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High-sensitivity C-reactive protein level is a significant risk factor for silent cerebral infarction in patients on hemodialysis

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Abstract

In patients with chronic renal failure on hemodialysis (HD), silent cerebral infarctions (SCIs) are associated with high mortality. The levels of high-sensitivity C-reactive protein (HSCRP), a marker of inflammation and atherosclerosis, elevate with increasing renal dysfunction. We tested the hypothesis that increased HSCRP levels correlate with the occurrence of SCI in HD patients. By brain magnetic resonance imaging findings, we divided 54 patients undergoing HD into a with-SCI group (61 ± 8 years, n = 30) and a without-SCI group (60 ± 7 years, n = 24). We compared sex, body mass index, metabolic profiles, HSCRP levels, and smoking habits in Japanese patients on HD with and without SCI. We made the following observations: (1) The number of patients with diabetes or hypertension did not differ between the 2 groups. (2) The levels of HSCRP were higher in the with-SCI group in comparison with the without-SCI group ($P < .0001$). (3) The proportion of smokers was higher in the with-SCI group than in the without-SCI group ($P < .05$). (4) Plasma levels of high-density lipoprotein cholesterol were lower, whereas uric acid was higher, in the with-SCI group than in the without-SCI group ($P < .05$ and $P < .0001$, respectively). (5) Multivariate logistic analysis identified HSCRP levels as being significantly associated with the presence of SCI (odds ratio, 1.61; 95% confidence interval, 1.17-2.85; $P < .001$). This study indicates that patients in chronic renal failure who are maintained on HD exhibit an increased prevalence of SCI and that HSCRP is significantly associated with the presence of SCI in HD patients.

1. Introduction

The mortality related to cerebrovascular events in chronic hemodialysis (HD) patients is 4 to 10 times higher relative to the general populations [1]. Strokes in HD patients are characterized by a high rate of intracerebral hemorrhage, and hypertension is a significant risk factor for stroke in this group [2-5].

Recent studies in vascular biology have demonstrated that chronic inflammation plays a critical role in the development of atherosclerosis [6]. Several lines of evidence suggest the value of measuring the serum levels of inflammatory markers, such as high-sensitivity C-reactive protein (HSCRP), as a method to predict stroke and other adverse cardiovascular events [7-9].

Silent cerebral infarction (SCI) can underlie or occur concomitantly with clinical subcortical brain infarction or brain hemorrhage [10]. In most cases, SCI is discovered as a lacunar infarct. This common form of subcortical infarction

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is defined by Fisher [11] as small, deep cerebral infarcts caused by occlusion of small penetrating cerebral arteries.

The significance of increased HSCRP levels in HD patients with SCI has not been adequately investigated. We hypothesized that increased HSCRP levels are associated with SCI in HD patients. To test this hypothesis, we compared magnetic resonance imaging (MRI) findings and metabolic profiles between Japanese HD patients with SCI and those without SCI and evaluated the independent predictors of SCI in these patients.

2. Subjects and methods

2.1. Patients

A total of 77 patients were maintained on HD from January 2005 to October 2005 at Oita Red Cross Hospital. Critical patients were excluded from the study, including 6 patients with atrial fibrillation, 5 patients with a history of symptomatic stroke, 4 cases with transient ischemic attacks, 3 patients with chronic inflammatory disease, 3 patients with other malignancies, and 2 cases of acute inflammatory disease. In this study, 8 patients had inflammatory diseases with high HSCRP levels (10.0 mg/L), whereas the remaining 69 patients did not exhibit high HSCRP values. Therefore, 54 of the original 77 patients, 30 men and 24 women (mean age, 60 ± 7 years), were selected for this study.

The primary renal disease causing chronic renal failure included diabetic nephropathy in 21 patients, chronic glomerulonephritis in 19 patients, chronic nephrosclerosis in 12 patients, and lupus nephritis in 2 patients.

All subjects gave written informed consent to participate in the study. The study protocol was approved by the ethics committee of Oita Red Cross Hospital.

2.2. Risk factors

To evaluate potential risk factors, we evaluated the patient cohort for hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease (IHD), and smoking history. *Essential hypertension* was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or treatment of the subject with antihypertensive drugs [12]. Twenty-three of 30 patients with SCI and 16 of 24 patients without SCI met this criterion; all of these patients were being treated with calcium channel antagonists, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers, either alone or in combination. *Diabetes mellitus* was recognized in patients using insulin or oral hypoglycemic agents and in patients whose fasting glucose concentration was greater than 126 mg/dL. *Dyslipidemia* was defined as fasting triglycerides ≥200 mg/dL; high-density lipoprotein cholesterol (HDL-C) <45 or <35 mg/dL in women and men [12], respectively; or current treatment of hyperlipidemia. *Ischemic heart disease* was defined as angina, history of myocardial infarction, prior coronary artery bypass surgery, or percutaneous coronary intervention. Smoking encompassed current cigarette smokers.

Blood samples were taken from the arterial line before HD treatment sessions. Serum from blood samples for these assays was stored at −20°C until tested. High-sensitivity assays for CRP were performed according to previously described methods (Dade Behring, Tokyo, Japan) [13]. The CRP levels in subjects' serum samples were measured [13]. Patients who exhibited high HSCRP levels (ie, >10.0 mg/L) were excluded from this study [14].

2.3. Hemodialysis method

Hemodialysis in these patients was performed using a 4F catheter micropuncture set or a 4F Kumpe access catheter (Cook Group, Bloomington, IN). In all cases, access to the graft or fistula was initially obtained with a 19-gauge needle. Hemodialysis patients received regular dialysis 3 times per week using a high-flux cellulose-triacetate dialyzer membrane in sessions lasting 4 hours. The dialysate flow rate was 500 mL/min; blood flow ranged from 120 to 200 mL/min. Dry weight was determined for each patient from the post-HD cardiothoracic ratio. During the HD session, we also noted several clinical observations, such as the presence of muscle cramps, general fatigue, thirst, or hypotension. All patients were maintained at their set dry weight. No differences in dialysis methods were observed between the 2 groups.

2.4. Evaluation of SCI

All participating patients had an MRI scan of the brain. T_1- and T_2-weighted axial images of 5-mm–thick slices were collected with a 1.5T field on proton density (Visart EX; Toshiba, Tokyo, Japan). The head position was oriented in the scanner and stabilized during the scanning procedure using a head support. To establish slice orientation, the first scanning sequence was a T_1-weighted sagittal series (repetition time [TR], 500 nanoseconds; echo time [TE], 15 milliseconds; matrix, 256 × 256) to define the orbitomeatal line. We oriented the second series of T_1-weighted (TR, 500 milliseconds; TE, 15 milliseconds; thickness, 8 mm; gap, 1.5 mm; matrix, 256 × 256) and T_2-weighted (TR, 4000 milliseconds; TE, 120 milliseconds; thickness, 8 mm; gap, 1.5 mm; matrix, 320 × 320) axial images parallel to the orbitomeatal line. Fourteen slices were inspected at each examination. The accuracy of this method has previously been validated [15].

Lacunar infarcts were identified by the presence of hyperintense areas on T_2-weighted images (5 mm ≤ diameter < 15 mm) that were visible as low-signal intensities on T_1-weighted images. As described by Braffman et al [16], lesions <5 mm were not counted as infarctions to exclude enlarged periventricular spaces.

Two neurologists blinded to the subjects names, characteristics, and clinical status interpreted the MRI images of the subjects that had been randomly stored.

2.5. Statistical analysis

All data are summarized as the means ± SD. Differences between the groups were examined using the Student t test for continuous variables and the χ^2 test for categorical variables. Logistic regression analysis was used to assess the influence of explanatory variables on SCI, in which sex, hypertension, diabetes mellitus, dyslipidemia, IHD, and smoking were represented by dummy variables (1 = male, 0 = female; 1 = present, 0 = absent). If x_i (i = 1,2,...,I) were the explanatory variables and Y was the dichotomous response variable, such that $Y = 0$ represented the without-SCI group and $Y = 1$ represented the with-SCI group, the conditional probability of $Y = 1$ in the logistic regression model given the explanatory variables is given as:

$$\Pr(Y = 1 | x_i, i = 1, 2, \ldots, I) = \frac{\exp\left(\sum_{i=1}^{I} \beta_i x_i\right)}{1 + \exp\left(\sum_{i=1}^{I} \beta_i x_i\right)}$$

A forward stepwise logistical regression was selected using a cutoff level of 0.05 for significance.

Differences were considered statistically significant at $P < .05$.

3. Results

The mean age of patients was similar between the with-SCI and without-SCI groups (Table 1). No significant differences were observed between the 2 groups with respect to sex; body mass index; HD duration; administered medications; or the proportion of patients with diabetes, hypertension, or dyslipidemia. The with-SCI group, however, had a higher percentage of smokers and patients with IHD than the without-SCI group (P = .0360, P = .0440).

There were no significant differences in hematocrit, fasting plasma glucose concentration, or hemoglobin A_{1c} (HbA_{1c}) levels between the 2 groups. Although serum HDL-C was lower in the with-SCI group than in the without-SCI group (P = .0105), serum total cholesterol and triglyceride levels were not significantly different between the groups. Uric acid was higher in the with-SCI group than in the without-SCI group (P = .0280).

The HSCRP levels were higher in the with-SCI group than in the without-SCI group (Fig. 1; 7.07 ± 2.33 vs 3.88 ± 1.51 mg/L, $P < .0001$).

By univariate logistic regression analysis, the risk of SCI was increased with smoking (odds ratio [OR], 3.82; 95% confidence interval [CI], 1.05-13.9; P = .0422) and with decreased HDL-C (OR, 0.94; 95% CI, 0.89-0.98; P = .0172), elevated uric acid (OR, 1.36; 95% CI, 1.03-1.81; P = .0330), and elevated HSCRP (OR, 1.61; 95% CI, 1.17-2.85; P = .0075) levels, each dependent metabolic parameters in HD patients (Table 2).

Table 1
Clinical characteristics of patients

	SCI(−)	SCI(+)	P
Age (y)	60 ± 7	61 ± 8	NS
Sex (men/women)	13/11	17/13	NS
Body mass index (kg/m^2)	22.0 ± 2.2	22.9 ± 2.4	NS
Dialysis duration (y)	1.8 ± 1.2	2.0 ± 1.4	NS
Diabetes mellitus (%)	57	67	NS
Hypertension (%)	67	77	NS
Dyslipidemia (%)	38	47	NS
Smoking habit (%)	17	43	.0360
IHD (%)	13	33	NS
Drug use (%)			
Sulfonylurea	29	33	NS
α-Glucosidase inhibitors	25	30	NS
Insulin	8	10	NS
Statin	33	40	NS
Antiplatelet agents	13	33	NS
Calcium channel antagonists	58	67	NS
ACE inhibitors	13	17	NS
Angiotensin receptor blocker	25	30	NS
β-Blocker	17	20	NS
Hematocrit (%)	30.1 ± 3.4	29.6 ± 2.9	NS
Total cholesterol (mg/dL)	156 ± 54	174 ± 63	NS
Triglyceride (mg/dL)	101 ± 28	120 ± 43	NS
HDL-C (mg/dL)	46 ± 13	38 ± 11	.0105
Fasting plasma glucose (mg/dL)	129 ± 21	133 ± 25	NS
HbA_{1c} (%)	6.2 ± 1.0	6.4 ± 1.2	NS
Uric acid (mg/dL)	6.8 ± 1.8	8.1 ± 2.2	.0280

Data are the means ± SD. NS indicates not significant.

Multiple logistic regression analysis included the following independent variables in the model: smoking, HDL-C, uric acid, and HSCRP as categorical variables. Multivariate logistic regression analysis identified plasma HSCRP in HD patients as a significant indicator associated with SCI (OR, 1.61; 95% CI, 1.17-2.85; P = .0075).

4. Discussion

In this study, the measurement of metabolic parameters revealed that serum HDL-C levels were lower and HSCRP levels were higher in the with-SCI group than in the without-SCI group. Multiple logistic analysis revealed that HSCRP levels were significantly associated with the presence of SCI in HD patients.

Silent cerebral infarction is an important risk factor for stroke; several reports have examined SCI in the general population. According to Kobayashi et al [10], MRI studies revealed an incidence of SCI of 10.6% in 993 neurologically normal adults without a history of cerebrovascular disease (mean age, 58 years). The National Institute for Longevity Sciences Longitudinal Study of Aging predicted an incidence of SCI of 10.3% (mean age, 59 years) [15]. The prevalence of SCI in HD patients is approximately 5 times greater than that seen in the normal population (mean ages, 54 and 56 years, respectively) [4,5]. This incidence of SCI is similar to that seen in HD patients (30 of 54 [55.6%] HD patients) in this study.

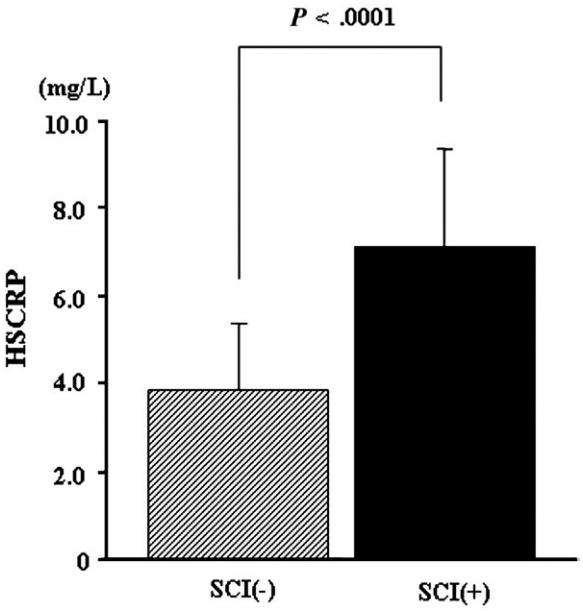

Fig. 1. Comparison of HSCRP levels between HD patients with (SCI+) and without (SCI−) SCI. Data represent the means ± SD.

Several studies have demonstrated a strong positive association between increasing serum HSCRP levels and risk of stroke, independent of other vascular risk factors [7-9]. In HD patients, increased serum HSCRP levels correlate with arteriosclerosis and the presence of cardiovascular disease [17]. Consistent with these results, this study demonstrated a correlation between HSCRP and SCI, supporting the hypothesis that inflammation helps mediate the pathologic changes in cerebral small vessels that cause lacunar infarction. The precise mechanism by which elevated HSCRP is linked to SCI and clinical stroke, however, remains unclear.

Measurement of soluble plasma markers, such as soluble intercellular adhesion molecule 1, soluble endothelial leukocyte adhesion molecule, and thrombomodulin, in previous studies demonstrated that inflammatory endothelial activation and endothelial cell dysfunction are some of the underlying causes for the small-vessel disease of the brain implicated in most SCI lesions [18,19]. Autopsy examinations revealed migration of foamy macrophages into the vessel walls of cerebral arterioles with hyaline thickening and ectasia of parenchymal arteries in 15 of 20 patients with ischemic vascular dementia [20]. Although it is not established if inflammatory endothelial activation induces arteriosclerosis and lipohyalinosis, it is likely that chronic inflammatory responses in cerebral small vessels function in the pathology of this microangiopathy. Furthermore, Clapp et al [21] reported that human CRP has direct effects on vascular function in vitro via increased nitric oxide production. Thus, HSCRP is both a risk factor for arteriosclerosis and a pathophysiological modulator of endothelial functions.

The proportion of smokers was increased in the with-SCI group. Howard et al [22] reported that smoking is related to the prevalence of SCI in the general population. Smoking affects the vasculature via multiple interactive mechanisms [23]. Nicotine and carbon monoxide each produce tachycardia, hypertension, and vasoconstriction; both damage the endothelium directly. Smoking also has vaso-occlusive effects, stimulating platelet aggregation, augmenting plasma viscosity, and increasing fibrinogen levels [23]. In addition, Frohlich et al [24] reported that the number of cigarettes smoked per day, pack-years of smoking, and duration of smoking are positively associated with CRP levels in men. Ohsawa et al [25] reported that the longer the smoking cessation period is, the lower the CRP levels in past smokers are.

Several possible mechanisms could explain the mechanisms by which smoking may be associated with systemic markers of inflammation, such as CRP. Certain compounds of smoke, such as free radicals [26] and phenol-rich glycoproteins [27], directly stimulate macrophages, which may trigger the production of inflammatory cytokines such as tumor necrosis factor α, interleukin 1, and interleukin 6 [26]. There may also be an indirect effect of nicotine-induced catecholamine release [28], which modulates both the systemic and local cytokine balances [29].

Univariate logistic regression analysis was performed for each factor in Table 2; the analysis demonstrated that HDL-C, uric acid, HSCRP, and smoking are all risk factors for SCI in HD patients. To determine significant risk factors from the above ones, we performed multiple logistic regression analysis. A model selection procedure used for this objective

Table 2
Univariate logistic regression analysis of HD patients with silent cerebral infarct as the dependent variable

	OR	SCI 95% CI	*P*
Age	1.02	0.95-1.10	NS
Sex	1.11	0.38-3.26	NS
Body mass index	1.20	0.94-1.53	NS
Dialysis duration	1.02	0.98-1.06	NS
Diabetes mellitus	1.53	0.49-4.85	NS
Hypertension	1.93	0.52-7.18	NS
Hyperlipidemia	1.63	0.53-4.98	NS
Smoking habit	3.82	1.05-13.9	.0422
IHD	4.05	0.98-16.8	NS
Hematocrit	0.95	0.79-1.13	NS
Total cholesterol	1.01	0.99-1.02	NS
Triglyceride	1.01	0.98-1.03	NS
HDL-C	0.94	0.89-0.98	.0172
Fasting plasma glucose	1.01	0.98-1.03	NS
HbA_{1c}	1.12	0.69-1.79	NS
Uric acid	1.36	1.03-1.81	.0330
HSCRP	1.61	1.17-2.85	.0075

We explored 6 parameters as significant predictors of SCI: sex (female = 0, men = 1), diabetes mellitus (absent = 0, present = 1), hypertension (absent = 0, present = 1), hyperlipidemia (absent = 0, present = 1), smoking (absent = 0, present = 1), IHD (absent = 0, present = 1), and HSCRP serum levels.

statistically identified HSCRP as a significant risk factor for the presence of SCI in HD.

There are several limitations to this study. A number of patients were receiving drugs that can reduce the HSCRP levels, such as statins, antiplatelet agents, and ACE inhibitors. Our small cross-sectional study was not of sufficient power to analyze and exclude the potential effects of these influences on HSCRP levels. Secondly, there are several reports that CRP is greater than 10.0 mg/L in 30% to 50% of HD patients [30,31]. We used a cutoff value of 10.0 mg/dL for HSCRP. Further assessment of patients with highly elevated HSCRP (>10.0 mg/L) for noncardiovascular causes of inflammation has been endorsed by the American Heart Association/Centers for Disease Control and Prevention scientific statement [14]. Further clinical investigation is needed to determine the relationship between HSCRP values, especially those above this cutoff, and SCI in HD patients.

Elevated HSCRP levels may be produced as a result of underlying ischemia. Their elevation in the context of this study represents an epiphenomenon. A prospective longitudinal study will be required to address these issues and to identify factors determining HSCRP plasma levels in relation to the development of stroke in HD patients.

In conclusion, our study indicates that chronic renal failure maintained by HD increases the prevalence of SCI. In addition, HSCRP levels are significantly associated with SCI in HD patients.

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