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Predictors for silent cerebral infarction in patients with chronic renal failure undergoing hemodialysis

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Abstract

In patients with chronic renal failure undergoing hemodialysis (HD), silent cerebral infarctions (SCIs) are associated with high mortality. Levels of hepatocyte growth factor (HGF) increase with renal dysfunction and may be a novel predictor of cerebrovascular events. We examined if HGF is a predictor of SCI in HD patients. Brain magnetic resonance imaging findings were used to divide 50 patients undergoing HD into 2 groups, a group with SCI (age, 61 ± 8 years, mean ± SD; n = 27) and a group without SCI (age, 60 ± 7 years; n = 23). These patients received 24-hour ambulatory blood pressure monitoring. The number of patients with diabetes or hypertension was not different between the 2 groups. We made the following observations: (1) The percentage of smokers was higher in the group with SCI than in the group without SCI ($P < .05$). (2) Plasma levels of high-density lipoprotein cholesterol were lower and HGF levels were higher in the group with SCI compared with the group without SCI ($P < .05$ and $P < .005$, respectively). (3) Systolic ambulatory blood pressure and mean heart rate at night were higher in the group with SCI than in the group without SCI ($P < .05$). Multiple logistic regression analysis identified HGF as a significant risk factor for SCI (odds ratio, 1.89; 95% confidence interval, 1.57-3.38; $P < .005$). Our findings indicate that HGF may be a novel useful predictor of SCI in patients with chronic renal failure undergoing HD.

1. Introduction

The mortality related to cerebrovascular events in patients undergoing long-term hemodialysis (HD) is 4 to 10 times higher relative to the general population [1]. Stroke in HD patients is characterized by a high rate of intracerebral hemorrhage, and hypertension is a significant risk factor for stroke in this group [2,3].

Silent cerebral infarction (SCI) is thought to be an underlying or concomitant condition of clinical subcortical brain infarction or brain hemorrhage [4]. In most cases, SCI is found as a lacunar infarction, the most common form of subcortical infarction, defined by Fisher [5] as small, deep cerebral infarctions caused by occlusion of small penetrating cerebral arteries.

Hepatocyte growth factor (HGF) is a mesenchyme-derived pleiotropic factor that regulates cell growth and motility and morphogenesis of various types of cells [6]. HGF has the unique ability to stimulate endothelial cell growth without affecting vascular smooth muscle cell growth [6]. Furthermore, HGF exerts an antiapoptotic effect on the endothelium [7]. Through these functions, tissue HGF has been shown to play an antiatherogenic role [8]. Although its origin is not fully known, HGF is present in the circulation [9-13]. The circulating level of HGF has been shown to be increased in cardiocerebrovascular disease, including hypertension [9], atherosclerosis [10], and myocardial infarction [11], as well as cerebral infraction [12], and end-stage renal disease (ESRD) [13].

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Table 1
Clinical characteristics of studied patients

	SCI(−)	SCI(+)	*P*
Age (y)	60 ± 7	61 ± 8	NS
Sex (male/female)	13/10	16/11	NS
Body mass index (kg/m^2)	22.1 ± 2.1	22.8 ± 2.5	NS
Dialysis duration (y)	1.7 ± 1.2	1.9 ± 1.4	NS
Diabetes mellitus (%)	57	67	NS
Hypertension (%)	74	81	NS
Dyslipidemia (%)	43	56	NS
Smoking habit (%)	17	44	.0410
Ischemic heart disease (%)	13	41	.0297
Drug use (%)			
Sulfonylurea	30	33	NS
α-Glucosidase inhibitors	26	29	NS
Insulin	9	11	NS
Statin	39	48	NS
Calcium channel antagonists	65	70	NS
ACE inhibitors	13	15	NS
Angiotensin receptor blocker	26	30	NS
β-Blocker	17	19	NS
Hematocrit (%)	30.3 ± 3.4	29.5 ± 2.9	NS
Total cholesterol (mg/dL)	157 ± 55	173 ± 61	NS
Triglyceride (mg/dL)	102 ± 29	116 ± 40	NS
HDL-C (mg/dL)	46 ± 13	37 ± 11	.0115
Fasting plasma glucose (mg/dL)	128 ± 21	132 ± 26	NS
HbA_{1c} (%)	6.2 ± 1.1	6.4 ± 1.3	NS
Uric acid (mg/dL)	6.9 ± 1.8	8.1 ± 2.1	.0465

Data are means ± SD unless otherwise indicated. ACE indicates angiotensin-converting enzyme; NS, not significant.

Nondippers, who show a diminished nocturnal blood pressure (BP) fall, have been shown to have an increased frequency of damage to target organs, including the brain, heart, and kidney, and poorer prognosis for cardiovascular events when compared with dippers with appropriate nocturnal BP fall [14-16]. Recent articles have also reported that serum HGF concentration was associated with nighttime BP, especially for non–dipper-type patients [17].

Renal failure is associated with a high prevalence of left ventricular hypertrophy, which is the strongest predictor of death in patients with ESRD [18].

The significance of increased HGF levels with SCI in HD patients has not been adequately investigated. We hypothesized that increased levels of HGF are associated with SCI in HD patients. To test our hypothesis, we compared the findings from magnetic resonance imaging (MRI), 24-hour ambulatory blood pressure (ABP) monitoring, echocardiography, and metabolic profiles in Japanese HD patients with and without SCI, followed by evaluation of independent predictors of SCI in these patients.

2. Subjects and methods

2.1. Patients

A total of 50 patients on HD (age, 60 ± 8 years, mean ± SD; 29 men and 21 women) who were admitted to the Oita Red Cross Hospital, Oita, Japan, between January 2002 and March 2006 were enrolled in this study. The clinical characteristics of the studied patients are summarized in Table 1. All HD patients received regular dialysis using a high-flux cellulose triacetate or polysulfone hollow-fiber dialyzer 3 times per week in sessions lasting 4 hours. The dialysate flow rate was 500 mL/min, and blood flow ranged from 120 to 200 mL/min. The dry weight was determined for each patient with the post-HD cardiothoracic ratio, and clinical observations such as presence of muscle cramps, general fatigue, thirst, or hypotension during the HD session were recorded. All patients were maintained at their set dry weight. No difference was observed between the 2 groups with respect to dialysis methods. Patients with atrial fibrillation, liver dysfunction, a history of symptomatic stroke, transient ischemic attacks, dementia, autosomal-dominant polycystic kidney disease, chronic infection, chronic inflammatory disease, or any other malignant disease were excluded from the study. All subjects gave their written informed consent to participate in the study. The study protocol was approved by the ethics committee of the Oita Red Cross Hospital.

2.2. Risk factors

To evaluate potential risk factors, we examined this patient cohort for the presence or absence of hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease (IHD), and smoking. Individuals with BP higher than 135/85 mm Hg measured at home or individuals treated with antihypertensive drugs are generally considered to be hypertensive [19]. Diabetes mellitus was designated as present if patients were using insulin or oral hypoglycemic agents or if their fasting glucose concentration was greater than 126 mg/dL. Twenty-two of 27 patients with SCI and 16 of 23 patients without SCI met this criterion; all of these patients were being treated with calcium channel antagonists, β-blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers. Dyslipidemia was defined as having fasting triglyceride levels of 200 mg/dL or greater or high-density lipoprotein (HDL) cholesterol (HDL-C) levels of less than 45 mg/dL for women and less than 35 mg/dL for men [20], or receiving medical treatment for hyperlipidemia. Ischemic heart disease was defined as having angina or a history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary intervention. Smoking was defined as current cigarette smoking. Serum from blood samples for these assays was separated and stored at −20°C until tested.

Serum or plasma HGF concentrations were measured with an enzyme-linked immunosorbent assay kit (Otsuka Assay Laboratories, Tokyo, Japan) using an anti–human HGF monoclonal antibody for the solid phase and an anti–human HGF rabbit polyclonal antibody for the liquid phase [21]. The coefficient of variation for this method has been reported to be less than 5.5% for 1 ng/mL of HGF [21].

2.3. Twenty-four-hour ABP monitoring

During admission, 24-hour ABP was measured with the cuff-oscillometric method using an ABP monitoring system

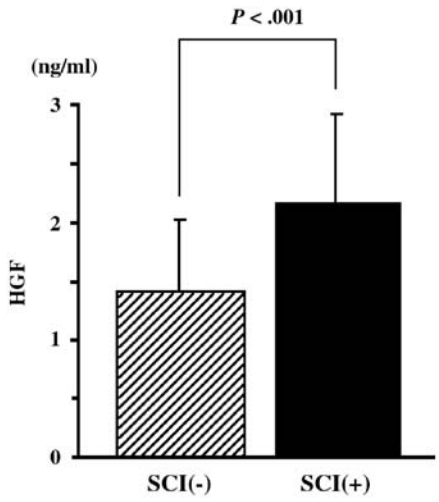

Fig. 1. Comparison of HGF levels between HD patients with silent cerebral infarction, SCI(+), and without silent cerebral infarction, SCI(−). Data represent means ± SD.

(TM-2425, A&D, Tokyo, Japan) with carbon dioxide gas–powered cuff inflation. The accuracy of these devices had been previously validated [22]. The ABP monitoring was initiated after dialysis treatment in a midweek period. Blood pressure was measured every 30 minutes from 6:00 AM to 10:00 PM, and every 60 minutes from 10:00 PM to 6:00 AM of the following day [23]. Blood pressure represents the mean value during the awake period between 6:00 AM and 10:00 PM and during the sleep period between 10:00 PM and 6:00 AM [23]. The waking time, time of falling asleep, and quality of sleep were assessed in interviews with each patient. Patients who complained of sleep disturbance during ABP monitoring were excluded from the study. Subjects whose mean nighttime systolic ABP (sABP) fell by more than 10% compared with their mean daytime sABP value were defined as "dippers." The remaining subjects were defined as "nondippers" [24].

2.4. Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained with a phase-array echo-Doppler system. Echocardiograms were obtained in a standard manner using standard parasternal, short axis, and apical views. Left ventricular mass was calculated as described previously [25]: left ventricular mass = {1.04 ([LVIDd + IVSTd + PWTd]^3 − LVIDd^3) − 14 g}, where LVIDd is the left ventricular internal dimension at end diastole, IVSTd is the interventricular septal thickness at end diastole, and PWTd is the posterior wall thickness at end diastole. Left ventricular mass was divided by body surface area to calculate the left ventricular mass index (LVMI). Pulsed Doppler recordings were made from the standard apical 4-chamber view. Mitral inflow velocity was recorded with the sample volume at the mitral annulus level; the average of 3 or more cardiac cycles was taken. The following measurements were made: peak velocity of early ventricular filling (E), peak velocity of late ventricular filling (A), their ratio (E/A), and deceleration time.

2.5. Evaluation of SCI

All participating patients had a brain MRI scan. T_1- and T_2-weighted images in axial planes at 5-mm-thick slices were collected with a field of 1.5T on proton density (Visart EX, Toshiba, Tokyo, Japan). Lacunar infarctions were identified by the presence of a hyperintense area on T_2-weighted images (5 mm $\leq$ diameter < 15 mm) that was visible as a low signal intensity on T_1-weighted images. To exclude enlarged periventricular spaces, lesions less than 5 mm were not counted as infarctions, as described by Braffman et al [26]. The MR images were evaluated by 2 neurologists independently.

2.6. Statistical analysis

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

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

A model selection procedure was used to select the simplest regression model, that is, to identify significant factors. A value of P < .05 was considered statistically significant.

Table 2
Ambulatory blood pressure monitoring findings

	SCI(−)	SCI(+)	P
24-h time			
sABP (mm Hg)	136 ± 6	139 ± 11	NS
dABP (mm Hg)	78 ± 9	77 ± 10	NS
Heart rate (beats/min)	70 ± 5	71 ± 5	NS
Daytime			
sABP (mm Hg)	140 ± 7	143 ± 10	NS
dABP (mm Hg)	81 ± 8	79 ± 10	NS
Heart rate (beats/min)	73 ± 6	74 ± 6	NS
Nighttime			
sABP (mm Hg)	124 ± 6	132 ± 12	.0101
dABP (mm Hg)	68 ± 8	71 ± 10	NS
Heart rate (beats/min)	61 ± 5	65 ± 5	.0120
Nondippers (%)	39	70	.0266

Data are means ± SD unless otherwise indicated. NS indicates not significant.

3. Results

As demonstrated in Table 1, the mean age was similar between the group with SCI and group without SCI. No significant differences were observed between the 2 groups with respect to sex, body mass index, or HD duration. The percentages of patients with diabetes, hypertension, dyslipidemia, and administered medications were similar between the 2 groups. However, the group with SCI had a higher percentage of smokers and IHD than the group without SCI (P = .0410, P = .0297, respectively).

There was no significant difference in hematocrit, fasting plasma glucose concentration, or hemoglobin A_{1c} (HbA_{1c}) levels. With regard to lipid metabolism, serum HDL-C level was lower in the group with SCI than in the group without SCI (P = .0115), whereas serum total cholesterol and triglyceride levels showed no significant difference between the groups. Uric acid level was higher in the group with SCI than in the group without SCI (P = .0465).

Hepatocyte growth factor levels in the 2 groups of HD patients are provided in Fig. 1. HGF was higher in the group with SCI than in the group without SCI (2.15 ± 0.78 vs 1.40 ± 0.66 ng/mL, P = .0008).

The ABP data are shown in Table 2. Systolic ABP, diastolic ABP (dABP), and heart rate during the day were similar between the groups. In contrast, nighttime sABP and heart rate were higher in the group with SCI (P = .0101, P = .0120, respectively). However, nighttime dABP was similar between the 2 groups. The 24-hour mean sABP, dABP, and heart rate were similar. The percentage of nondippers was higher in the group with SCI (P = .0266).

The echocardiographic findings are summarized in Table 3. Ejection fraction and left ventricular dimensions at end diastole and end systole were similar in the 2 groups. However, the IVSTd, PWTd, and LVMI were higher in the group with SCI than in the group without SCI (P = .0324, P = .0099, and P = .0113, respectively). With regard to the left ventricular diastolic function, the ratio of peak velocities of early to late ventricular filling (E/A ratio) was lower in the group with SCI (P = .0470). Deceleration time was similar between the 2 groups.

In simple logistic regression analysis, the risk of SCI was associated with smoking (odds ratio [OR] 3.80; 95% confidence interval [CI] = 1.02-14.2; P = .0472), IHD (OR, 4.58; 95% CI, 1.09-19.3; P = .0377), HDL-C (OR, 0.94; 95% CI, 0.89-0.99; P = .0189), HGF (OR, 1.89; 95% CI, 1.57-3.38; P = .0034), IVSTd (OR, 1.49; 95% CI, 1.02-2.18; P = .0384), PWTd (OR, 1.66; 95% CI, 1.10-2.50; P = .0155), and LVMI (OR, 1.02; 95% CI, 1.00-1.04; P = .0178) as the dependent metabolic and echocardiographic parameters in HD patients (Table 4). In addition, the risk of SCI was associated with nighttime sABP (OR, 1.10; 95% CI, 1.02-1.20; P = .0191), nighttime heart rate (OR, 1.17; 95% CI, 1.03-1.33; P = .0193), and nondippers (OR, 3.69; 95% CI, 1.14-12.0; P = .0294) as the dependent hemodynamic parameters in HD patients. Finally, multiple logistic regression analysis identified plasma HGF in the HD patients as a significant risk factor for SCI (OR, 1.89; 95% CI, 1.57-3.38; P = .0034).

Table 3
Echocardiographic findings

	SCI(−)	SCI(+)	P
Ejection fraction (%)	63 ± 7	61 ± 8	NS
LVIDd (mm)	46 ± 3	48 ± 4	NS
LVIDs (mm)	32 ± 4	33 ± 5	NS
IVSTd (mm)	9.7 ± 1.8	10.7 ± 1.4	.0324
PWTd (mm)	10.0 ± 1.5	11.2 ± 1.5	.0099
LVMI (g/m^2)	126 ± 29	152 ± 39	.0113
E/A ratio	0.83 ± 0.11	0.76 ± 0.15	.0470
Deceleration time (ms)	258 ± 31	275 ± 28	NS

Data are means ± SD. LVIDs indicates left ventricular internal dimension at end systole; NS, not significant.

Table 4
Univariate logistic regression analysis with silent cerebral infarct as the dependent variable in HD patients

	SCI		
	OR	95% CI	P
Age	1.02	0.95-1.10	NS
Sex	1.12	0.36-3.45	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	3.80	1.02-14.2	.0472
Ischemic heart disease	4.58	1.09-19.3	.0377
Hematocrit	0.93	0.77-1.11	NS
Total cholesterol	1.00	0.99-1.02	NS
Triglyceride	1.01	0.98-1.03	NS
HDL-C	0.94	0.89-0.99	.0189
Fasting plasma glucose	1.01	0.98-1.03	NS
HbA_{1c}	1.12	0.72-1.89	NS
Uric acid	1.35	0.99-1.82	NS
HGF	1.89	1.57-3.38	.0034
Ejection fraction	0.98	0.90-1.05	NS
LVIDd	1.10	0.94-1.28	NS
LVIDs	1.08	0.94-1.24	NS
IVSTd	1.49	1.02-2.18	.0384
PWTd	1.66	1.10-2.50	.0155
LVMI	1.02	1.00-1.04	.0178

Significant predictors of SCI were explored among 6 parameters: sex (female = 0, men = 1), diabetes mellitus (absent = 0, present = 1), hypertension (absent = 0, present = 1), hyperlipidemia (absent = 0, present = 1), smoking habit (absent = 0, present = 1), and IHD (absent = 0, present = 1).

4. Discussion

In the present study, measurement of metabolic parameters revealed that serum HDL-C levels were lower and HGF levels higher in the group with SCI than in the group without SCI. With regard to ABP findings, the nighttime sABP and heart rate were higher in the group with SCI than in the group without SCI. Furthermore, multiple logistic regression analysis revealed that HGF is a risk factor for the presence of SCI in HD patients.

Silent cerebral infarction is an important risk factor for stroke and there are several reports examining SCI in the

general population. From the results of MRI studies, Kobayashi et al [4] reported that the incidence of SCI was 10.6% in 993 neurologically healthy adults without a history of cerebrovascular diseases. The Hisayama community-based study revealed that the incidence of SCI was 12.9% [27]. The prevalence of SCI in HD patients is thought to be about 5 times greater than that in the healthy population [2,3]. This incidence of SCI is similar to the proportion observed in the present study (27 [54.0%] of 50 HD patients).

In general, heparin increases circulating HGF levels [28]. Thus, in the present study, we obtained the blood samples in the morning before heparin administration prior to dialysis. There are several reports regarding the levels of HGF in the sera [29-31]. Sugimura et al [29] reported that the range of HGF level in the sera was 0.33 to 0.45 ng/mL. Similarly, Rampino et al demonstrated that the level of HGF in the sera was 0.24 ng/mL before dialysis [30].

On the contrary, Malatino et al [31] reported that HGF level was divided into 2 groups, that is, high ($\geq$1.85 ng/mL) and low ($<$1.85 ng/mL). The results are compatible with our findings. What could have caused the different results? HGF has a short half-life and is cleared mainly by the liver [29]. Although the precise mechanisms responsible for the high levels of serum HGF in ESRD are still unclear, it appears that this phenomenon does not represent the mere effect of reduced removal of HGF by the kidney. Further studies are needed to clarify this point.

The underlying mechanism of the links between serum HGF and SCI remains to be elucidated. In our opinion, several mechanisms could explain this observation.

First, Ma et al [32] reported that HGF is expressed in human atherosclerotic plaques and colocalizes with vascular smooth muscle cells, microvascular endothelial cells, and monocytes/macrophages. Second, Makondo et al [33] reported that HGF directly stimulates endothelial nitric oxide synthase activity in vascular endothelial cells by a phosphoinositide 3-kinase/Akt–dependent phosphorylation in a calcium-sensitive manner. Thus, HGF appears to be not only a risk factor for arterial sclerosis, but possibly may act as a pathophysiologic modulator of other endothelial dysfunctions. The possibility of the association between HGF levels and risk of lacunar infarction detected in our study was suggested.

The lack of a nocturnal fall in BP (nondipper) is common among HD patients [34]. Liu et al [35] concluded that nondipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in HD patients. In addition, Hayashi et al [17] reported that serum HGF concentration was associated with nighttime BP, especially for nondipper-type patients. In the present study, the percentages of nondippers, night sABP, night heart rate, and LVMI were all higher in the group with SCI than in the group without SCI.

The percentage of smokers was higher in the group with SCI as well. Howard et al [36] reported that smoking is related to the prevalence of SCI. Smoking affects the vasculature via several different interactive mechanisms [37]. Nicotine and carbon monoxide separately produce tachycardia, hypertension, and vasoconstriction, and both damage the endothelium directly. Smoking also affects vaso-occlusive factors such as platelet aggregation, plasma viscosity, and fibrinogen levels [37].

First, simple logistic regression analysis was performed for each parameter in Table 4 and the analysis showed that HDL-C, HGF, nighttime sABP, nighttime heart rate, non-dipper, IVSTd, PWTd, LVMI, IHD, and smoking are all risk factors for SCI in HD patients. Second, to determine significant risk factors from the above ones, multiple logistic regression analysis was performed. A model selection procedure was used for this objective, and HGF was statistically decided to be a significant risk factor for the presence of SCI in HD.

There are several limitations to this study. First, this study included a relatively small number of patients and did not include age-matched control subjects. Second, there is a general limitation associated with the interpretation of data in a cross-sectional study. In this case, the long-term consistency of plasma levels of HGF will need to be demonstrated. Finally, the relationship between HGF and atherosclerosis (cerebrovascular disease, coronary artery disease) in population-based samples has been reported in previous studies, with conflicting results [9-13,32,38-40]. The circulating form of HGF has been used as a clinical marker for many target organs, such as the brain, heart, and kidney. Many studies to investigate their possible usefulness for measurement of the serum concentration of HGF as the indicator of atherosclerotic complications have been performed [9-13,32]. However, recent studies have demonstrated the potential application of HGF to treat cardiovascular disease such as peripheral vascular disease [38], cerebrovascular disease [40], and coronary artery disease.

Taken together, elevated HGF levels may be produced as a result of underlying ischemia, and their elevation in the context of this study represents an epiphenomenon. A prospective longitudinal study will be necessary to address these issues as well as to identify factors determining the plasma level of HGF in response 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 and that HGF is significantly associated with SCI in HD patients.

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