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Silent cerebral infarction predicts vascular events in hemodialysis patients

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Silent cerebral infarction predicts vascular events in hemodialysis patients.

Background. Cardiovascular disease is the leading cause of death in hemodialysis (HD) patients. We have previously reported a higher incidence of silent cerebral infarction (SCI) in HD patients compared with the control group using MRI studies. In the present study, we examined whether or not SCI could predict vascular events in HD patients.

Methods. Cranial magnetic resonance imaging (MRI) was performed on 119 HD patients without symptomatic cerebrovascular disease. SCI was detected by MRI, and the patients were prospectively followed up. The end points of the study were the incidence of major events related to vascular events (cerebral events, cardiac events, and sudden deaths). We investigated the prognostic role of SCI in cerebral, cardiac, and vascular events by using the Kaplan-Meier method and Cox proportional hazards analysis.

Results. The prevalence of SCI was 49.6% in HD patients. During a follow-up period of maximum 60 months, vascular events, which included 13 cerebral events, 5 cardiac events, and 3 sudden deaths, occurred in 21 patients. The presence of SCI was predictive for a higher cerebral and vascular morbidity compared to the absence of SCI [18.6% ($N = 11$) vs. 3.3% ($N = 2$), $P = 0.0169$, and 30.5% ($N = 18$) vs. 5.0% ($N = 3$), $P = 0.0006$, respectively]. By multivariate Cox proportional hazards analysis, SCI remained a powerful independent predictor of cerebral and vascular events (hazard ratio for cerebral events 7.33, 95% CI 1.27–42.25: for vascular events 4.48, 95% CI 1.09–18.41).

Conclusion. The findings of the present study indicate that the presence of SCI is a new risk factor for vascular events in HD patients.

Silent cerebral infarction (SCI) is thought to be an underlying or concomitant condition of clinical subcortical brain infarction or brain hemorrhage in the general population [1]. In most cases, SCI is found as a lacunar infarction, the most common form of subcortical infarction, defined by Fisher as a small, deep cerebral infarction caused by occlusion of small penetrating cerebral arteries [2]. The lacunar infarction results from the arteriolosclerotic change of cerebral arteries, which is related to aging and is accelerated by hypertension [3]. From the results of magnetic resonance imaging (MRI) studies, Kobayashi et al [1] reported that the incidence of SCI was 10.6% in 993 neurologically normal adults without history of cerebrovascular disease. Howard et al [4] also reported that the incidence of SCI was 11% using MRI studies. The Hisayama community-based study showed that the incidence of SCI was 12.9% [5]. SCI is considered an important risk factor for clinical cerebrovascular disease in the general population [1].

We have previously reported a higher incidence of SCI in hemodialysis (HD) patients compared with the control group using MRI studies (48.8% vs. 9.6%, respectively) [6]. It is also well known that HD patients have a much higher incidence of cardiovascular disease than normal populations [7–11]. In spite of the high incidence of SCI, the clinical significance of SCI in HD patients has not yet been elucidated. In the present study, we investigated whether or not SCI is associated with clinical vascular events.

METHODS

Study design

We performed a prospective cohort study to investigate whether or not SCI is associated with clinical vascular events.

Patients

The cohort consisted of 119 neurologically normal HD patients in stable conditions who agreed to undergo MRI, and were diagnosed with the presence or absence of SCI. They were selected from a total of 175 HD patients, and were enrolled in the trial between April 1998 and October

Key words: magnetic resonance imaging, silent cerebral infarction, stroke, cardiovascular disease, risk factor, hemodialysis.

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Table 1. Characteristics of patients with and without SCI[a]

	Total ($N = 119$)	No SCI ($N = 60$)	SCI ($N = 59$)	P value[b]
Age *years*	56.0 ± 12.7	49.2 ± 12.8	62.9 ± 8.1	<0.0001
Males/females	84/35	43/17	41/18	NS
Hematocrit %	31.6 ± 3.4	31.7 ± 3.2	31.6 ± 3.6	NS
Systolic blood pressure *mm Hg*	152.0 ± 20.7	150.9 ± 24.3	153.0 ± 18.1	NS
Diastolic blood pressure *mm Hg*	77.8 ± 10.8	79.4 ± 11.7	76.7 ± 10.1	NS
Hypertension No.	102	51	51	NS
Diabetes mellitus No.	34	10	24	0.0070
Total cholesterol *mg/dL*	155.5 ± 40.7	158.0 ± 40.9	153.8 ± 41.1	NS
Triglycerides *mg/dL*	94.2 ± 53.7	104.1 ± 12.8	87.2 ± 52.1	NS
HDL cholesterol *mg/dL*	41.2 ± 12.6	42.0 ± 14.0	40.3 ± 11.5	NS
Dyslipidemia No.	15	4	11	NS
Ischemic heart disease No.	20	3	17	0.0012
Smoking habit No.	30	8	22	0.0051
Dialysis duration *years*	6.0 ± 5.5	6.5 ± 5.3	5.4 ± 5.6	NS
Serum albumin *g/dL*	3.8 ± 0.4	3.9 ± 0.4	3.8 ± 0.3	0.0334
Body mass index kg/m^2	21.3 ± 3.3	21.2 ± 3.3	20.5 ± 2.9	NS

Abbreviations are: SCI, silent cerebral infarction; HDL, high density lipoprotein.
[a]Plus-minus values are mean ±SD, [b]SCI vs. no SCI.

2000. All subjects had no past history or symptoms of strokes, transient ischemic attacks, and dementia based on their self-reports as well as their medical records. We prospectively followed these patients until March 2003. The end points of this study were the incidence of major events related to cardiovascular disease. Patients with autosomal-dominant polycystic kidney disease, chronic infection, chronic inflammatory disease, or malignant disease were excluded at the beginning of this study. Table 1 shows the patient characteristics in 119 HD patients. The patients with SCI were significantly older than those without SCI. The prevalence of diabetes mellitus, ischemic heart disease, and smoking habits were significantly higher in patients with SCI than in patients without SCI. In addition, serum albumin levels were significantly lower in patients with SCI than in patients without SCI.

All HD patients received regular dialysis using the high-flux cellulose-triacetate or polysulfone hollow-fiber dialyzer three times per week in sessions lasting 3 to 4.5 hours. The dialysate was buffered bicarbonate and contained 140 mmol/L sodium. The dialysate flow rate was 500 mL/min, and blood flow ranged from 120 to 200 mL/min. The dry weight was individually determined for each patient on the basis of post-HD cardiothoracic ratio, atrial natriuretic peptide levels, and clinical observations, such as presence of muscle cramps, general fatigue, thirst, or hypotension during the HD session, and all patients were maintained at their set dry weight. Informed consent was obtained from all for participation in the study.

Vascular events

In the present study, we defined vascular events as comprising cerebral events, cardiac events, and sudden deaths. Cerebral events were brain infarction, brain hemorrhage, subarachnoid hemorrhage, transient ischemic attack (TIA), and prolonged reversible ischemic neurologic defect (PRIND). Cardiac events were myocardial infarction, the need for coronary angioplasty or coronary bypass surgery, and congestive heart failure. All these diseases were diagnosed by standard clinical criteria. Sudden death was defined as a witnessed death that occurred within one hour after the onset of acute symptoms, and without evidence of accident or violence.

Risk factors

Hypertension was defined by the administration of antihypertensive agents and/or a history of this disorder, a systolic blood pressure greater than 140 mm Hg, or a diastolic blood pressure greater than 90 mm Hg. Blood pressure was determined at the end points of HD sessions with a standard mercury sphygmomanometer and cuffs adapted to arm circumference. The systolic blood pressure was taken as the point of appearance of Korotokof sounds, and the diastolic blood pressure as the point of disappearance of the sounds.

Dyslipidemia was defined as present if the subject had total cholesterol (TC) >220 mg/dL, triglyceride (TG) >150 mg/dL, and high-density lipoprotein (HDL) cholesterol <40 mg/dL, according to the criteria of the Japan Atherosclerosis Society, or had received medical treatment for hyperlipidemia. In HD patients, blood samples were taken from the arterial line before HD sessions.

Ischemic heart disease (IHD) was defined as either angina, history of myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal angioplasty. Angina was diagnosed by exercise electrocardiography or myocardial perfusion imaging.

Smoking habit was defined as those respondents who currently smoked cigarettes.

Outcome

We collected the patients' clinical outcome data by reviewing all medical records directly. Concerning the 25 patients who moved out of our dialysis hospitals during the follow-up period, all their outcome data were obtained through questionnaire forms filled out by the present attending physicians. All vascular events were

diagnosed carefully by the attending physicians, who had not been notified of this study. In cases that presumable vascular events happened out of hospital, the patient's family was interviewed by telephone to ascertain the circumstances.

Magnetic resonance imaging

All participating patients had a brain MRI that used a superconducting magnet at a field strength of 1.5 T on proton density, T1-, and T2-weighted images in axial planes at 10 mm thick slices. Infarction was defined as a focal area larger than 3 mm in diameter in both T1- and T2-weighted images that was visible as low-signal intensity areas on T1-weighted image and as high-signal intensity areas on T2-weighted image. The MR images were assessed independently by two neuroradiologists who had not been notified of any clinical information. Cases with inconsistencies were excluded from the study. From 125 patients with MRIs taken, six cases with diagnostic inconsistencies were excluded, resulting in 119 cases in this cohort study.

Statistical analysis

All data are presented as the mean ± SD. Differences between groups were examined by Student *t* tests. Categorical variables were compared using chi-square analysis. The risks for cerebral, cardiac, and vascular events between patients with or without SCI were compared using Kaplan-Meier analysis. Differences between the groups were analyzed by the log-rank test. The independent power of different variables to predict cerebral or vascular morbidity was assessed using Cox proportional hazards regression analysis. Gender and presence of hypertension, diabetes mellitus, dyslipidemia, IHD, and SCI were represented by dummy variables (1 = male, 0 = female; 1 = presence, 0 = absence) in the analysis. The value of $P < 0.05$ was considered statistically significant. These results were obtained on a Macintosh computer using the Stat View V Statistical System (Cary, NC, USA).

RESULTS

Prevalence of SCI in HD patients

Fifty-nine patients (49.6%) had SCI. Among the 59 HD patients with SCI, 56 cases had lacunar infarction, and three cases had cortical infarction.

Outcome

No patients received kidney transplantation during the follow-up period. Seven patients who died of nonvascular diseases during this period (four infectious diseases and three malignant diseases) were censored when they died. Vascular events occurred in 21 patients (Table 2), where 11 events were lethal. Cerebral events were observed in 13 cases, namely, brain infarction ($N = 6$), brain hemorrhage ($N = 4$), and TIA ($N = 3$), in which two cases of cerebral infarction, and three of cerebral hemorrhage caused deaths. Cardiac events in five cases were congestive heart failure ($N = 1$), coronary bypass surgery ($N = 1$), and myocardial infarction ($N = 3$), where two cases of myocardial infarction, and one case of congestive heart failure were lethal. In addition, sudden death happened in three cases. The mean follow-up periods to cerebral, cardiac, and vascular events were 40.2 ± 12.2, 42.1 ± 10.8, and 39.3 ± 12.4 months, respectively (range 1 to 60 months).

Table 2. Details of the study subjects with clinical stroke onset

Subject/ age/sex	SCI	Hemodialysis duration *years*	Event	Interval *months*
1/71/male	1	6.2	BI	55
2/63/female	1	3.0	CHF[a]	30
3/61/male	1	3.2	Sudden death[a]	19
4/55/male	1	4.1	BH[a]	39
5/55/male	1	5.0	CBS	45
6/77/female	1	6.5	BH[a]	1
7/70/male	1	1.0	Sudden death[a]	10
8/63/male	1	1.2	BI	25
9/63/male	1	22.8	BH	20
10/70/male	1	14.0	BH[a]	10
11/65/male	1	6.3	BI	63
12/51/male	1	1.3	BI	5
13/72/female	1	12.5	TIA	34
14/69/female	1	17.5	Sudden death[a]	29
15/46/male	1	22.0	AMI	40
16/53/female	0	5.0	AMI[a]	35
17/68/male	1	6.1	BI[a]	36
18/69/male	1	10.1	BI[a]	45
19/53/female	0	14.3	TIA	43
20/70/male	1	24.9	AMI[a]	23
21/38/male	0	5.1	TIA	42

Abbreviations are: SCI, silent cerebral infarction (absent = 0, present = 1): BI, brain infarction; CHF, congestive heart failure; BH, brain hemorrhage; BS, coronary bypass surgery; TIA, transient ischemic attack; AMI, acute myocardial infarction.

[a]Case of death.

Kaplan-Meier analyses based on the presence or absence of SCI for cerebral, cardiac, and vascular morbidity are shown in Figures 1 to 3. The group with SCI had a significantly higher cerebral morbidity than that without SCI [18.6% ($N = 11$) vs. 3.3% ($N = 2$), $P = 0.0169$, Fig. 1]. Although cardiac morbidity was also higher in the patients with SCI than in those without SCI, there was no significant difference [6.8% ($N = 4$) vs. 1.6% ($N = 1$), $P = 0.1659$, Fig. 2]. The three sudden death cases were all with SCI. Accumulating cerebral events, cardiac events, and sudden deaths together, vascular morbidity was significantly higher in the presence of SCI than in the absence of SCI [30.5% ($N = 18$) vs. 5.0% ($N = 3$), $P = 0.0006$, Fig. 3].

Predictors of cerebral morbidity in HD patients (model 1)

Using univariate and multivariate Cox proportional hazards analysis, 11 clinical variables, including SCI, were

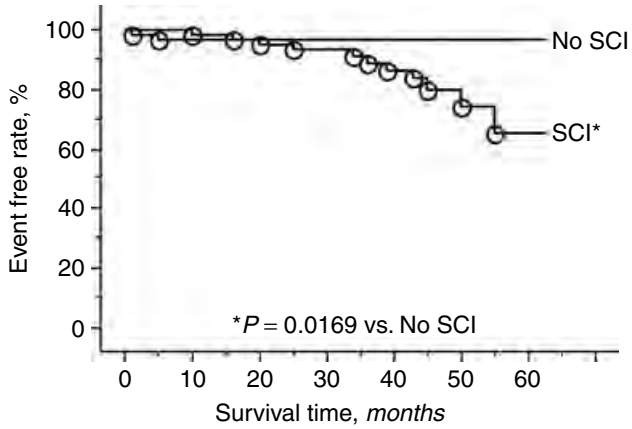

Fig. 1. Kaplan-Meier analysis of cumulative rate of cerebrovascular event-free survival in hemodialysis patients stratified into two groups with/without silent cerebral infarction.

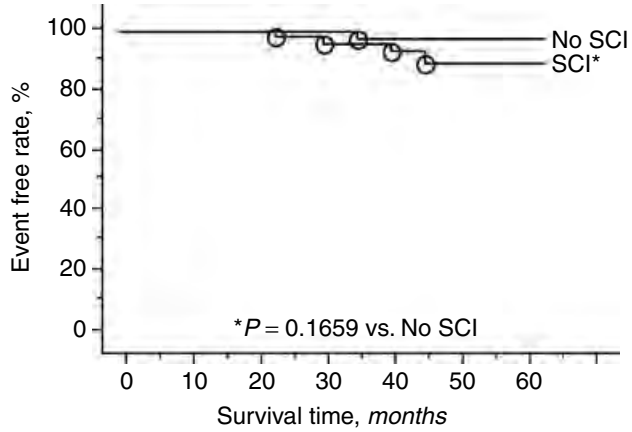

Fig. 2. Kaplan-Meier analysis of cumulative rate of cardiac event-free survival in hemodialysis patients stratified into two groups with/without silent cerebral infarction.

examined for predicting cerebral morbidity. By univariate analysis, two variables (duration of HD and SCI) were shown to be significant predictors of cerebral morbidity. Moreover, multivariate analysis demonstrated that SCI was a significant independent predictor. In the present study, the relative risk ratio of SCI was 7.33 (95% CI 1.27–42.25) (Table 3).

Predictors of vascular morbidity in HD patients (model 2)

Using univariate and multivariate Cox proportional hazards analysis, 11 clinical variables, including SCI, were examined for predicting vascular morbidity. By univariate analysis, four variables (age, duration of HD, IHD, and SCI) were shown to be significant predictors of vascular morbidity. Moreover, multivariate analysis demonstrated that SCI was a significant independent predictor. In the present study, the relative risk ratio of SCI was 4.48 (95% CI 1.09–18.41) (Table 4).

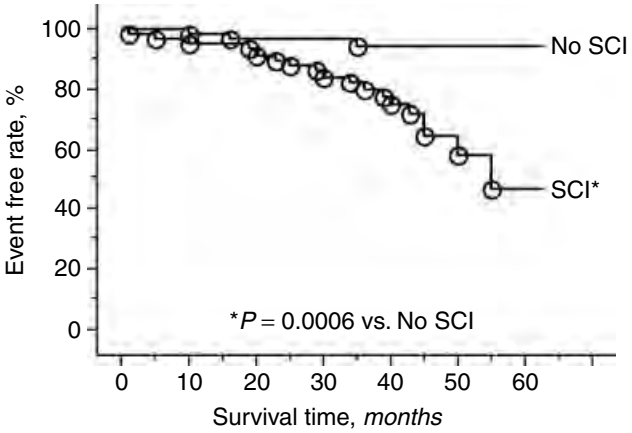

Fig. 3. Kaplan-Meier analysis of cumulative rate of vascular event-free survival in hemodialysis patients stratified into two groups with/without silent cerebral infarction.

When evaluating the association between hypertension and vascular events, we examined a continuous variable (blood pressure), as well as a categorical variable (presence of hypertension), but no association was found by using either variable.

DISCUSSION

Cardiovascular disease is the leading cause of death in HD patients [11]. It is well known that the increased risk of cardiovascular disease is attributable to advanced atherosclerotic vascular changes [12, 13]. Degrees of atherosis and sclerosis have been evaluated noninvasively by measuring the intima-media thickness of the carotid artery (CA-IMT) and aortic pulse wave velocity (PWV), respectively. Shoji et al [13] showed that aortic stiffness is an independent predictor of cardiovascular deaths in patients with ESRD. Nishizawa et al [12] showed that increased CA-IMT is an independent predictor of cardiovascular mortality in the HD population.

SCI is a clinical end-organ manifestation of arteriolosclerosis in the brain, as well as retinal arterial sclerosis in eyes and renal sclerosis in kidneys [2, 3]. Atherosclerosis or microemboli from large arteries and the heart is not considered to be a major pathogenesis of lacunar SCI [2, 3]. In a prospective study of the general population, Kobayashi et al [1] reported that subjects with SCI were considered at high risk for clinical cerebrovascular diseases. However, there have been no studies reported as to whether SCI is a risk factor for cerebrovascular disease in HD patients.

In the present study, we showed that the group with SCI had a significantly higher cerebral and vascular morbidity than the group without SCI. The group with SCI also tended to have a higher cardiac morbidity than that without SCI. This is the first report to evaluate the predictive role of SCI for vascular events in HD patients. It

Table 3. Univariate and mutivariate predictors of cerebral events in 119 hemodialysis patients

Variable	Unit increase	Univariate Hazard ratio (95% CI)	*P*	Multivariate Hazard ratio (95% CI)	*P*
SCI		5.22 (1.15–23.63)	.030	7.33 (1.27–42.25)	.026
Age	1 year	1.04 (0.99–1.09)	NS	1.04 (0.98–1.11)	NS
Duration	1 year	1.11 (1.02–1.20)	.014	1.09 (0.98–1.20)	NS
Sex		0.66 (0.21–2.00)	NS	0.50 (0.09–2.77)	NS
Ischemic heart disease		0.85 (0.18–3.88)	NS	0.59 (0.11–3.08)	NS
Diabetes mellitus		0.40 (0.09–1.82)	NS	0.32 (0.05–1.97)	NS
Hypertension		2.12 (0.28–16.33)	NS	3.25 (0.37–28.55)	NS
Dyslipidemia		0.83 (0.11–6.40)	NS	0.89 (0.08–9.48)	NS
Smoking habit		1.39 (0.42–4.53)	NS	1.96 (0.45–8.52)	NS
Serum albumin	1 g/dL	1.56 (0.30–7.98)	NS	6.18 (0.47–81.98)	NS
Body mass index	1 kg/m^2	0.86 (0.70–1.06)	NS	0.95 (0.74–1.22)	NS

SCI, silent cerebral infarction; 95% CI, 95% confidence interval.

Table 4. Univariate and mutivariate predictors of vascular events in 119 hemodialysis patients

Variable	Unit increase	Univariate Hazard ratio (95% CI)	*P*	Multivariate Hazard ratio (95% CI)	*P*
SCI		6.50 (1.91–22.06)	.002	4.48 (1.09–18.41)	.038
Age	1 year	1.04 (1.00–1.08)	.044	1.03 (0.98–1.08)	NS
Duration	1 year	1.09 (1.02–1.16)	.014	1.08 (0.99–1.17)	NS
Sex		0.66 (0.27–1.06)	NS	0.70 (0.19–2.58)	NS
Ischemic heart disease		3.38 (1.33–8.23)	.010	2.36 (0.82–6.80)	NS
Diabetes mellitus		0.99 (0.38–2.60)	NS	0.72 (0.21–2.41)	NS
Hypertension		1.69 (0.39–7.27)	NS	2.40 (0.52–11.02)	NS
Dyslipidemia		1.12 (0.26–4.90)	NS	0.86 (0.15–4.95)	NS
Smoking habit		2.24 (0.93–5.43)	NS	3.04 (0.95–9.75)	NS
Serum albumin	1 g/dL	0.78 (0.21–2.93)	NS	2.09 (0.29–15.12)	NS
Body mass index	1 kg/m^2	0.85 (0.73–1.00)	NS	0.90 (0.74–1.10)	NS

SCI, silent cerebral infarction; 95% CI, 95% confidence interval.

has been reported that SCI predicts the progression of systemic atherosclerosis that is manifested in the conduit arteries [14], suggesting the increased risk for vascular events in the presence of SCI. It is most likely that systemic arteriolosclerotic vascular changes are advanced in HD patients with SCI, which may also increase the risk of cardiac events as well as cerebral events.

Our multivariate analysis showed that SCI was a powerful independent predictor of cerebral and vascular events. In a cohort study of the general population, SCI was shown to be an independent risk factor for clinical stroke in multiple logistic regression analysis including age, sex, and presence of hypertension, diabetes, alcohol habits, and retinal arterial sclerosis [1], which is consistent with our findings.

HD duration was also an independent predictor of both cerebral and vascular events by our univariate analysis. This finding is consistent with the recent report by Angela et al [15] that increased mortality is the consequence of a prolonged dialysis duration, which may be explained by HD duration-dependent vascular calcification. Age and IHD were also independent predictors of vascular events in our univariate analysis, as shown by previous reports on the general population [16, 17] and HD patients [12, 18, 19]. However, the impact of HD duration, age, and IHD was not as strong as that of SCI, and was no longer significant by our multiple regression analysis.

It is well established that hypertension is an important risk factor for clinical cerebral stroke and cardiovascular disease, both in the general population [17] and in HD patients [7–10, 18]. However, hypertension was not a significant risk factor for cerebral or vascular events in our present study, where most of the hypertensive HD patients had received long-term antihypertensive treatments that may have had a beneficial effect on cerebral and coronal arteries.

Because a relatively small sample size of our study limited the statistical power of the analysis, our study never denies the other possible risk factors, such as hypertension or smoking. In addition, it should be noted that there are the other dialysis-related cardiovascular risk factors such as left ventricular hypertrophy, atherosclerosis (e.g., CA-IMT or PWV), or Kt/V that were previously reported but not assessed in this study.

Thirteen cerebrovascular events we observed were brain infarction, brain hemorrhage, and TIA, suggesting that SCI may be an important marker for predicting both ischemic stroke and hypertensive brain hemorrhage. All six cases of brain infarction were the same lacunar infarction as SCI, and all four cases of brain hemorrhage were typical hypertensive putaminal hemorrhage, which was

thought to have resulted from arteriolosclerosis as well as SCI. In comparison with Kobayashi's observation [1] that strokes occurring in subjects with SCI were ischemic stroke (74%) and brain hemorrhage (26%), brain hemorrhage seemed to occur more frequently in HD patients with SCI, which can be attributed to heparinization or hemostatic disorders in HD patients [8, 9]. Therefore, antiplatelet therapy in patients with SCI is controversial, although antithrombotic drugs can reduce the recurrence of brain infarction in subjects with brain infarction or coronary heart disease [20]. There have been no data concerning the effect of antithrombotic drugs on the primary prevention of clinical stroke in patients with SCI.

CONCLUSION

The presence of SCI is a new risk factor for vascular events in HD patients, and vascular complications should be checked carefully for the HD patients with SCI. Because chronic renal failure, hypertension, smoking habits, and aging are independent risk factors for SCI, as shown in our previous cross-sectional study [6], HD patients having high risks of SCI should be screened for SCI by MRI, and hypertension and smoking habits should be thoroughly controlled in HD patients.

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REFERENCES

1. Kobayashi S, Okada K, Koide H, *et al*: Subcortical silent brain infarction as a risk factor for clinical stroke. *Stroke* 28:1932–1939, 1997
2. Fisher CM: Lacunar strokes and infarcts: A review. *Neurology* 32:871–876, 1982
3. Bruno A, Rosenberg GA: The spectrum of lacunar infarction in the elderly. *Clin Geriatr Med* 7:443–453, 1991
4. Howard G, Wagenknecht LE, Cai J, *et al*: Cigarette smoking and other risk factors for silent cerebral infarction in the general population. *Stroke* 29:913–917, 1998
5. Shinkawa A, Ueda K, Kiyohara Y, *et al*: Silent cerebral infarction in a community-based autopsy series in Japan. The Hisayama Study. *Stroke* 26:380–385, 1995
6. Nakatani T, Naganuma T, Uchida J, *et al*: Silent cerebral infarction in hemodialysis patients. *Am J Nephrol* 23:86–90, 2003
7. Iseki K, Kinjo K, Kimura Y, *et al*: Evidence for high risk of cerebral hemorrhage in chronic dialysis patients. *Kidney Int* 44:1086–1090, 1993
8. Onoyama K, Ibayashi S, Nanishi F, *et al*: Cerebral hemorrhage in patients on maintenance hemodialysis. CT analysis of 25 cases. *Eur Neurol* 26:171–175, 1987
9. Onoyama K, Kumagai H, Miishima T, *et al*: Incidence of strokes and its prognosis in patients on maintenance hemodialysis. *Jpn Heart J* 27:685–691, 1986
10. Iseki K, Fukiyama K: Predictors of stroke in patients receiving chronic hemodialysis. *Kidney Int* 50:1672–1675, 1996
11. United States Renal Data System: Causes of death. *Am J Kidney Dis* 32:S81–88, 1998
12. Nishizawa Y, Shoji T, Maekawa K, *et al*: Intima-media thickness of carotid artery predicts cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 41:S76–79, 2003
13. Shoji T, Emoto M, Shinohara K, *et al*: Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol* 12:2117–2124, 2001
14. Hoshide S, Kario K, Mitsuhashi T, *et al*: Different patterns of silent cerebral infarct in patients with coronary artery disease or hypertension. *Am J Hypertens* 14:509–515, 2001
15. Wang AY, Wang M, Woo J, *et al*: Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: A prospective study. *J Am Soc Nephrol* 14:159–168, 2003
16. Kannel WB, Wolf PA, Verter J: Manifestations of coronary disease predisposing to stroke. The Framingham study. *JAMA* 250:2942–2946, 1983
17. Stamler J, Stamler R, Neaton JD: Blood pressure, systolic and diastolic, and cardiovascular risks. U.S. population data. *Arch Intern Med* 153:598–615, 1993
18. Brown JH, Hunt LP, Vites NP, *et al*: Comparative mortality from cardiovascular disease in patients with chronic renal failure. *Nephrol Dial Transplant* 9:1136–1142, 1994
19. Silberberg JS, Barre PE, Prichard SS, *et al*: Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 36:286–290, 1989
20. Shinoda-Tagawa T, Yamasaki Y, *et al*: A phosphodiesterase inhibitor, cilostazol, prevents the onset of silent brain infarction in Japanese subjects with type II diabetes. *Diabetologia* 45:188–194, 2002