Association of Ultrasonography and MRI Findings with Stroke Recurrence: Differences Between Patients with Past Histories of Atherothrombotic Versus Lacunar Infarctions

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Objective: This study investigated the association of MRI and ultrasonography findings with stroke recurrence in patients with past histories of atherothrombotic infarctions (ATIs) or lacunar infarctions (LIs). *Methods:* We prospectively analyzed the incidence of stroke recurrence. Deep and lobar cerebral microbleeds (MBs), asymptomatic lacunae, asymptomatic intracerebral hemorrhages (ICHs), severe white matter lesions (WML), and intima-media thickness (IMT) were investigated on enrollment. Stroke recurrence rates were compared by using the log-rank test. The odds ratios for recurrent strokes were derived using multivariate logistic regression models, adjusted for risk factors. *Results:* We evaluated the stroke recurrence rate in 362 ATI patients and 309 LI patients. The log-rank test and multivariate analyses revealed that the incidence of recurrent stroke was significantly higher in ATI patients with mean IMT greater than or equal to 1.1 mm, asymptomatic ICHs, or lobar MBs than in those without. The incidence was significantly higher in LI patients with asymptomatic ICHs, asymptomatic LIs, and severe WMLs than in those without. In ATI patients, those with strictly lobar MBs or mixed MBs (deep and lobar MBs) had significantly higher recurrence rates than those without MB. In LI patients, those with strictly deep MBs or mixed MBs had higher recurrence rates than those without MB, and the incidences of those with mixed MBs was larger than those with strictly deep MBs. *Conclusions:* There were differences between ATI and LI patients in terms of the association of MRI and ultrasonography findings, in particularly strictly lobar or deep MBs, with the incidence of stroke recurrence.

Key Words: Cerebral microbleeds—IMT—lacunar infarction—atherothrombotic infarctions—recurrence—risk factor

Introduction

Both atherothrombotic infarctions (ATIs) and lacunar infarctions (LIs) are associated with several of the same risk factors, including older age and hypertension, and are often investigated together as noncardioembolic infarctions. However, these 2 conditions have different origins. ATIs arise from atherosclerosis, whereas LIs result from microangiopathy, including hypertensive microangiopathy (HypM). Clinical findings on ultrasonography and MRI may provide useful information about stroke occurrence and recurrence. The mean intima-media thickness (IMT) of the carotid artery, measured noninvasively by ultrasonography, has been the focus of numerous investigations, and greater IMT is related to systemic atherosclerosis and is directly associated with an increased risk of stroke occurrence.[1] Both symptomatic and asymptomatic LIs and intracerebral hemorrhages (ICHs) originate from HypM, but with differences in locations and/or sizes. White matter lesions (WMLs), LIs, and deep cerebral microbleeds (MBs) originate from small vessel diseases. Previous studies demonstrated that nascent and pre-existing lobar and deep MBs, as well as severe WMLs, were associated with stroke recurrences presenting as LIs and ICHs.[2-6]

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Amyloid concentrations were found to be elevated at lobar MBs sites and to decline with increasing distance from MBs, and were also associated with cerebral amyloid angiopathy (CAA).[7] Strictly lobar MBs may originate from CAA and/or may be related to apolipoprotein ε4 (APOE4),[8,9] but some lobar MBs may be associated with HypM.[3,10]

Ultrasonography and MRI findings have been found to be related to higher incidences of stroke recurrences. However, little is known about the relationship between preexisting findings and stroke types. We speculated that patients with past histories of ATIs and LIs might differ in terms of recurrent stroke incidence and related preexisting findings. Specifically, we formulated the following 2 hypotheses. (1) Only HypM-associated findings elevate the risk of recurrence in patients with a past history of LIs (LI patients). On the other hand, only atherosclerosis-related findings increase the incidence of recurrence in patients with a past history of ATIs (ATI patients). (2) Several risk factors are related to both HypM and atherosclerosis. Therefore, findings associated with both conditions may elevate the recurrence rates in ATI and LI patients. In this study, to investigate the relationship between the rate of stroke recurrence and preexisting findings, we evaluated recurrences in ATI and LI patients.

Subjects and Methods

Subjects

From April 2004 to December 2011, we enrolled patients who were consecutively admitted to our hospital within 7 days of experiencing ATIs or LIs (index strokes). Follow-up took place until March 2017 at the latest, and stroke recurrences were evaluated in all patients. We excluded patients with follow-up durations of less than 1 week, as well as those with unclear findings on MRIs due to motion or metal artifacts. All study procedures were approved by the Ethics Committee of Kushiro City General Hospital (IRB 2004-1).

Radiological Examinations

At least 2 physicians with Japanese Board Certifications in Neurosurgery and in Stroke diagnosed stroke types based on radiological findings. Imaging findings were reviewed by at least 1 physician without knowledge of clinical information or treatment assignment. Patients lacking neuroradiological findings related to index strokes on CT and MRI were excluded from this study.

The severity of white matter hyperintensity (WMH) or periventricular hyperintensity (PVH) on FLAIR imaging was rated according to the Fazekas grade (F Gr).[11] Dot-like, low-intensity spots on T2*-weighted (T2*-w) MRI with diameters less than 10 mm were defined as MBs. Low-intensity spots on T2*-w MRI with diameters more than or equal to 10 mm were defined as ICHs. The locations of MBs were grouped according to brain area according to the Microbleed Anatomical Rating Scale (MARS).[12] Deep areas included the territories of the perforating arteries and the infratentorial regions (brain stem and cerebellum). Lobar areas included subcortical and cortical areas. MRI parameters were described in previous manuscripts.[2,3] To clarify the contribution of MBs to stroke recurrence, we divided MBs into 3 groups: strictly deep MBs, strictly lobar MBs, and mixed MBs (coexistence of deep and lobar MBs) and compared to the group without MB.

Lacunar infarctions were diagnosed as infarctions with diameters less than 15 mm at the site fed by perforating arteries without the surface of cerebellum or brain stem. Small infarctions associated with the areas of perforating arteries fed by stenotic parent arteries (atheromatous findings) were excluded. Brunch atheromatous diseases (BADs) were diagnosed carefully and excluded.

Common carotid artery IMTs were measured at 5, 17.5, and 30 mm from the origin of the internal carotid arteries within 2 weeks after hospital admission. Mean IMT was calculated based on all 3 points, while maximum IMT was measured between 30 mm and 5 mm of the origin. For both the mean and maximum IMT, the larger of the values on the right and left sides was used.

Patients' medications were recorded when stroke recurrences occurred, when repeat MRIs were performed around 1 year after index stroke onset in patients without recurrence, or when final medical examinations were performed in cases with less than 1 year of follow-up after index stroke onset. Fasting blood samples were obtained the morning after initial admission. Diabetes mellitus was defined according to the National Diabetes Data Group diagnostic criteria. In terms of smoking history, patients were categorized into ''cigarette smoking'' or ''nonsmoking'' groups on admission; the latter included regular cigarette smokers who quit 1 year earlier. The analysis methods, diagnostic approaches, and treatment of risk factors in this study were described in detail in our previous studies.[2,3]

Statistics

To investigate the association of ultrasonographic and radiological findings with stroke recurrence, patients were divided into subgroups based on imaging findings. Stroke recurrence rates were compared by the log-rank test. Overall frequencies of categorical variables were calculated in the form of odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate analyses were also performed using a regression model. Where applicable, 95% CIs were calculated for the estimated ORs. A P value of less than .05 was considered statistically significant.

Results

Patients with ATIs as Index Strokes (ATI Patients)

We consecutively enrolled 382 ATI patients during the study period. Of these, 7 died within 7 days after ATI onset.

We excluded 6 with unclear findings on MRIs, 3 with insufficient data, and 4 with pacemakers. Thus 362 patients were divided into 2 groups based on whether or not they experienced stroke recurrence. Table 1 presents the stroke-related variables in the 2 groups. The mean follow-up period was 41 ± 52 months, and 79 recurrent strokes occurred, including 7 LIs, 54 ATIs, 13 cardioembolic infarctions (CEIs), and 5 ICHs (3 deep ICHs, 2 lobar ICHs). Univariate analyses demonstrated significant differences between the groups in terms of age (≥65 years old), number of lobar MBs, strictly lobar MBs, mixed MBs, mean IMT more than or equal to 1.1 mm, maximum IMT more than or equal to 1.1 mm, hypertension, and F Gr 2-3 (Table 1).

Table 2 shows the results of log-rank tests and multivariate analyses when adjusting for female gender, age more than or equal to 65 years old, hypertension, diabetes mellitus, low-density lipoprotein (LDL) cholesterol more than or equal to 150 mg/dl, high-density lipoprotein (HDL) cholesterol less than 40 mg/dl, triglycerides more than or equal to 150 mg/dl, hemodialysis, smoking, statin use, anti-platelet drug use, and anticoagulant drug use, all of which have been previously found to be related to strokes. Multivariate analysis revealed that strictly lobar MBs, mixed MBs, asymptomatic ICH, and mean IMT greater than or equal to 1.1 mm were associated with a significantly higher rate of overall stroke recurrence (i.e., all types) and recurrence presenting as ATIs (Table 2). Log-rank tests and multivariate analysis demonstrated that asymptomatic LIs were associated with a significantly higher rate of LIs, and that asymptomatic ICHs were associated with a significantly higher rate of ATIs (Table 2). Log-rank tests demonstrated that patients with F Gr 2-3 had significantly higher rates of LIs, ATIs, and strokes (all types) presenting as stroke recurrences, but multivariate analyses did not confirm these findings. The rate of overall stroke recurrence (all types) was significantly higher in ATI patients with strictly lobar MBs or mixed MBs (deep and lobar MBs) than in those without MB, whereas the rate was similar between ATI patients without MB and those with strictly deep MBs.

Table 1. *Baseline characteristics of ATI patients with and without recurrent strokes*

Factors	Recurrence (−) n = 292	(+) n = 70	Unadjusted univariate analysis		
			OR	95% CI	*P* value
Gender, age					
Female	124 (42%)	27 (39%)			>.20
Age (years old)	71.6 ± 12.5	74.1 ± 9.6			.034 (TT)
Age ≥ 65years old	209 (72)	59 (84)	2.1	1.1-4.3	.032
Initial radiological findings					
No of deep MBs	.75 ± 2.09	1.65 ± 4.58			.064 (TT)
No of lobar MBs	.43 ± 1.94	0.83 ± 1.65			.040 (TT)
Strictly deep MBs (+)	47 (16)	8 (11)			>.20
Strictly lobar MBs (+)	12 (3)	8 (11)	3.01	1.2-7.7	.021
Mixed MBs (+)	29 (10)	14 (20)	2.27	1.1-4.6	.022
Asymptomatic ICH	5 (2)	4 (6)	3.5	.91-13	.069
Asymptomatic LI	78 (27)	26 (37)	1.6	.94-2.8	.085
F Gr 2-3 (severe WML)	93 (32)	29 (41)	1.5	.89-2.6	.129
Mean IMT ≥1.1 mm	111 (48) (n = 232)	38 (67) (n = 57)	2.2	.2-4.0	.012
Maximum IMT ≥ 1.1 mm	157 (68) (n = 232)	47 (82) (n = 57)	2.2	1.1-4.7	.031
Medical history and laboratory data					
Diabetis mellitus	87 (30)	14 (20)	.59	0.31-1.1	.104
Hypertension	194 (66)	42 (60)			>.20
Smoking	91 (31)	18 (26)			>.20
HDL cho <40 mg/dl	85 (29)	22 (31)			>.20
LDL cho ≥ 140 mg/dl	53 (18)	8 (11)	.58	.26-1.3	.181
Triglyceride ≥ 150 mg/dl	54 (18)	12 (17)			>.20
Hemodialysis	14 (5)	4 (6)			>.20
Drug use					
Statin	61 (21)	14 (20)			>.20
Anti-platelet drugs	221 (76)	57 (81)			>.20
Warfarin or DOAC	12 (4)	5 (7)			>.20

Abbreviations: ATI, atherothrombotic infarction; CEI, cardioembolic infarction; CI, confidence interval; DOAC, direct oral anticoagulants; F Gr, Fazeka's grade of white matter lesions; HDL cho, high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; IMT, intima-media thickness; LDL cho, low-density lipoprotein cholesterol; LI, lacunar infarction; MBs, cerebral microbleeds; n, number; No, number; OR, odds ratio; TT, *t*-test; WML, white matter lesion.

Table 2. *Log-rank test and multivariate analyses of the findings in ATI patients*

Image findings	Recurrence presenting as	Log-rank test *P* value	Multivariate analyses		
			OR	95% CI	*P* value
Strictly deep MBs	LI	NP		NP	
	ATI	>.20			>.20
	CEI	>.20			>.20
	ICH	.095	5.7	.59-55	.133
	All types	>.20			>.20
Strictly lobar MBs	LI	>.20			>.20
	ATI	.102	2.5	.22-1.2	.13
	CEI	.102			>.2
	ICH	NP		NP	
	All types	.0025	3.2	1.2-8.8	.026
Mixed MBs	LI	.147			>.20
	ATI	.0074	2.9	1.2-6.8	.018
	CEI	NP		NP	
	ICH	NP		NP	
	All types	.0055	2.5	1.1-5.4	.022
Asymptomatic LI	LI	.021	6.7	1.1-39	.035
	ATI	.134	1.8	.96-3.4	.067
	CEI	>.20			>.20
	ICH	>.20			>.20
	All types	>.2	1.7	.93-3.0	.088
Asymptomatic ICH	LI	NP		NP	
	ATI	.027	4.7	1.1-19	.032
	CEI	NP		NP	
	ICH	NP		NP	
	All types	.125	3.9	.96-16	.058
F Gr 2, 3 (severe WML)	LI	.007	3.8	.65-20.3	.136
	ATI	0.004	1.7	.90-3.2	.102
	CEI	NP		NP	
	ICH	.156	3.8	.52-28	.188
	All types	.014			>.20
Mean IMT ≥ 1mm	LI	>.20	.172	.01-2.0	.158
	ATI	.001	3.2	1.4-7.1	.005
	CEI	>.20			>.20
	ICH	>.20			>.20
	All types	.01	2.5	1.3-4.9	.007
Maximum IMT ≥ 1mm	LI	>.20			>.20
	ATI	.11	2.4	.96-5.9	.062
	CEI	.133	7.2	.62-83	.116
	ICH	>.20			>.20
	All types	.053	2.3	1.0-5.1	.041

Multivariate analyses were performed with adjustment for female gender, age ≥65 years old, hypertension, diabetes mellitus, LDL cholesterol ≥150 mg/dl, HDL cholesterol <40 mg/dl, triglycerides ≥150 mg/dl, hemodialysis, smoking, statin use, anti-platelet drug use, and anti-coagulant drug use; NP: not applicable; other abbreviations are described in Table 1.

Patients with LIs as Index Strokes (LI Patients)

We consecutively enrolled 337 LI patients during the study period. Twenty-eight patients were excluded, including 7 who died within 7 days after index stroke onset, 6 with pacemakers, 5 with unclear findings on MRIs, and 10 with insufficient records. Thus 309 of the initial 337 LI patients were followed and stroke recurrence rates were investigated. The 309 patients were divided into 2 groups based on whether or not they experienced stroke recurrence. Table 3 presents stroke-related variables in the 2 groups. The mean follow-up period was 51 ± 33 months, and the total number of recurrent strokes was 64, including 31 LIs, 13 ATIs, 4 CEIs, 14 ICHs (13 deep ICHs, 1 lobar ICHs), and 2 others. Univariate analyses demonstrated significant differences between the 2 groups in terms of the number of deep and lobar MBs, incidence of mixed MBs, asymptomatic LIs, F Gr 2-3, hypertension, and LDL cholesterol more than or equal to 150 mg/dl (Table 3).

Log-lank tests and multivariate analyses demonstrated that strictly deep MBs, mixed MBs, asymptomatic LIs,

Table 3. *Baseline characteristics of LI patients with and without recurrent stroke*

Factors	Recurrence (−) n = 255	(+) n = 54	Unadjusted univariate analysis OR	95% CI	*P* value
Gender, age					
Female	119 (47%)	21 (39%)			>.20
Age (years old)	70.2 ± 11.8	70.9 ± 11.2			>.20 (TT)
Age ≥ 65 years old	172 (67)	41 (76)			>.20
Initial radiological findings					
No of deep MBs	.75 ± 2.43	2.37 ± 5.26			.016 (TT)
No of lobar MBs	1.42 ± 3.92	3.22 ± 4.89			.007 (TT)
Strictly deep MBs (+)	44 (17)	13 (24)			>.20
Strictly lobar MBs (+)	10 (4)	2 (4)			>.20
Mixed MBs (+)	45 (18)	23 (43)	3.7	2.0-7.0	<.001
Asymptomatic ICH	8 (3)	5 (9)	3.2	.99-10	.052
Asymptomatic LI	87 (34)	28 (52)	2.1	1.1-3.8	.016
F Gr 2-3 (severe WML)	79 (31)	30 (56)	2.7	1.5-5.1	.001
Mean IMT ≥1.1mm	103 (46) (n = 225)	23 (50) (n = 46)			>.20
Maximum IMT ≥1.1 mm	163 (72) (n = 225)	31 (67) (n = 46)			>.20
Medical history and laboratory data					
Diabetis mellitus	81 (32)	14 (26)			>.20
Hypertension	166 (65)	27 (50)	.54	.3-9.7	.039
Smoking	77 (30)	16 (30)			>.20
HDL cho < 40 mg/dl	62 (24)	17 (31)			>.20
LDL cho ≥ 140 mg/dl	75 (29)	10 (19)	.34	.13-.89	.028
Triglyceride ≥ 150 mg/dl	63 (25)	13 (24)			>.20
Hemodialysis	6 (2)	3 (6)			>.20
Drug use					
Statin	62 (24)	8 15)	.54	.24-1.2	.134
Anti-platelet drugs	239 (94)	48 (89)			>.20
Warfarin or DOAC	15 (6)	3 (6)			>.20

Abbreviations are described in Table 1.

asymptomatic ICHs, and F Gr 2-3 were associated with a significantly higher rate of stroke recurrence (all types) (Table 4), whereas neither max IMT greater than or equal to 1.1 mm nor mean IMT greater than or equal to 1.1 mm demonstrated any correlation.

Multivariate analyses demonstrated that the incidence of LIs and ICHs presenting as recurrence in LI patients was significantly and independently associated with F Gr 2-3 when adjusted for the same factors listed above (Table 4). The incidence of LIs presenting as recurrence in LI patients was significantly and independently associated with mixed MBs and asymptomatic LIs when adjusted for the same variables, but these variables showed no significant association with ICHs presenting as recurrences (Table 4).

In LI patients, the stroke recurrence rate was higher in patients with mixed MBs than in those with strictly deep MBs, but both of these groups had a significantly higher recurrence rate than LI patients without MB. In contrast to the results in LI patients, the recurrence rate in ATI patients with mixed MBs was lower than in those with strictly lobar MBs. Together these findings indicate that specific MBs contribute differently to stroke recurrence.

Discussion

The Association of Ultrasonography and MRI Findings with Stroke Recurrence

The log-rank test and multivariate analyses demonstrated that strictly deep MBs and asymptomatic LIs were surrogate markers for recurrent strokes (all types) in patients whose index strokes were LI but not ATI. Mean IMT greater than or equal to 1.1 mm was a surrogate marker for recurrent stroke (all types) in ATI patients but not in LI patients. Thus, there are apparent differences in terms of the surrogate markers for stroke recurrence in LI and ATI patients. Strictly deep MBs and asymptomatic LIs are associated with HypM related to LIs, whereas mean IMT greater than or equal to 1.1 mm is based on atherosclerosis related to ATIs.

Since physicians at our hospital did not completely exclude misdiagnosis of LIs originating from microangiopathies, some of the LIs in this study may have arisen from other conditions. LIs associated with deep MBs may have been more likely to originate from microangiopathies than from other pathologies. Therefore, there might be significant differences between LI patients with and without MBs in terms of the rate of stroke recurrence

Table 4. *Log-rank test and multivariate analyses of the findings in LI patients*

Image findings	Recurrence presenting as	Log-rank test *P* value	Multivariate analyses		
			OR	95% CI	*P* value
Strictly deep MBs	LI	>.20			>.20
	ATI	>.20			>.20
	CE	.09	10.6	.68-165	.092
	ICH	.0058	6.43	0.92-45	.06
	All types	.009	2.63	1.04-6.7	.041
Strictly lobar MBs	LI	.0034	7.9	.92-67	.06
	ATI	NP		NP	
	CE	NP		NP	
	ICH	NP		NP	
	All types	.176			>.20
Mixed MBs	LI	.0001	6.6	1.8-25	.005
	ATI	.077			>.20
	CE	>.20			>.20
	ICH	.0006	7	.98-50	.052
	All types	<.0001	4.7	1.9-11	.001
Asymptomatic LI	LI	.0005	5.8	2.1-16	.01
	ATI	>.20			>.20
	CE	NP		NP	
	ICH	.144	2.1	.68-6.7	.195
	All types	.018	2.5	1.3-4.7	.006
Asymptomatic ICH	LI	NP		NP	
	ATI	>.20			>.20
	CE	NP		NP	
	ICH	<.0001	16	3.1-83	.001
	All types	.012	5.4	1.5-20	.012
F Gr 2, 3 (severe WML)	LI	.006	4.1	1.6-11	.004
	ATI	>.20			>.20
	CE	>.20			>.20
	ICH	.033	3.5	1.0-12	.048
	All types	<.0001	2.9	1.5-5.6	.001
Mean IMT ≥ 1mm	LI	>.20			>.20
	ATI	>.20			>.20
	CE	>.20	11	.36-330	.168
	ICH	>.20			>.20
	All types	>.20			>.20
Maximum IMT ≥ 1mm	LI	>.20			>.20
	ATI	.126			>.20
	CE	>.20			>.20
	ICH	>.20	.36	.09-1.4	.143
	All types	>.20			>.20

Analyses were performed with adjustment for variables described in Table 2.
Abbreviations are described in Tables 1 and 2.

presenting as deep ICHs or LIs. The inaccurate diagnosis of LIs may have affected the results of our statistical analyses. Similarly, ATIs associated with a mean IMT greater than or equal to 1.1 mm may have been more likely to originate from atherosclerosis rather than other pathologies, and a mean IMT greater than or equal to 1.1 mm was associated with higher stroke recurrence rate than a maximum IMT greater than or equal to 1.1 mm.

WML was reported to originate from chronic ischemia related to severe microangiopathy and several other risk factors.[3,13,14] Infarcted areas may be larger under ischemic conditions with severe WML.[15] In LI patients, severe WML (F Gr 2-3) increased the rates of recurrences presenting as all stroke types, LIs, and ICHs, but not ATIs or CEs. In ATI patients, the log-rank test revealed that severe WML (F Gr 2-3) elevated the overall stroke recurrence rate, but multivariate analysis did not demonstrate the significance with risk factors. These factors, in particular age more than or equal to 65 years, might have influenced the statistical results.

We cannot explain why asymptomatic ICHs were related to the occurrence of ATIs. Only 9 of 362 ATI

patients had asymptomatic ICHs; thus, the statistical power of this study may be inadequate.

MBs and Stroke Recurrence

MBs and Stroke Recurrence in LI Patients

MBs in LI Patients

We investigated the relationship between stroke recurrence and each type of MBs. Our findings showed that strictly deep MBs and mixed MBs were associated with an increased stroke recurrence rate in LI patients. Strictly lobar MBs might be slightly related to the recurrence presenting as only LIs in patients with LIs (Table 4). These results suggest that strictly lobar MBs in LI patients may not be strongly associated with HypM. A previous investigation revealed that nascent lobar MBs were associated with pre-existing and nascent deep MBs, as well as with recurrent strokes presenting as LIs or ICHs in patients with original strokes of all types.[3] Pathological investigations revealed that some lobar MBs might originate from HypM, while others lobar MBs originate from CAA.[3,7,8,10]

Mixed MBs in LI Patients

In this study, MRI identified mixed MBs in 22% of LI patients, but the origins of these mixed MBs were unknown. Mixed-location ICHs/MBs, found in both deep and lobar areas, were associated with risk factors similar to those of hypertensive ICHs located strictly in deep areas, and differed from ICHs related to CAA.[16] These mixed-location ICHs/MBs were associated with more severe risk factors, including higher creatinine values, many lacunar infarctions, many MBs, older age, and perivascular spaces in basal ganglia.[16] Finally, mixed-location ICHs/MBs demonstrated more severe parenchymal damage and higher ICH recurrence risk than hypertensive ICHs located strictly in deep areas.[16] Both deep and lobar hemorrhagic lesions might contribute synergistically to cerebrovascular events.

In this study, the stroke recurrence rate in LI patients with mixed MBs was higher than in patients with strictly deep MBs. Mixed MBs might be more closely related to advanced HypM than strictly deep MBs. In LI patients, strictly lobar MBs did not increase the stroke recurrence rate. Strictly lobar MBs might differ from lobar MBs that coexist with deep MBs (mixed MBs). In contrast to LI patients, however, there was an association between strictly lobar MBs and a higher stroke recurrence rate in ATI patients (described below).

MBs and Stroke Recurrence in ATI Patients

Strictly Lobar MBs in ATI Patients

In ATI patients, strictly deep MBs did not increase the stroke recurrence rate, suggesting no apparent relationship between deep MBs and atherosclerosis. By contrast, strictly lobar MBs were associated with a higher stroke recurrence rate. In patients whose index strokes were ATIs, more than half of recurrences were also ATIs. The above findings suggest a significant relationship between strictly lobar MBs and atherosclerosis.

Strictly lobar MBs were reported to be related to CAA. In CAA patients, lobar MBs were associated with an increased incidence of cortical microinfarctions,[17] indicating a relationship with ischemic conditions in the cortex. Mild atherothrombosis might result in infarcted lesions in addition to ischemic conditions in CCA, though cortical microinfarctions are different from ATIs. In ATI patients with strictly lobar MBs, concomitant CAA might increase the stroke recurrence rate.

The APOE gene plays a multifaceted role in ischemic stroke and subclinical intracranial atherosclerosis.[18] The promoter variants affecting APOE4 synthesis were significant predictors of ischemic stroke.[18] A recent investigation demonstrated that lobar MBs were associated with APOE4, but not deep MBs, in Japanese individuals.[9] Furthermore, many investigations revealed a relation between lobar MBs and APOE4.[8,19] Therefore, ATI patients with lobar MBs might have a higher stroke recurrence rate. However, this study found that mean IMT was not associated with lobar MBs in multivariate analyses (data was not shown), indicating that lobar MBs are not directly related to atherosclerosis.

Mixed MBs in ATI Patients

In patients with cerebral amyloid deposition demonstrated by positron emission tomography, coexisting amyloid-related pathology and hypertensive small vessel disease play a synergistic role in the development of lobar MBs.[20] It would be reasonable to surmise that the coexistence of CAA and HypM might increase the stroke recurrence rate in ATI patients. However, our results showed that in these patients, mixed MBs were not associated with a higher rate of stroke recurrence than strictly lobar MBs, and pathology with mixed MBs might not be simply advanced from that with strictly lobar MBs. The recurrence rate in LI patients with mixed MBs was higher than in those with strictly deep MBs, showing that mixed MBs originated from more severe HypM, as mentioned above.

Limitations

This study had several limitations. The follow-up periods of patients with severe conditions or with advanced dementia were short, although the majority of outpatients who were investigated understood the importance of follow-up and were able to visit our hospital. This study utilized a cohort design, and thus the potential for bias cannot be eliminated. Possible sources of bias include a

heterogeneous population, a random selection of drugs, and a variety of unselected risk factors. In addition, patients' follow-up periods were inconsistent in duration. The small number of IMT measurements may also have led to bias. In this study, the numbers of ATI and LI patients with strictly lobar MBs were particularly small, so the significance of these MBs could not be investigated in detail. Further studies with larger numbers of patients are needed in the future.

Summary

In this study, we examined the differences between patients with past histories of ATIs and LIs in terms of the association between ultrasonographic and MRI findings and stroke recurrence. The rate of stroke recurrence was significantly higher in LI patients with strictly deep MBs, mixed MBs, or other HypM-related findings than in those without these findings. In ATI patients, the recurrence rate was significantly higher in patients with strictly lobar MBs, mixed MBs, or mean IMT greater than or equal to 1.1 mm compared to those without these characteristics. There were differences between ATI and LI patients in terms of the association of pre-existing findings, particularly strictly lobar and strictly deep MBs, with stroke recurrence.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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