ORIGINAL CONTRIBUTION

Strong Independent Correlation of Proteinuria With Cerebral Microbleeds in Patients With Stroke and Transient Ischemic Attack

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Objective: To assess the association of proteinuria with the frequency and number of cerebral microbleeds (CMB), a harbinger of future hemorrhagic stroke.

Design: Cross-sectional analysis.

Patients: Patients with consecutive ischemic stroke and transient ischemic attack admitted to a university hospital during a 22-month period.

Interventions: Presence and number of CMB were evaluated using gradient-echo T2*-weighted magnetic resonance imaging. Multivariable models were generated to determine the contribution of proteinuria to the frequency and number of CMB after adjusting for confounders.

Results: Of 236 patients (mean age, 70 years; 53% female), 72 (31%) had CMB present on gradient-echo imaging and 89 (38%) had evidence of proteinuria. In multivariable analyses with presence of CMB as the outcome, higher urinary protein (odds ratio [OR], 2.33; 95% confidence interval [CI], 1.10-4.95), being female (OR, 2.29; 95% CI, 1.19-4.49), history of atrial fibrillation (OR, 2.49; 95% CI, 1.14-5.44), elevated serum homocysteine (OR, 1.19; 95% CI, 1.09-1.29), and small-vessel disease subtype (OR, 2.95 95% CI, 1.43-6.10) were all significantly associated with presence of CMB. Logistic regression analysis by number of CMB showed similar findings.

Conclusions: Proteinuria is strongly associated with both the frequency and number of CMB in patients with recent cerebral ischemia. Urinary protein excretion may be a CMB risk marker or potential therapeutic target for mitigating the untoward clinical sequela of CMB.

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PROTEINURIA OCCURS LARGELY as a consequence of the abnormal transglomerular passage of proteins due to increased permeability of the glomerular capillary wall as well as their resultant impaired reabsorption by the epithelial cells of the proximal tubuli.[1] Proteinuria is a strong predictor of renal disease progression, adverse changes in vascular risk factors, incident stroke or myocardial infarction, and premature death of vascular origin.[1] Given these widespread associations, it is believed that proteinuria may either reflect a systemic process that adversely affects the glomeruli and intima of large vessels in several vascular beds simultaneously or generalized endothelial dysfunction enhancing atherogenesis.[1] Several studies have associated the presence of proteinuria with stroke occurrence,[2-4] and a recent analysis of the Cardiovascular Health Study[5] suggested that the relationship between albuminuria and stroke was greater with the more catastrophic form of stroke, hemorrhagic stroke, than with ischemic stroke. Another association between urinary protein and cerebral bleeding was shown in a study that found albuminuria to be an independent predictor of hemorrhagic transformation, particularly of the most severe bleedings, in patients with acute ischemic stroke.[6]

Cerebral microbleeds (CMB) are discrete or isolated punctate hypointense lesions smaller than 5 mm that are evident on gradient-echo T2*-weighted magnetic resonance imaging (MRI) (GRE).[7] Prior pathologic studies of CMB have demonstrated focal deposition of hemosiderin in the perivascular space associated with abnormal small blood vessels affected by lipofibrohyalinosis or amyloid angiopathy.[8] Cerebral microbleeds may persist indefinitely after initial detection and are frequently noted in patients with spontaneous intracerebral hemorrhage, ischemic stroke, and in asymptomatic or healthy elderly persons.[9-16]

Cerebral microbleeds are generally considered to be clinically silent but are strongly associated with advanced small-vessel or microvascular ischemic disease[13,14] and may be a marker for increased risk of future intracranial bleeding.[9,17] Although CMB have been associated with hypertension, prior clinical stroke, leukoaraiosis, cholesterol levels, and cognitive dysfunction in patients with ischemic stroke,[11,14,16,18-20] further studies are needed to investigate other potential risk markers and/or factors for the occurrence of CMB in patients who have had ischemic cerebrovascular events.

In this study, we aimed to evaluate the independent relationship between proteinuria and the presence and number of CMB in a cohort of patients with recent brain ischemia.

METHODS

DATA COLLECTION

Data were collected prospectively on consecutive patients older than 18 years who were admitted to a university hospital stroke program with ischemic stroke or transient ischemic attack during a 22-month period beginning April 1, 2004. Medical history was obtained directly from the patient, family, or caregiver. All patients had a detailed diagnostic assessment that included neurological investigations, blood pressure measurements, blood tests including fasting lipids, MRI (unless contraindicated), and echocardiography. Ischemic stroke was defined as a measurable neurologic deficit (confirmed with radiography) for more than 24 hours due to presumed ischemic etiology. Only patients admitted within 48 hours of ictus who had a brain MRI with GRE sequences before any thrombolytic agent was given were included in the study. Patents were also excluded if urinalysis was obtained more than 24 hours from the time of hospital admission. Clinical personnel were unaware of the goals of this study at the time of patient and urinalysis evaluation.

Magnetic resonance imaging was performed on a 1.5-T Siemens Visions scanner (Siemens Medical Solutions, Munich, Germany). The GRE sequences were obtained using 7-mm slice thickness; no gap; field of view, 220 mm; time to repetition, 800 milliseconds; echo time, 15 milliseconds; and flip angle, 30°. Echoplanar imaging–susceptibility-weighted imaging (EPI-SWI) sequences were obtained using 5- to 7-mm slice thickness; no gap; field of view, 240 mm; time to repetition, 2000 milliseconds; and echo time, 60 milliseconds. The GRE sequences were reviewed for evidence of old, clinically silent microbleeds. The CMB were defined as punctate, homogeneous, rounded, hypointense lesions smaller than 5 mm visualized on GRE and were counted throughout the brain. Hypointense lesions in the subarachnoid space were considered likely to represent adjacent pial blood vessels and therefore were not included. Symmetrical hypointensities in the globi pallidi (likely to represent calcification or iron deposition) and flow voids from cortical vessels were disregarded. These criteria are similar to those used in previous studies.[7,9] Intracerebral ischemic lesions with a hemorrhagic component were excluded. Subjects with small hemorrhagic lesions of known or presumed pathogenesis (head trauma, arteriovenous malformation, cavernous angiomas) were also excluded from the analysis. Scan interpretation was performed by a neurologist with experience in neuroimaging who was blinded to the clinical details (D.S.L.).

Urine protein was recorded as negative (less than 10 mg/dL), trace (10 to 20 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), or 4+ (1000 mg/dL). To make these continuous variables, negative results were coded as 0, trace as 1, 1+ as 2, etc, yielding a scale of 0 through 5. Urinary protein on admission was analyzed by the hospital's central laboratory using the iQ 200 automated urinalysis system (Iris Diagnostics, Chatsworth, California). The 5% sulfosalicylic acid method was used whenever necessary for further confirmation.[21]

Stroke subtypes were classified by the use of modified Trial of ORG 10172 in Acute Stroke (TOAST) classification.[22] Potential predictors for the presence and number of CMB were then evaluated bivariately and in multivariable modeling and included:

1. Demography: age, sex, and race and ethnicity
2. Medical history: stroke, hypertension, diabetes, atrial fibrillation, hypercholesterolemia, and smoking status (current smoker or an ex-smoker who quit smoking within 5 years of index hospital admission)
3. Premorbid medications: antithrombotics, statins, antihypertensive, and warfarin
4. Admission laboratory findings: lipid panel (obtained within 24 hours of admission after an overnight fast) including low-density lipoprotein cholesterol, serum homocysteine (obtained within 24 hours of admission after an overnight fast), and glycosylated hemoglobin
5. Stroke subtype: small vessel disease vs others (large vessel atherothrombotic disease, cardioembolism, unknown, or other)

The study was approved by the university hospital institutional review board.

STATISTICAL ANALYSIS

Bivariate

Categorical/ordinal predictors were compared between those who had CMB vs those who did not by cross-tabulating each variable with CMB (yes/no). For categorical predictors, *P* values were computed using the χ^2 test. For proteinuria grade, an ordinal predictor, *P* value was computed using the Wilcoxon rank sum test. For continuous predictors, medians were compared using the nonparametric Wilcoxon rank sum test. The variable for creatinine was log transformed because the log-transformed values more closely resembled a normal distribution.

Multivariable

All of the predictors from the aforementioned list were included in the initial multivariable models even if they were not bivariately significant. We used the logistic regression model to assess the relationship between proteinuria vs CMB as a binary (yes/no) outcome after adjusting for the above list of covariates. For the analysis of CMB as an ordinal outcome (0, 1-3, or 4+) we used the corresponding ordinal logistic regression model. For the purpose of this analysis, we created a binary proteinuria predictor by collapsing trace and no proteinuria into a single category, and then collapsing proteinuria grades 1+, 2+, and 3+ into another category. In the case of the former, this was done to accommodate the potential false-positive result of trace proteinuria, which can sometimes occur during acute stress, dehydration, or infections. In the case of the latter, the individual proteinuria grades 2+, 3+, and 4+ were relatively less frequent. For variable selection, we used the backward stepwise procedure with $P < .15$ significance as a retention criterion. We also computed the Spearman correlation for proteinuria grade vs number of CMB.

Table 1. Summary Statistics for the Final Sample Used for Multivariable Analysis

Variable	Patients, No. (%) (n=236)
Median age, y (range)	74 (23-100)
Female sex	124 (52.5)
White, non-Hispanic	166 (70.3)
Black, non-Hispanic	25 (10.6)
Asian	23 (9.8)
Hispanic	22 (9.3)
Any presence of cerebral microbleeds on MRI	72 (30.5)
Any presence of protein in urine	89 (37.7)
Proteinuria grade	40 (44.9)
Trace	
1+	28 (31.5)
2+	8 (9.0)
3+	11 (12.3)
4+	2 (2.3)

Abbreviation: MRI, magnetic resonance image.

Missing Values

The variables for glycosylated hemoglobin and serum homocysteine were missing values (16% and 17%, respectively) and were therefore imputed for the purpose of the multivariate analysis, using nearest neighbor (hot deck) imputation to impute the missing values.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 11.0 (SPSS, Chicago, Illinois).

RESULTS

Of 319 patients with ischemic stroke and transient ischemic attack who were hospitalized during the study period, 236 (74%) met the study criteria. Reasons for study ineligibility included evaluation more than 48 hours after symptom onset (n=54) or MRI scanning–related issues (n=29), ie, presence of a pacemaker, contraindication and/or intolerability to MRI, or intravenous thrombolysis initiated before MRI was performed. Summary statistics of the eligible patients are shown in **Table 1**. These patients were mostly older, female, and non-Hispanic white. **Table 2** and **Table 3** compare the demographic, clinical, and laboratory variables of patients with CMB with those without. In patients with CMB, the mean number of CMB was 4.99 (median, 3; range, 1-65).

Table 2 also displays the bivariate analysis, which evaluated the relationship between the dichotomized variables and presence of CMB. Presence of CMB was significantly more common in patients with a history of atrial fibrillation as well as those whose presumed stroke mechanism was due to small-vessel disease. Proteinuria in the unadjusted analysis was not a significant predictor of CMB (Table 2). Bivariate analysis of the continuous variables (Table 3) showed that older age, elevated serum homocysteine levels, and higher log serum creatinine levels were associated with the presence of CMB.

Table 4 summarizes the results of the logistic regression model of the presence or absence of CMB using backward stepwise selection. Based on this model, a greater amount of protein in urine, being female, a history of atrial fibrillation, elevated serum homocysteine, and presumed small-vessel disease subtype were all associated with an increase in the chance of having CMB (odds ratio [OR], >1). Logistic regression analysis by number of CMB showed similar findings for elevated pro-

Table 2. Bivariate Assessment of Categorical/Ordinal Predictors vs Cerebral Microbleeds

Variable	Patients, No. (%)		*P* Value
	CMB Present	CMB Not Present	
Sex			.24
Female	49 (31.6)	106 (68.4)	
Male	38 (25.5)	111 (74.5)	
Race/ethnicity			.96
White, non-Hispanic	59 (28.1)	151 (71.9)	
Black, non-Hispanic	9 (27.3)	24 (72.7)	
Asian	10 (32.3)	21 (67.7)	
Hispanic	9 (30)	21 (70.0)	
Medical history			.69
Stroke			
Yes	19 (30.7)	43 (69.3)	
No	68 (28.1)	174 (71.9)	
Hypertension			.11
Yes	65 (31.6)	141 (68.4)	
No	22 (22.7)	75 (77.3)	
Diabetes			.66
Yes	18 (26.5)	50 (73.5)	
No	69 (29.2)	167 (70.8	
Hypercholesterolemia			.62
Yes	31 (27.0)	84 (73.0)	
No	56 (29.6)	133 (70.4)	
Atrial fibrillation			.006
Yes	22 (44.9)	27 (55.1)	
No	65 (25.5)	190 (74.5)	
Smoker[a]			.23
Yes	8 (20.5)	31 (79.5)	
No	79 (29.8)	186 (70.2)	
Premorbid medication			
Antithrombotic			.90
Yes	44 (28.9)	108 (71.1)	
No	43 (28.3)	109 (71.7)	
Statin			.69
Yes	33 (30.0)	77 (70.0)	
No	54 (27.8)	140 (72.2)	
Antihypertensive			.32
Yes	53 (40)	118 (69)	
No	34 (25.8)	98 (74.2)	
Warfarin			.59
Yes	8 (33.3)	16 (66.7)	
No	79 (28.2)	201 (71.8)	
Stroke subtype			
Small vessel			.002
Yes	27 (45.0)	33 (55.0)	
No	60 (24.6)	184 (75.4)	
Proteinuria			.21
Absent	42 (28.6)	105 (71.4)	
Trace	9 (22.5)	31 (77.5)	
1+	12 (42.9)	16 (57.1)	
2+	4 (50.0)	4 (50.0)	
≥3+	5 (38.5)	8 (61.5)	

Abbreviation: CMB, cerebral microbleeds.
[a] Within 5 years of admission.

Table 3. Bivariate Assessment of Continuous Predictors vs Cerebral Microbleeds

Variable	Mean (SE)		Median (Range)		*P* Value
	CMB Absent	CMB Present	CMB Absent	CMB Present	
Age, y	66.18 (1.09)	73.43 (1.45)	70.0 (23 to 100)	76.0 (24 to 98)	<.001
SBP on admisson, mm Hg	149.43 (1.93)	154.72 (3.20)	147.0 (84 to 268)	154.0 (79 to 240)	.11
LDL-C, mg/dL	102.91 (2.61)	102.88 (4.07)	98.0 (38 to 279)	99.0 (39 to 201)	.97
Serum homocysteine, mg/L	9.07 (0.25)	10.71 (0.53)	8.0 (4 to 22)	9.5 (50 to 32)	.002
Glycosylated hemoglobin, %	0.10 (0.03)	0.22 (0.11)	0.06 (0.04 to 6.3)	0.06 (0.05 to 5.8)	.43
Log creatinine	−0.02 (0.01)	0.02 (0.02)	−0.05 (−0.01 to 0.72)	0.00 (−0.03 to 0.66)	.04

Abbreviations: CMB, cerebral microbleeds; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
SI conversion factors: To convert LDL-C to millimoles per liter, multiply by 0.0259; serum homocysteine to micromoles per liter, 7.397; and glycosylated hemoglobin to proportion of total hemoglobin, 0.01.

Table 4. Logistic Regression for the Assessment of Proteinuria (1-4+ vs Trace/None) Compared With Cerebral Microbleeds as a Binary (Yes/No) Outcome[a]

Parameter	$\log_e$ OR (SE)[b]	OR (95% CI)	*P* Value
Protein in urine (1-4+ vs trace/none)	0.85 (0.38)	**2.33 (1.10-4.95)**	**.03**
Female vs male	0.83 (0.33)	**2.29 (1.19-4.41)**	**.01**
History of diabetes (yes/no)	−0.73 (0.42)	0.48 (0.21-1.10)	.84
History of atrial fibrillation (yes/no)	0.91 (0.40)	**2.49 (1.14-5.44)**	**.02**
Serum homocysteine	0.17 (0.04)	**1.19 (1.09-1.29)**	**<.001**
Small vessel mechanism vs others[c]	1.08 (0.37)	**2.95 (1.43-6.10)**	**.004**
Premorbid statin use (yes/no)	0.63 (0.34)	1.88 (0.97-3.64)	.06

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Statistically significant values are in boldface.
[b] A negative log OR corresponds to an OR less than 1 and a decreased risk of cerebral microbleeds; positive, an OR greater than 1 and increased risk of cerebral microbleeds.
[c] Index cerebrovascular event.

tein in the urine (OR, 2.23; 95% confidence interval [CI], 1.10-4.53; *P*=.03), being female (OR, 1.89; 95% CI, 1.02-3.51; *P*=.04), history of atrial fibrillation (OR, 2.18; 95% CI, 1.04-4.55; *P*=.04), elevated serum homocysteine (OR, 1.16; 95% CI, 1.07-1.25; *P*<.001), and presumed small-vessel disease subtype (OR, 2.95; 95% CI, 1.50-5.83; *P*=.002) all being associated with an increase in the number of CMB (OR, >1). The Spearman correlation of proteinuria grade vs number of CMB was 0.4 (*P*<.001).

Of the 2 variables with missing data, glycosylated hemoglobin and serum homocysteine, the glycosylated hemoglobin level was not statistically significant either in a complete case (n=199) or an imputation (n=236) analysis and therefore did not affect the multivariable results. Regarding serum homocysteine, after controlling for the other variables, the estimated log OR (β [standard error]) for serum homocysteine using 236 observations including 37 imputed homocysteine values was 0.17 (0.04), which was statistically significant (Table 4). Using only the 199 complete cases gave a log OR (SE) of 0.13 (0.05) (OR, 1.14; 95% CI, 1.04-1.25; *P*=.004), which was also statistically significant. The complete case and imputation results were similar for the remaining variables.

COMMENT

We observed a strong independent association of a higher grade of proteinuria with CMB detected on MRI GRE in patients with ischemic stroke and transient ischemic attack. Specifically, patients with a proteinuria grade of 1+ or more had at least twice the odds of having CMB compared with patients with trace proteinuria or none at all. Strengthening the validity of this relationship, a similar independent association was separately noted between proteinuria and number of CMB.

We are unaware of any relationship between CMB and proteinuria being published previously. Although the exact mechanism by which proteinuria confers greater vascular risk is not well established, several plausible explanations have been proposed, the most appealing of which is that urinary protein is a marker of impaired endothelial function not just in the glomerulus, but also throughout the vascular tree. Our study lends additional support to the hypothesis that proteinuria probably reflects a more generalized process indicative of underlying vascular damage, not just the complication of preclinical renal disease. Indeed, there are several hemodynamic similarities between the vascular beds of the kidney and the brain,[23] so it is conceivable that proteinuria may reify the relationship between lipofibrohyalinosis or amyloid angiopathy and the occurrence of CMB. Proteinuria may serve as an important surrogate marker for development and progression of CMB. In a study of mice, there was increased fragility of brain microvessels in response to several stressors including albuminuria.[24] Other indices of end-organ damage, like left ventricular hypertrophy, have been linked to presence of CMB[25] but tracking or modifying proteinuria with regard to the effectiveness of specific interventions would likely be clinically easier and cheaper than monitoring left ventricular hypertrophy.

Management of CMB will likely necessitate medical therapies that protect the cerebral microvasculature from injury.[26] Optimal blood pressure lowering is regarded as the premier determinant of cerebrovascular, cardiovascular, and renal protection. However, modulators of the renin angiotensin system are more effective than other traditional antihypertensive agents in reducing the onset of clinical proteinuria, even in normotensive patients, and are the agents preferred by national experts

for limiting urinary protein excretion.[27] Interestingly, preclinical studies have identified common molecular components of small-vessel physiology that may also mediate microvascular dysfunction or injury, including angiotensin II; thus, renin angiotensin system modulators may be worthy of testing in a trial geared at preventing or limiting CMB.[28]

Consistent with community-based studies[16,29] as well as individuals hospitalized with lacunar infarcts[20] we noted a positive association of CMB with age and creatinine in bivariate analysis, but these associations did not persist following multivariate analyses. Our multivariable analysis showed an association between elevated serum homocysteine level and CMB, which may reflect the role of elevated plasma homocysteine as a risk factor for arteriosclerosis through its potent induction of endothelial dysfunction in cerebral arterioles.[30] It has been suggested that the observed positive association between proteinuria and cardiovascular disease may be related to elevated homocysteine[4] but our results indicate that, at least with regard to CMB occurrence, these variables have distinct relationships with CMB.

Small-vessel disease stroke mechanism was also shown to be independently linked with presence of CMB, a finding consistent with several studies indicating a strong connection between CMB and cerebral small-vessel disease, each different expressions of microangiopathy.[8,11,13,14] History of atrial fibrillation was also independently linked to CMB. We speculate that because atrial fibrillation is often a consequence of underlying cardiac disease including ischemic heart disease, atherosclerosis, and hypertension,[31,32] the relationship between CMB and atrial fibrillation might be a reflection of the presence and severity of underlying cardiac disease, perhaps representing yet another example of CMB association with end-organ (heart) damage.[25] It is not immediately clear why women had a higher association with CMB. This relationship has not been noted in prior CMB studies, but is a finding that needs to be further explored.

Our study's strengths include the collection of sociodemographic and clinical information in a prospective fashion. Nonetheless, our study was limited by its single-center hospital design and modest sample size. The cross-sectional analysis prevents any causal inferences from being made. Furthermore, we based our diagnosis of proteinuria on only one urine sample, whereas it would have been ideal to verify the diagnosis in several samples. We also controlled for several variables but unmeasured confounding could have affected our results. Finally, we did not have pathological verification that the MRI lesions represented residual blood products, and description of CMB distribution in our series may have provided further insight into CMB heterogeneity.[33]

In conclusion, our study of patients with transient ischemic attack and ischemic stroke found a strong independent relationship between urinary protein excretion vs presence and frequency of CMB. Future larger-scale prospective studies will be needed to confirm this relationship.

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