Cerebral Microbleeds in Patients with Cerebral Ischemic, Hemorrhagic Stroke and Traumatic Brain Injury

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Introduction
Cerebral microbleeds (CMB) are seen as small, homogenous, round, low signal intensity on magnetic resonance gradient echo image (GRE) T2* sequences and susceptibility–weighted sequences. Histologically, CMBs are correlated with focal hemosiderin deposition and considered to represent lipofibrohyalinosis or amyloid angiopathy. CMBs have been an important image marker of cerebral small vessel disease, the safety of antithrombotic use, the risk of intracerebral hemorrhage, and cognitive impairment. The aim of this study was to evaluate risk factors association with CMBs of cerebral ischemic disease, spontaneous intracerebral hemorrhage, and traumatic brain injury.

Materials and methods
Patients: Ilsan Paik Hospital Ethics Committee and Review Board approved this study. Data for all the patients hospitalized at this hospital are kept in separate data bases approved for both clinical research and quality assurance purposes. We retrospectively reviewed the records of all patients presenting with acute ischemic and hemorrhagic stroke, and traumatic brain injury from January 2016 to December 2017. Patients were excluded who did not have a brain MRI during their hospital stay or outpatient clinic. Demographic variables (age, sex), medical information (history of hypertension, diabetes mellitus, stroke, coronary artery disease, tobacco use, arterial fibrillation, hyperlipidemia, acute and chronic kidney disease, benign prostate hypertrophy, cnacer), medication history (anti–HT, antiplatelet agent, antithrombotic agent) and stroke characteristics (NIHSS score, TOAST criteria, GCS score) were all analyzed.

Image: MRI of the brain were performed on a 1.5 Tesla MRI scanner (Symphony Ultra Gradient; Siemens AG, Erlangen, Germany). The whole brain of each patient was scanned including diffusion,T1, T2 weighted images. T28 gradient echo sequence (GRE) were obtained with a slice thickness of 5mm, slice gap of 6mm, TR/TE:800/26 ms, flip angle:20°, FOV:230mm.

CMBs characterization: We only count “definite CMBs” using the Microbleed anatomical Rating Scale, witch were small, round or ovoid, well defined hypointense lesions within brain parenchyma with a clear margins ranging from 2 to 10mm in size on GRE T2* image. The distribution of CMBs was described as lobar, deep, and infratentorial as previous mentioned guideline. CMB burden was defined as 0: absent, 1~5: mild, >5: multiple.

Statistical analysis: IBM SPSS statistics version 21.0 (IBM, Armonk, New York) Continuous variables were described using mean with standard deviation (SD), or median and analyzed using Student’s t–tests, or Mann–Whitney U test for independent variables, as appropriate. Categorical variables were described as percentages and analyzed using Pearson’s chi–square or Fisher’s exact analyses. Logistic regression was used to determine the influence of multiple risk factors. Variables significant in the univariable analysis and those of particular interest were included in the multivariable modeling, with a *p*–value of 0.05 considered statistically significant.

Results
We identified a total 320 patients with 112 spontaneous intracerebral hemorrhages, 100 ischemic stroke, and 108 traumatic brain injury patients. Baseline characteristics of each group are shown in Table 1.

Mean age of traumatic brain injury patients was more younger than ischemic or hemorrhagic stroke patients (*p* = .000). History of hypertension was more frequent in ischemic or hemorrhagic stroke patients than trauma patients (*p* = .000). Renal dysfunction was more frequent in in ischemic or hemorrhagic stroke patients (*p* = .043). Recurrence of hemorrhage or ischemia was only in in ischemic or hemorrhagic stroke patients (*p* = .006). CMBs burden was high in hemorrhagic patient and one third was multiple CMBs (*p* = .000).

The only factor associated with CMBs in hemorrhagic stroke was history of hypertension (*p* = .024) in Table2. Rebleeding in patients with hemorrhagic stroke only occurred at the patients with CMBs (*p* = .006). According to CMBs burden, advanced age (p = .05), history of hypertension (*p* = .030), renal dysfunction (*p* = .018) were the factors in Table 3. Also more CMBs has frequent rebleedings (*p* = .015). Antihypertensive and/or antiplatelet medication were the significant factors in CMBs burden, however, it was associated with history of hypertension. Mutivariate logistic regression analysis reveals that history of hypertension was the only factor of CMBs in hemorrhagic stroke (Table 4). However, Medication of antihypertension was not related to the CMBs (Table 5). There was multiple CMBs only in diffuse axonal injury among traumatic brain injury patients.

	ICH (n=112)	Ischemia (n=100)	Trauma (n=108)	p-value
Age, yrs	60.3+15.9	65.8+12.2	48.8+24.5	0.000
Male, n (%)	76 (67.9)	59 (59.0)	81 (75.0)	0.282
Hypertension history	79 (70.5)	74 (74.0)	39 (36.1)	0.000
Diabetes	24 (21.4)	39 (39.0)	19 (17.6)	0.590
Atrial fibrillation	5 (4.5)	14 (14.0)	2 (1.9)	0.500
Dyslipidemia	27 (24.1)	42 (42.0)	18 (16.7)	0.257
Benign prostatic hypertrophy	6 (5.4)	11 (11.0)	8 (7.4)	0.618
Angina	11 (9.8)	14 (14.0)	6 (5.6)	0.308
Dementia	5 (4.5)	1 (1.0)	2 (1.9)	0.285
Smoking history	29 (25.9)	25 (25.0)	37 (34.3)	0.133
CVA history	10 (8.9)	2 (5.0)	8 (11.1)	0.491
eGFR<60	15 (13.4)	16 (16.2)	5 (4.6)	0.043
Medication Use				
Antihypertensive use	44 (39.3)	61 (61.0)	39 (36.1)	0.787
Antiplatelet use	29 (25.9)	32 (32.0)	19 (17.6)	0.186
CMBs presence	72 (64.3)	26 (26.0)	19 (17.6)	0.000
CMBs burden(count)				0.000
0	40 (35.7)	74 (74.0)	89 (82.4)	
1<CMBs<5	45 (40.2)	23 (23.0)	13 (12.0)	
5≤	27 (24.1)	3 (3.0)	6 (5.6)

Fig. 51 years–old male patient left temporal ICH with one infratentorial CMB. Six years after follow–up loss without any medication, he developed new left occipital hemorrhage with multiple CMBs (infratentoreal, deep, and lobar location).

Conclusions
✓We found that **hypertension, age, and renal dysfunction** were independently associated with presence of CMBs in patient with ischemic and hemorrhagic stroke. **CMB burden was independently associated with rebleeding in hemorrhagic stroke**. Multiple CMBs may predict subsequent recurrence in hemorrhagic stroke. Our results are consistent with a recent meta–analysis showing significant correlation between hypertension and CMBs in patients with ischemic and hemorrhagic stroke. **Multiple CMBs are the diagnostic marker of diffuse axonal injury** in traumatic brain injury patient, however, these CMBs disappear later. CMBs are mainly associated with **hypertensive arteriopathy**, espially in **hemorrhagic stroke**.

	All (n=112)	No CMBs (n=40)	CMBs (n=72)	p-value
Age, yrs	60.3+15.9	57.9+16.7	61.6+15.4	0.239
Male, n (%)	76 (67.9)	27 (67.5)	49 (68.1)	0.952
Hypertension history	79 (70.5)	23 (57.5)	56 (77.8)	0.024
Diabetes	24 (21.4)	9 (22.5)	15 (20.8)	0.837
Atrial fibrillation	5 (4.5)	1 (2.5)	4 (5.6)	0.653
Dyslipidemia	27 (24.1)	8 (20.0)	19 (26.4)	0.449
Benign prostatic hypertrophy	6 (5.4)	2 (5.0)	4 (5.6)	1.000
Angina	11 (9.8)	1 (2.5)	10 (13.9)	0.093
Dementia	5 (4.5)	1 (2.5)	4 (5.6)	0.653
Smoking history	29 (25.9)	12 (30.0)	17 (23.6)	0.506
CVA history	10 (8.9)	2 (5.0)	8 (11.1)	0.491
eGFR<60	15 (13.4)	2 (5.0)	13 (18.1)	0.052
Medication Use				
Antihypertensive use	44 (39.3)	9 (22.5)	35 (48.6)	0.009
Antiplatelet use	29 (25.9)	5 (12.5)	24 (33.3)	0.016
Rebleeding	12 (10.7)	0 (0)	12 (16.7)	0.006

Fig. 59 years–old male patient had ACA territory infarction and multiple artherosclerotic carotid and vertebral arteries, with multiple deep CMBs. Six years later with antihypertensive, antilipid, and dual antiplatelet medication, he developed massive left basal ganglia hemorrhage. He could not followed GRE.

	No CMBs (n=40)	1<CMBs<5 (n=45)	5< CMBs (n=27)	p-value
Age, yrs	57.9+16.7	58.5+16.3	66.8+12.2	0.050
Male, n (%)	27 (67.5)	29 (64.4)	20 (74.1)	0.694
Hypertension history	23 (57.5)	34 (75.6)	22 (81.5)	0.030
Diabetes	9 (22.5)	6 (13.3)	9 (33.3)	0.455
Atrial fibrillation	1 (2.5)	2 (4.4)	2 (7.4)	0.387
Dyslipidemia	8 (20.0)	8 (17.8)	11 (40.7)	0.085
BPH	2 (5.0)	1 (2.2)	3 (11.1)	0.421
Angina	1 (2.5)	8 (17.8)	2 (7.4)	0.412
Dementia	1 (2.5)	1 (2.2)	3 (11.1)	0.145
Smoking history	12 (30.0)	12 (26.7)	5 (18.5)	0.227
CVA history	2 (5.0)	4 (8.9)	4 (14.8)	0.199
eGFR<60	2 (5.0)	6 (13.3)	7 (25.9)	0.018
Medication Use				
Antihypertensive	9 (22.5)	19 (42.2)	16 (59.3)	0.002
Antiplatelet	5 (12.5)	12 (26.7)	12 (44.4)	0.004
Rebleeding	0 (0)	7 (15.6)	5 (18.5)	0.015