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Ischemic Stroke in Patients with Renal Transplantation

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Background: Impaired renal function may contribute to development of stroke and small vessel pathology in the brain. We investigated whether stroke subtype, initial stroke severity, early neurologic outcomes, time to cerebral infarction occurrence, and the presence of small vessel pathology in the brain are different between patients with end stage renal disease (ESRD) and those with renal transplantation (RT). **Methods:** A total of 57 consecutive de novo RT patients (RT group) and 120 patients undergoing dialysis due to ESRD (ESRD group) who developed a first-ever acute cerebral infarction were enrolled. We compared stroke subtypes based on the Trial of Org 10172 in Acute Stroke Treatment classification, the presence of small vessel pathology (cerebral microbleed, leukoaraiosis and silent lacunar infarction) on MRI, stroke severity based on the National Institutes of Health Stroke Scale (NIHSS) and in-hospital mortality between the groups. **Results:** The stroke subtypes, NIHSS scores at admission and in-hospital mortality were not different between the two groups. On multivariate analysis, the presence of high grade periventricular white matter changes tended to be more frequently detected in the ESRD group than the RT (P=0.078). The time from starting dialysis to stroke was longer in the RT group (129.9±60.9 months) than in the ESRD group (51.1±46.1 months). **Conclusion:** The stroke patterns, severity and short term outcomes were not different between RT and ESRD. The risk of cerebral infarction and high grade periventricular white matter changes may be reduced after RT in patients with ESRD. (Korean J Stroke 2012;14:122-127)

KEY WORDS: Renal transplantation, End stage renal disease, Stroke, Cerebral infarction, Cerebral microbleeds, Leukoaraiosis

Introduction

Cerebral infarction occurs often in patients with end stage renal disease (ESRD).[1] Most patients with ESRD who are treated with hemodialysis (HD) have classic risk factors for ischemic stroke,[2] and HD itself is an independent risk factor for stroke.[2] Patients who are treated with continuous ambulatory peritoneal dialysis (CAPD) may have a greater risk of ischemic and hemorrhagic strokes because high blood pressure is often less well controlled due to excessive hydration during CAPD.[3] Cerebral small vessel pathology including silent lacunar infarction (SLI), leukoaraiosis (LA), and cerebral microbleeds (CMBs) were reported as being associated with impaired renal function possibly due to the hemodynamic similarities between the vascular beds of the kidney and those of the brain.[4-7]

Renal transplantation (RT) is the best treatment for overcoming many clinical problems associated with ESRD. Endothelial vascular damage and oxidative stress, which are caused by renal dysfunction and uremic toxin, are decreased after RT. Arterial stiffness, which is associated with small artery disease and intracranial cerebral atherosclerosis, is improved.[8-10] Additionally, the risk for vascular events is decreased in RT recipients with sustained graft function.[11] However, underlying vascular risk factors may be present in spite of RT, and the immunosuppressive agents that are used in patients with RT may aggravate vascular diseases and hypertension through catecholamine-related vaso-

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constriction.[12] Therefore, RT may both positively and negatively affect stroke occurrence and outcomes.

Considering that impaired renal function is associated with small vessel disease and that the renal function can be improved after RT, stroke types, small vessel pathologies and outcome may be different between ESRD patients who received RT and those who did not. There have been several reports on the characteristics, incidence and classification of cerebral infarction in patients with ESRD[2,13,14] and RT.[15-19] However, no study has investigated differences in stroke type and outcomes between ESRD patients who received RT and those who did not. The aim of this study was to compare stroke subtype, initial stroke severity and early neurologic outcomes between these groups. We also investigated whether the frequency of small vessel pathologies such as CMBs, SLI, and LA are different between the groups

Subjects and Methods

Study Subjects

We retrospectively reviewed medical records of patients treated with dialysis (HD or CAPD) or those who received a first (de novo) renal transplantation between January 1995 and January 2011 at a single university hospital. Among the 2,321 patients who received a renal transplantation, 57 patients were identified as having a first-ever acute cerebral infarction. Among the 6,999 ESRD patients treated with HD or CAPD during the same study period, 120 patients with a first-ever acute cerebral infarction were identified. All enrolled patients were confirmed as cerebral infarction by brain CT and/or magnetic resonance image. Patients with transient ischemic attack were excluded. This study was approved by the Severance Hospital Institutional Review Board of the Yonsei University Health System.

Study Group and Comparison Between the Groups

Demographic characteristics, laboratory findings, and time intervals from the initiation of dialysis or RT to stroke onset were compared between patients with RT (RT group) and those undergoing dialysis due to ESRD but who did not receive RT (ESRD group). The stroke subtype was determined based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[20] based on a neuroradiologist's report and the consensus of stroke specialists. Severity of neurologic deficits was determined using the National Institutes of Health Stroke Scale (NIHSS) at admission. Data for in-hospital mortality was obtained from medical records.

Small artery pathologies were evaluated using MRI. CMBs were defined as punctuate hypointense lesions less than 10 mm in size on gradient echo (GRE) MRI images, which were based on previously reported methods.[21] Silent lacunar infarction (SLI) was defined when a small (<15 mm) lesion in the perforating artery territory showed a high signal intensity on fluid attenuated inversion recovery (FLAIR) or T2 weighted and iso- or low signal intensity on T1 weighted image.[22] We also assessed the severity of LA. The extents of LA in the periventricular white matter (PVWM) and deep white matter (DWM) were determined on the FLAIR images according to the Fazekas' scoring system.[23] Briefly, LA in PVWM was categorized as: grade 0, absent; grade 1, caps or pencil-thin lining; grade 2, smooth halo; and grade 3, irregular PVWM extending into DWM. LA in DWM was categorized as: grade 0, absent; grade 1, punctuate foci; grade 2, beginning confluence of foci; and grade 3, large confluent areas. PVWM and DWM changes were dichotomized into high grade (2-3) or low grade (0-1) LA.

Risk Factors

Hypertension was diagnosed when a patient had been taking anti-hypertensive medication or had resting systolic blood pressures ≥140 mmHg or diastolic blood pressures ≥90 mmHg on repeated measurements. Diabetes mellitus was diagnosed if the patient had fasting blood glucose ≥7.0 mmol/L or was being treated with anti-diabetic medications or insulin. Hyperlipidemia was diagnosed if the patient had low-density lipoprotein cholesterol ≥4.1 mmol/L, total cholesterol ≥6.2 mmol/L, or if the patient was treated with lipid lowering agents after diagnosis of hyperlipidemia. Patients were defined as smokers if they were current smokers or had stopped smoking within one year prior to the index ischemic stroke.

Statistical Analysis

Statistical analysis was performed with SPSS (version 18.0, SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation and categorical variables were reported as frequency and percentage. The variables were compared by independent *t*-tests, Chi-square tests, or Fisher's exact test, as appropriate. A two-tailed value of $P<0.05$ was considered significant. Adjusting the age and sex factors, variables

with $P<0.1$ in the univariate analysis were entered for multivariate binary logistic regression analyses were performed to determine independent factors for cerebral small vessel pathologies.

Results

Comparison of Demographic and Clinical Characteristics

The demographic data and the results of comparison for clinical characteristics are shown in Table 1, 2. When compared with the RT group, the ESRD group was older, more frequently female, and had higher creatinine levels. Previous use of statins and hemodialysis were more frequently observed in the RT group. The cause of renal disease was different between the two groups in that chronic glomerular nephritis, including hypertensive and diabetic nephropathy, was more frequently observed in the dialysis group while nephrotic syndrome was more frequently observed in the RT group (Table 1). In the RT group, the mean time interval from starting dialysis to stroke onset was 129.9±60.9 months, and that from RT to stroke onset was about 102.2±60.3 months. These intervals were significantly longer than that in the ESRD group (51.1±46.1 months) (Table 2).

Comparison of Stroke Subtypes and Small Vessel Pathology

Large artery atherosclerosis was most common in the RT group (31.6%) and small vessel occlusion was most common in the ESRD group (26.7%); however, there was no statistical difference between the two groups. Brain MRI was performed in 160 (90.3%) patients (52 [91.2%] patients in the RT group and 108 [90.0%] patients in the ESRD group). GRE images were available in 124 (70.0%) patients (44 [77.1%] patients in the RT group and 80 [66.7%] in the ESRD group).

On univariate logistic analysis, ESRD (P=0.018), high grade DWM changes (P=0.001), SLI (P=0.001), CMBs (P=0.001), older age (P=0.002) and diabetes mellitus (P=0.021) were associated with high grade PVWM changes (Table 2). On multivariate analysis, SLI and CMBs were not entered because of their multicollinearity with LA. After adjusting for sex and significant

TABLE 1. Demographic data of renal transplantation and end stage renal disease

	RT (n=57)	ESRD (n=120)	*P*-value
Sex, male	43 (75.4)	63 (52.5)	0.005
Age, yr	53.8±9.2	61.1±12.3	0.001
Risk factors			
Hypertension	54 (94.7)	108 (90.0)	0.392
Diabetes mellitus	36 (63.2)	76 (63.3)	0.982
Atrial fibrillation	7 (12.3)	24 (20.0)	0.290
Dyslipidemia	29 (50.9)	49 (40.8)	0.209
Smoking	13 (22.8)	19 (15.8)	0.260
Coronary artery occlusive disease	14 (24.6)	53 (44.2)	0.012
Previous statin use	39 (68.4)	46 (38.3)	0.001
Previous antiplatelet medication	15 (26.3)	58 (48.3)	0.006
Hemodialysis	48 (84.2)	67 (56.8)	0.001
Serum creatinine level, mg/dL	1.6±1.2	7.0±2.4	0.001
Serum albumin level, mg/dL	3.7±0.7	3.8±0.7	0.399
Causes of renal disease			0.001
Chronic hypertensive nephropathy	22 (38.6)	43 (35.8)	
Diabetic nephropathy	5 (8.8)	5 (4.2)	
Hypertensive and diabetic nephropathy	11 (19.3)	68 (56.7)	
Primary nephrotic syndrome	12 (21.1)	2 (1.7)	
Eclampsia	3 (5.3)	0 (0.0)	
Tuberculous nephritis	2 (3.5)	0 (0.0)	
APCKD	1 (1.8)	1 (0.8)	
Drug induced	1 (1.8)	1 (0.8)	

Data are shown as mean±SD, median (interquartile range), or number (%). RT: renal transplantation, ESRD: end stage renal disease, APCKD: adult polycystic kidney disease.

TABLE 2. Clinical findings between renal transplantation and end stage renal disease

	RT (n=57)	ESRD (n=120)	*P*-value
NIHSS at admission	3 (2-8)	3 (1-7)	0.565
Imaging findings			
High grade PVWMC	18 (34.6)	60 (55.6)	0.018
High grade DWMC	17 (32.7)	52 (48.1)	0.088
Silent lacunar infarction	22 (42.3)	64 (59.3)	0.062
Cerebral microbleeds	5 (11.4)	23 (28.8)	0.042
In hospital mortality	12 (21.0)	19 (15.8)	0.194
TOAST classification			0.070
Large artery atherosclerosis	18 (31.6)	25 (20.87)	
Cardioembolism	11 (19.2)	30 (25.0)	
Small vessel occlusion	10 (17.5)	32 (26.7)	
Undetermined negative	12 (21.1)	25 (20.8)	
Multiple causes	3 (5.3)	8 (6.7)	
Undetermined incomplete	3 (5.3)	0 (0.0)	
Time interval from ESRD, months	129.9 ± 60.1	51.1 ± 46.1	0.001
Time interval from RT, months	102.2 ± 60.3		

Data are shown as mean±SD, median (interquartile range), or number (%). RT: renal transplantation, ESRD: end stage renal disease, NIHSS: national Institutes of Health Stroke Scale, PVWMC: periventricular white matter change, DWMC: deep white matter change, TOAST: trial of Org 10172 in Acute Stroke Treatment.

TABLE 3. Multivariate analysis for high grade periventricular white matter change and cerebral microbleeds

	High grade PVWM change		Cerebral microbleeds	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex	0.987 (0.500–1.950)	0.970	1.283 (0.511–3.211)	0.596
Age	1.043 (1.010–1.078)	0.011	1.055 (1.008–1.105)	0.021
Diabetes mellitus	2.585 (1.277–5.233)	0.008		
ESRD	1.962 (0.962–4.155)	0.078	2.153 (0.698–6.640)	0.182

PVWM: periventricular white matter, OR: odds ratio, CI: confidence interval, ESRD: end stage renal disease.

factors on univariate analysis, ESRD tended to be associated with high grade PVMW changes (*P*=0.078) (Table 3).

Comparison of Neurologic Severity and Outcomes

The NIHSS scores at admission did not differ between the RT and ESRD groups. In-hospital mortality (12 patients in RT versus 16 patients in ESRD, *P*=0.194) also did not differ between the two groups.

Discussion

This study showed that the high grade PVWM changes tended to be more frequently detected in ESRD patients than in RT patients. Our findings, along with findings in previous studies, suggest that impaired renal function is associated with small vessel pathology in the brain,[4-6] and its risk may be reduced when renal function is improved by RT. Arterial stiffness, which is associated with vessel wall damage in the microvessels of the end-organs and intracranial artery atherosclerosis, improved after RT.[9,24] RT can improve endothelial dysfunction induced by a state of continuous renal dysfunction because uremic toxins cause oxidative stress on vasculature, endothelial damage, and acceleration of atherosclerosis.[10,25] Those changes may underlie a decreased risk of small vessel pathologies following RT in ESRD patients.

The incidences of stroke and cardiovascular disease were lower in the RT group than the ESRD group.[26,27] Renal dysfunction increases the risk of ischemic and hemorrhagic stroke in the general population.[28] Function of kidney on admission appears to be a significant independent prognostic factor for long term mortality and new cardiovascular morbidity.[29] In contrast, RT with sustained graft function seems to reduce the risk for stroke.[11] In this

regard, recovery of renal dysfunction following RT could reduce the risk of stroke. The time from starting dialysis to stroke onset was longer in the RT group than in the ESRD group in our study. The longer time interval in the RT group might be related to the reduced risk of stroke following RT in patients with ESRD.

In our study, there were no differences in initial stroke severity and in-hospital mortality after stroke between the two groups. These findings suggest that stroke severity as well as short term outcomes were not substantially affected by renal transplantation and recovery of renal dysfunction, although stroke onset could be delayed. Renal dysfunction is associated with more severe stroke at admission and is a strong negative predictor of 30-day survival after acute ischemic stroke.[30,31] Although renal transplantation may improve clinical outcomes by improving renal and endothelial function,[10] which may positively affect stroke severity, the use of immunosuppressive agents may produce neurotoxicity,[24] which may offset the protective effect of RT. The small sample size in our study may be in part responsible for the absence of differences between the groups.

Our study has limitations. First, the size of population of our study was not large, which might be due to few events of cerebral infarction in both RT and dialysis patients. Therefore, all subtypes of stroke might not be represented sufficiently for the purpose of our study which includes comparison of the differences in occurrence of stroke subtypes between the groups. Second, although the longer time intervals from starting dialysis to stroke onset in the RT group in our study were speculated to be associated with a reduced risk of stroke after RT, the incidence of stroke could not be investigated by our study design. Therefore, our speculation regarding this issue is inconclusive and further studies may be necessary to determine whether RT is protective for stroke.

Conflicts of Interest

The authors have no financial conflicts of interest.

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