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Cerebral microbleeds in predialysis patients with chronic kidney disease

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Abstract

Background. Gradient-echo T2*-weighted magnetic resonance imaging (T2*-weighted MRI) is highly sensitive for detecting cerebral microbleeds (CMBs). CMBs have been reported to be a risk factor for future cerebrovascular events and a marker of cerebral small vessel disease in the general

population. Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease. The relationship between CKD and CMBs, which has not been clarified to date, is examined.

Methods. In this cross-sectional study, T2*-weighted MRI of brain was performed with a 1.5-T MRI system in 162 CKD patients (CKD stages 1–5, excluding CKD stage 5 (D)) and 24 normal subjects.

Results. CMBs were found in 35 CKD patients (25.6%), but not in control subjects. CMBs were more prevalent in male patients, in those with higher blood pressure, advanced age and poor kidney function. There was a significant association between the prevalence of CMBs and the CKD stage, with higher prevalence of CMBs as the CKD stages advanced ($P < 0.01$). Estimated glomerular filtration rate was a significant factor associated with the prevalence of CMBs, independent of age, gender and hypertension. There was no significant relationship between CMBs and the presence of diabetes mellitus and dyslipidemia.

Conclusions. Decreased renal function is a significant risk factor for CMBs, independent of the presence of hypertension. Poor kidney function could be associated with future cerebrovascular events.

Keywords: arteriosclerosis; chronic kidney disease; microbleeds; T2*-weighted magnetic resonance imaging

Introduction

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease [1–4]. CKD patients generally have more risk factors, such as increased arteriosclerosis and hypertension, which are associated with cardiovascular events, compared with normal subjects [1–7]. Several reports have indicated that CKD is associated with a high prevalence of stroke [8–11].

Recently, cerebral microbleeds (CMBs) have become detectable to a high degree of sensitivity with Gradient-echo T2*-weighted magnetic resonance imaging (T2*-weighted MRI), while they can barely be visualized with other conventional scans [12,13]. T2*-weighted MRI sensitively detects small areas of signal loss, which represent remnants of previous CMBs [12,13] (Figure 1). This T2* effect occurs through local magnetic field inhomogeneities caused by haemosiderin deposits [12–14]. It has been confirmed pathologically that the CMBs on T2*-MRI represent minor blood leakage through damaged blood vessels, in addition to minor hemorrhage [12–14]. The presence of CMBs has been reported to be associated with cerebrovascular events [13–17]. It has been reported to suggest that the microangiopathy has reached an advanced stage, in which the blood vessels are prone to bleeding [13–17]. Kato *et al.* reported that 71.4% of patients with symptomatic cerebral hemorrhage had CMBs. Thus, CMBs have been reported to indicate a higher risk of future intracerebral haemorrhage and to be a marker of cerebral small vessel disease in the general population [12–14,16–19].

The prevalence of CMBs in healthy populations without cerebrovascular disease ranges from 3.1 to 6.4% [16,17,19]. In haemodialysis patients, there is a significantly higher prevalence of CMBs compared with normal subjects [20,21]. However, there have been no reports on the prevalence of CMBs in CKD patients without dialysis therapy. In the present study, we investigated the prevalence of CMBs in CKD patients without dialysis therapy and examined the relationship between the prevalence of CMBs and clinical factors.

Materials and methods

Patients

All patients in this study were admitted to the Department of Nephrology or Urology of Osaka City University Hospital, for treatment and education for CKD from January 2008 to April 2009. A total of 162 consecutive CKD patients without dialysis therapy and without neurological abnormalities were enrolled in this study. They had no past history or symptoms of stroke based on their medical records. There were 85 patients with diabetes and 77 without. In this study, all patients had haematuria, proteinuria and/or albuminuria, as determined by dip-stick examination or turbid immunoassay of the urine, at least >3 months. In all patients, serum creatinine was measured at least three times during admission, and it was confirmed that the levels of serum creatinine were not substantially changed during admission. Serum creatinine concentrations at the time of MRI were entered for the statistical analysis. CKD was defined as patients with kidney damage, as reported by KDIGO [22]. None of the healthy subjects we examined as controls exhibited proteinuria or had any history of past kidney diseases. Patients with vasculitis, rapidly progressive glomerulonephritis, polycystic kidney disease and malignancy were excluded from the present study. As a control, 24 healthy subjects who visited Ohno Memorial Hospital for screening checkup of the brain were also examined. Written informed consent was obtained from each of the patients and healthy subjects. This study protocol was approved by the ethical committee of Osaka City University Hospital (no. 1415).

Blood pressure was measured with the patients resting in a supine position for at least 10 min on the day of MRI, using a standard mercury sphygmomanometer and cuffs adapted to their arm circumference. The systolic blood pressure was taken as the point of appearance of Korotokof sounds, and the diastolic blood pressure was the point at which the sounds disappeared. In this study, hypertension was defined by (i) administration of antihypertensive agents or a history of hypertension, (ii) systolic pressure ≥140 mm Hg or (iii) diastolic pressure ≥90 mm Hg. Diabetes mellitus was defined by (i) administration of insulin or oral antidiabetic agents or (ii) prior diagnosis according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association (1998) [23].

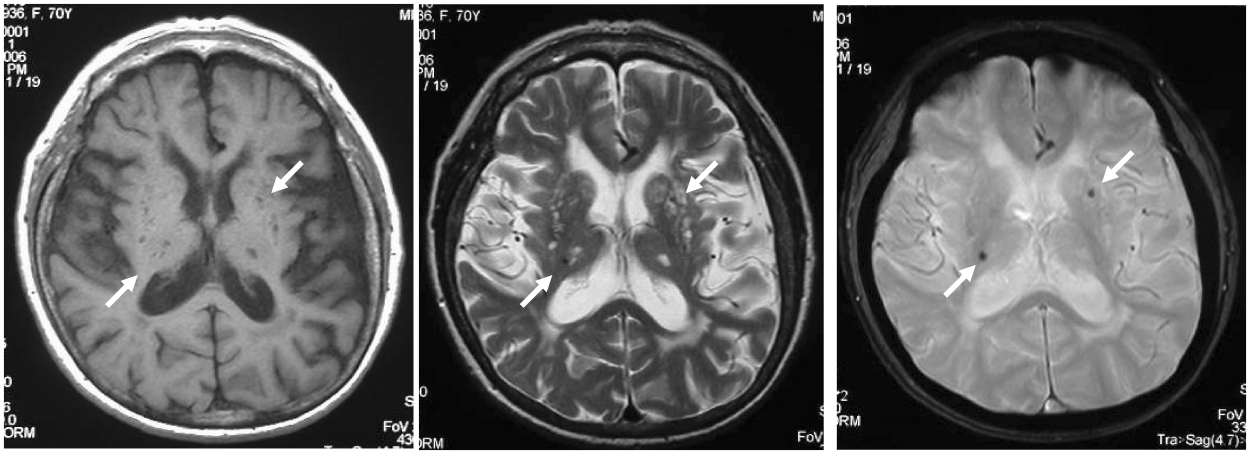
Blood samples were obtained from patients after overnight fasting. Total protein, serum albumin, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, blood urea nitrogen (BUN), C-reactive protein and haemoglobin (Hb) were measured by routine laboratory methods. Hb A1C was measured using high performance liquid chromatography. Estimated glomerular filtration rate (eGFR) was calculated using the following formula:

$$\text{eGFR}[\text{ml/min/1.73 m}^2 = 194 \times (\text{serum creatinine})^{-1.084} \times (\text{age})^{-0.287}]$$

The value was multiplied by 0.739 for women. This formula represents the eGFR for Japanese reported by Japanese Society of Nephrology [24]. We stratified eGFR into the following ranges: ≥90 ml/min/1.73 m^2 (stage 1), 60–89 ml/min/1.73 m^2 (stage 2), 30–59 ml/min/1.73 m^2 (stage3), 15–29 ml/min/1.73 m^2 (stage 4) and <15 ml/min/1.73 m^2 (stage 5), according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative classification and staging system [22].

Magnetic resonance imaging

All participating patients underwent a brain MRI that used a superconducting magnet at a field strength of 1.5 T on proton density, T1-weighted, T2-weighted, FLAIR images and two-dimensional T2*-weighted MRI in axial planes at 5 mm thick slices with an interslice gap of 1.5 mm. The MR



T1-weighted **T2-weighted** **T2*-weighted**

Fig. 1. Cerebral microbleeds (CMBs) examined by MRI, including T1, T2 and T2*-weighted MRI images in which T2*-weighted MRI clearly demonstrates the presence of CMBs (arrows), although T1 or T2 MRI can barely demonstrate its presence (70-year-old woman with CMBs).

images were assessed independently by two neuro-radiologists who had not been notified of the clinical information.

Statistical analysis

All data are expressed as the mean ± SD. Differences between groups were examined by unpaired Student's *t*-test. Categorical variables were compared, using χ^2 test. Multiple logistic regression analyses were used to assess the combined influence of variables on the presence of CMBs. Gender, diabetes mellitus, current smoking and presence of hypertensive were represented by dummy variables (0 = male, 1 = female; 0 = absence, 1 = presence) in logistic regression analyses. A P value <0.05 was considered statistically significant. These results were determined on a Windows computer using the Stat View V Statistical System (SAS Institute, Cary, NC).

Results

Prevalence of CMBs in CKD patients

Of the 162 CKD patients, CMBs were found in 35 (21.6%). In Table 1, the clinical characteristics are shown, according to the presence or absence of CMBs, in addition to those of

Table 1. Clinical characteristics of patients with and without CMBs and healthy subjects

	Patients			
	Without CMBs	With CMBs	P^a	Healthy subjects
Number (male/female)	66/61	26/9	0.1830	14/10
Age (years)	62.0 ± 14.3	75.2 ± 25.7	0.0019	59.7 ± 5.8
BMI (kg/m^2)	22.8 ± 4.0	22.7 ± 3.5	0.8436	22.9 ± 2.9
History of smoking (presence/absence)	44/83	12/23	0.9684	7/17
Systolic pressure (mm Hg)	127.0 ± 12.0	153.9 ± 28.6	<0.0001	122.9 ± 15.0
Diastolic pressure (mm Hg)	69.1 ± 12.0	75.2 ± 9.5	0.0058	79.8 ± 9.4
Pulse pressure (mm Hg)	58.0 ± 17.2	78.7 ± 25.7	<0.0001	43.1 ± 10.3
History of hypertension (presence/absence)	75/52	31/4	0.0012	6/18
History of diabetes (presence/absence)	62/65	23/12	0.0764	0/24
Anticoagulation or anti-platelet therapy (yes/no)	44/83	18/17	0.1322	0/24
BUN (mg/dl)	36.0 ± 24.8	63.9 ± 36.4	<0.0001	13.7 ± 3.0
Creatinine (mg/dl)	2.91 ± 2.53	5.03 ± 2.88	<0.0001	0.60 ± 0.14
eGFR (ml/min)	35.7 ± 33.7	15.0 ± 12.9	0.0005	97.5 ± 19.8
Total protein (g/dl)	6.17 ± 1.09	6.15 ± 0.80	0.9274	7.10 ± 0.31
Albumin (g/dl)	3.26 ± 0.75	3.25 ± 0.67	0.8973	4.21 ± 0.23
Total cholesterol (mg/dl)	213.1 ± 80.1	182.9 ± 52.2	0.0388	208.8 ± 32.1
Triglyceride (mg/dl)	163.1 ± 120.9	137.6 ± 77.5	0.2538	98.9 ± 48.2
LDL cholesterol (mg/dl)	124.8 ± 50.3	103.4 ± 33.4	0.0317	120.0 ± 29.2
HDL cholesterol (mg/dl)	48.6 ± 16.4	42.5 ± 9.9	0.0600	68.3 ± 18.3
Hb (g/dl)	11.5 ± 2.3	10.6 ± 1.9	0.0398	13.9 ± 1.4
C-reactive protein (mg/dl)	0.59 ± 1.68	0.45 ± 0.67	0.6407	0.14 ± 0.11
Fasting blood glucose (mg/dl)	116.0 ± 66.4	107.2 ± 36.0	0.4867	100.5 ± 9.7
Haemoglobin A1C (%)	6.56 ± 1.61	6.45 ± 1.27	0.7108	5.23 ± 0.38

Data are number or means ± SD. BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein.
[a]Patients with vs without CMBs.

Table 2. Number of patients with CMBs according to CKD stages

CKD stage	Stage 1 or 2	Stage 3	Stage 4	Stage 5	Total number	Healthy subjects
Without CMBs	31	24	32	40	127	24
With CMBs	1	4	9	21	35	0
Total number	32	28	41	61	162	24

$P = 0.0041$ (χ^2 test).

Table 3. Odds ratios of potentially predictive variables for the presence of CMBs in CKD patients

	Unadjusted			Adjusted[a]		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Age (year)	1.058	1.019–1.098	0.028	–	–	
Gender (female vs male)	0.375	0.163–0.863	0.0210	–	–	–
BMI (kg/m^2)	0.990	0.899–1.090	0.8424	1.019	0.913–1.138	0.7351
History of smoking (presence vs absence)	0.984	0.448–2.164	0.9684	0.769	0.317–1.864	0.5611
Systolic pressure (mm Hg)	1.044	1.026–1.062	<0.0001	1.040	1.022–1.059	<0.0001
Diastolic pressure (mm Hg)	1.046	1.012–1.080	0.0074	1.067	1.028–1.107	0.0006
Pulse pressure (mm Hg)	1.046	1.026–1.067	<0.0001	1.040	1.018–1.062	0.0002
Hypertension (presence vs absence)	5.373	1.789–16.140	0.0027	4.209	1.353–12.095	0.0131
Creatinine (mg/dl)	1.297	1.135–1.481	0.0001	1.291	1.117–1.492	0.0005
eGFR (ml/min)	0.953	0.926–0.981	0.0011	0.953	0.924–0.983	0.0005
Total cholesterol (mg/dl)	0.992	0.985–1.000	0.0392	0.994	0.986–1.002	0.1389
Triglyceride (mg/dl)	0.997	0.992–1.001	0.2488	1.000	0.995–1.004	0.8940
LDL cholesterol (mg/dl)	0.989	0.978–0.999	0.0567	0.989	0.978–1.000	0.0516
HDL cholesterol (mg/dl)	0.967	0.934–0.993	0.0351	0.972	0.937–1.008	0.1312
Hb (g/dl)	0.817	0.672–1.291	0.0427	0.826	0.663–1.028	0.0861
C-reactive protein (mg/dl)	0.925	0.662–1.237	0.6452	0.877	0.589–1.306	0.5178
Hb A1C (%)	0.951	0.732–1.237	0.7088	0.927	0.695–1.237	0.6063
History of diabetes (presence vs absence)	2.009	0.921–4.383	0.0795	1.789	0.783–4.085	0.1675

CI, confidence interval.
[a]Adjusted by age and gender.

the healthy subjects. The patients with CMBs were significantly older than in those without. Both systolic and diastolic pressures and prevalence of hypertension were significantly higher in patients with CMBs than in those without. Pulse pressure was significantly greater in the former than in the latter group. The prevalence of CMBs was significantly higher in patients with a history of hypertension than in those without. BUN and serum creatinine were significantly higher in patients with CMBs than in those without. eGFR was significantly lower in patients with CMBs than in those without. LDL cholesterol and Hb levels were significantly lower in the former than in the latter group. However, there were no significant differences in the prevalence of diabetes mellitus between the patients with and without CMBs. There were no significant differences in the prevalence of CMBs between patients with and without anticoagulation and/or anti-platelet therapy. There were no significant differences in the other clinical parameters.

Prevalence of CMBs according to CKD stage

Table 2 shows the prevalence of CMBs in CKD patients according to the CKD stages and in healthy subjects. There were no CMBs in healthy subjects or in patients that were CKD stage 1. One patient with CKD stage 2 had CMBs. The prevalence of CMBs increased as the CKD stage advanced. In the patients with CKD stage 3 ($n = 28$), four (14.3%) had CMBs. In the patients with CKD stage 4 ($n = 41$), nine (22.0%) had CMBs. In the patients that were CKD stage 5, 21 patients (34.4%) out of 61 exhibited CMBs. χ^2 test revealed significantly higher prevalence of CMBs as the stages of CKD advanced ($P = 0.0041$).

Factors associated with CMBs in CKD patients

A univariate logistic regression analysis was performed to examine the factors associated with the presence of CMBs (Table 3). Significant factors were age, male gender, presence of hypertension, systolic pressure, diastolic pressure, pulse pressure, creatinine, eGFR, total cholesterol, HDL cholesterol and Hb. However, in a logistic regression analysis after adjustment for age and gender, which were unmodifiable, basic clinical factors of the patients, presence of hypertension, systolic pressure, diastolic pressure, pulse pressure, creatinine and eGFR remained significant. These significant factors are related to blood pressure and renal function.

Independent association of blood pressure and renal function with CMBs

Next, we performed multivariate logistic analyses to examine the independent association of eGFR and blood pressure with the presence of CMBs (Table 4). In models 1, 2 and 3 of logistic regression analyses, systolic pressure, diastolic pressure and pulse pressure were significantly associated

Table 4. Odds ratio for the presence of CMBs adjusted by variables

	Model 1			Model 2			Model 3		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Age (year)	1.050	1.001–1.102	0.0466	1.076	1.022–1.132	0.0051	1.036	0.989–1.085	0.1331
Gender (female vs male)	0.347	0.131–0.919	0.0311	0.328	0.127–0.845	0.0209	0.337	0.131–0.864	0.0236
eGFR (ml/min)	0.971	0.942–1.000	0.0528	0.956	0.926–0.988	0.0067	0.967	0.939–0.996	0.0274
Systolic pressure (mm Hg)	1.034	1.034–1.014	0.0006	–	–	–	–	–	–
Diastolic pressure (mm Hg)	–	–	–	1.058	1.019–1.099	0.0035	–	–	–
Pulse pressure (mm Hg)	–	–	–	–	–	–	1.030	1.008–1.053	0.0072

with the presence of CMBs, independent of age, gender and eGFR, respectively. Furthermore, eGFR was a significant factor associated with the presence of CMBs, independent of diastolic pressure and pulse pressure. eGFR was also a factor associated with the presence of CMBs, independent of systolic pressure in a border line significance ($P = 0.0528$).

Discussion

In the present study, using T2*-weighted MRI, we examined the prevalence of CMBs in CKD patients. We found that the prevalence of CMBs was significantly higher as the CKD stage was advanced. Logistic regression analyses revealed that significant factors associated with CMBs were older age, male gender, higher blood pressure, higher pulse pressure and lower eGFR. Furthermore, these factors were significantly and independently associated with the presence of CMBs.

In the general population, CMBs have been reported to be related to older age, hypertension, smoking, leukoaraiosis, paraventricular hyperintensity, lacuna infarcts and stroke [12,14–19,25–28]. In the present study, we also found that CKD patients with CMBs were significantly older than those without and that the blood pressure of patients with CMBs was significantly higher than those without, which was consistent with previous reports [17–19,25,28]. In this study, one of the most significant factors associated with the presence of CMBs in CKD patients was blood pressure. In both univariate logistic regression analysis and logistic regression analysis, after adjustment for age and gender, systolic pressure, diastolic pressure and pulse pressure were strong, significant factors for the presence of CMBs. This result showed that presence of hypertension is a common risk factor in both normal subjects and CKD patients.

In haemodialysis patients, there was a significantly higher prevalence of CMBs compared with normal subjects, as high as 19.3 to 35.0% [16,21]. In the present study of predialysis CKD patients, 35 out of 162 CKD patients exhibited CMBs (21.6%), while none of the healthy control subjects exhibited CMBs. We found that the prevalence of CMBs in predialysis patients was associated with BUN, serum creatinine and eGFR. There was a significantly higher prevalence of CMBs as the stage of CKD advanced. Considering both the previous study of haemodialysis patients and the present study, it is suggested that advanced renal failure could be associated with increased prevalence of CMBs. Kobayashi *et al*. examined silent brain infarction in CKD patients and reported that CKD progression was associated significantly with the increased prevalence of silent brain infarction, one of the cerebrovascular diseases. In their report, age, prevalence of hypertension and systolic pressure were higher in patients with silent brain infarction, whereas eGFR was significantly lower in patients with silent brain infarction. Our study, which examined CMBs, was similar to their study of silent brain infarction, in that advanced CKD was associated with cerebrovascular disease. In multivariate logistic analysis of factors in the study of Kobayashi *et al*., significant factors associated with silent brain infarction were lower eGFR, older age and higher systolic pressure [29]. Similarly, several reports have indicated that CKD is associated with a high prevalence of overt clinical stroke [8–11,30]. These reports and our results could indicate that decreased renal function is associated significantly with cerebrovascular disease and that poor kidney function indicates an increased risk for clinical and subclinical stroke.

In general, diabetes mellitus and dyslipidaemia are independent risk factors for cardiovascular disease [31]. Recently, however, several studies have reported that small cerebral vessel diseases, such as CMBs, are not associated with diabetes [4,16,17,19,28,29] or dyslipidaemia [4,17,19]. Consistent with these reports, there was no significant association between the prevalence of diabetes mellitus or dyslipidaemia and the prevalence of CMBs in the present study. Taken together with previous studies and ours, it is indicated that renal failure is an independent risk factor for the prevalence of subclinical cerebrovascular disease in patients both with and without diabetes and dyslipidaemia.

Anticoagulation or anti-platelet therapy in patients with small vessel cerebrovascular disease and a past history of ischaemic stroke have a higher risk of intracerebral haemorrhage [32]. It is particularly important to identify and remove such patients who are prone to bleeding complication after anticoagulation or anti-platelet therapy [13]. In the present study, however, there were no significant differences in the prevalence of CMBs between patients with and without anticoagulation and/or anti-platelet therapy. Since there is no consistent evidence for therapeutic efficacy, further studies are required to explore whether anticoagulation and/or anti-platelet therapy should be ceased in CKD patients with CMBs. In the present study, we could not measure the amount of proteinuria/albuminuria. Since increased excretion of urinary protein has been reported to be significantly associated with cardiovascular mortality

[33], further studies are required to explore whether amount of proteinuria/albuminuria could affect the presence of CMBs.

In conclusion, we demonstrated that decreased renal function and hypertension were significantly and independently associated with the presence of CMBs in predialysis CKD patients. Our findings suggest that CKD patients should be considered as a high risk population for cerebrovascular events. Treatment of hypertension in predialysis CKD patients is considered to be very important for the prevention of CMBs and probably for clinically overt strokes. CMBs in predialysis CKD patients, as assessed by T2*-weighted MRI, would be a useful and feasible clinical marker for the prediction of future cerebrovascular events. This study also suggested that careful attention should be paid to cerebrovascular disease in predialysis CKD patients.

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