained p value of education level was 0.029 with adjusted OR of 5.713 (95% CI 1.195 - 27.314). Hypertension obtained p = 0.053 with adjusted OR (95% CI 0.978 - 27.933). Meanwhile, high levels of hs-CRP did not have a significant correlation to the executive function with the p = 0.149 with adjusted OR 5.629 (95% CI 0.538 - 58.860).

Table 1. The Basic characteristics of Subjects

Characteristics	Groups				Totaln=36	P
	Case n=18		Control n=18			
Sex						
Male	3 (16,7%)		4	(22,2%)	7	1,000
Female	15 (83,3%)		14 (77,8%)		29	
Age		56,17		53,22		0,169
Education Level						
Elementary, Junior High	11 (61,1%)		4 (22,2%)		15	0,018
Senior High, College	7 (38,9%)		14 (77,8%)		21	
Hypertension						
Yes	9	(50,0%)	3	(16,7%)	12	0,034
No	9 (50,0%)		15 (83,3%)		24	
Dyslipidemia						
Yes	6	(33,3%)	5	(27,8%)	11	0,717
No	12 (66,7%)		13 (72,2%)		15	
Obesity						
Yes	12 (66,7%)		8 (44,4%)		20	0,180
No	6	(33,3%)	10 (55,6%)		16	
Use of NSAID						
Yes	8 (44,4%)		6 (33,3%)		14	0.494
No	10 (55,6%)		12 (66,7%)		22	
High Hs-CRP Levels						
Yes	17 (94,4%)		11 (61,1%)		28	0,041
No	1	(5,6%)	7	(38,9%)	8	

Table 2. The Correlation between High Hs-CRP level and Executive Function

High hs-CRP Levels	Executive Function				P	OR (CI 95%)
	Case		Control			
	N	%	N	%		
Yes	17	94,4	11	61,1	0,041	10,818
No	1	5,6	7	38,9		(1,165-100,439)
Total	18	100	18	100		

Discussion

In our study, sex did not have a significant correlation to the executive function. The data were in accordance with the previous studies that showed no correlation between sex and TMT B. Studies conducted in 1447 healthy people aged >18 years reported that sex did not affect the results of TMT examination B.[21] Other studies conducted in Korea with 997 subjects aged 60-90 years, indicating sex also had no significant correlation to TMT B.[23] The sex effects on TMT examination results in the elderly population were still under debate.[24] Meanwhile, another study reported the results of the Concept Shifting Test (CST) showed that women were superior. CST was a TMT modification that aimed to measure shifting and executive functions [12].

The median age of the subjects in our study showed that the age of case group was the older one. However, there was no difference in the mean age of executive function. Demographic data on other studies used a cross-sectional method with the aim of finding a relationship between hs-CRP with executive function and cerebral microstructural integrity, and obtained that the age range of subjects was 40-80 years, with average of 63.3 ± 0.4 years . Lukas et al reported that individuals aged> 50 years associated with abnormal TMT results. Previous studies have shown that increasing age was associated with duration to complete an executive function examination. The studies with similar results were also reported in the Dutch population, Korea, Americans, and Brazil [13].

Based on our research, the level of education had a significant correlation with the executive function. The subjects with primary education level and junior high school had a probability of 5.713 times more often to experience executive function disorder than those with high senior education level and college. Our results were consistent with the study by Hamdan AC et al. which

reported that the subjects with an educational level of ≥9 years completed TMT B shorter than subjects with low education level (2-8 years). However, there was no significant difference between subjects with average education period of <9 years and subjects with education period of ≥9 years.[28] Another study also proved that low levels of education was related to completion duration of TMT examination B [5].

In our study, there was no relationship between hypertension and executive function. In addition, variable dyslipidemia and obesity had no significant correlation with executive function. Our results did not match with the cross sectional study conducted by Collinson et al that consisted of 55 asian subjects aged >55 years were suffering from metabolic sydrome and 44 healthy people as the control. The definition of metabolic syndrome in the study used the International Diabetes Federation modification criteria of obesity (BMI >23) followed by at least 2 of hypertensive risk factors, type 2 DM, triglyceride elevation and low HDL. The results showed that subjects suffering from metabolic syndrome were associated with disorders in the memory domain and executive function rather than with the control group [5].

The characteristic of NSAID use had no significant correlation with executive function. Our results also did not match with the Baltimore Longitudinal Study on Aging, Rotterdam, the Cache County Memory Study, which indicated that the strongest dementia risk reduction occured in people who have been using NSAIDs for more than two years. Thal et al reported that if the COX-2 inhibitor (rofecoxib 25 mg)/day was adminstered for 4 years, it could not prevent the progression of Alzheimer's Disease in patients with MCI.

Our study showed that there was no correlation between high hs-CRP levels and executive function in

elderly patients. The results of this study were according to the Longitudinal Aging Study Amsterdam. The study used a cohort method, involving 1,284 subjects with an age range of 62-85 years. The cognitive examination of MMSE, memory (auditory verbal learning test), Intelligence (Raven's Colored Progressive Matrices) and information processing (coding test) were performed then followed up after 3 years. The CRP levels were not associated with cognitive disorder in all examination modalities in the study (Dik et al, 2006). Another study investigated subjects included 97 women aged 60-70 years, who were examined the levels of hs-CRP and cognitive function (MMSE, word recall test, and Stroop test). Other cross-sectional study of 1331 subjects with age >65 years proved that high hs-CRP levels did not related with the domain of executive function and language interference [14].

However, several studies had shown that high levels of hs-CRP were correlated with cognitive function disorder. One of them, was a cross-sectional study by Rizzi and his colleagues on 149 CHD patients aged ≥50, then did the MMSE examination. The result showed that 34 subjects had cognitive disorder (case group) and the rest were in the control group. Subjects with high CRP levels (≥5 mg / L) had 2.9 (95% CI 1.26 - 6.44) times more often suffering from cognitive disorder (p = 0.012) and leukoaraiosis was only 5.98% (p = 0.005). Thus high hs-CRP levels were associated with an increased risk of cognitive disorder in elderly patients. The results of other studies also showed that high levels of hs-CRP were associated with executive function disorder aged of 40-80 years old [15].

In this study, there was no correlation between the high hs-CRP levels and the executive function in elderly patients. This might be due to the significant differences in the number of subjects, racial differences from the study subjects and might also be influence of the confounding factors. It was such as the educational level that makes it difficult to ascertain whether the cause of impaired executive function was found purely because of high levels of hs-CRP alone [16]. Vijay & Kumar reported that the inflammatory parameters measured from peripheral blood did not directly describe the inflammatory process in the brain.[7] In addition, although CRP was a marker of vascular disease, elevated CRP levels did not directly affect vascular outcomes [17].

Conclusion

There was no correlation between the high hs-CRP levels and executive function disorder in elderly patients.

Ethical Clearance: The research process involves participants in the survey using a questionnaire that was accordant with the ethical research principle based on the regulation of research ethic committee. The present study was carried out in accordance with the research principles. This study implemented the basic principle ethics of respect, beneficence, nonmaleficence, and justice.

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