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Relationship Between White Matter Hyperintensities Penumbra and Cavity Formation

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Background: Penumbra has been detected on the edge of white matter hyperintensities (WMH). The aim of our study was to investigate whether cavity formation is different between acute infarcts on the edge of WMH and those away from the edge.





Material/Methods: Ninety-six subjects with acute lacunar infarct ≤ 25 mm in diameter were recruited. Subjects with infarct contacting or overlapping with WMH (on axial T2 or coronal FLAIR) were defined as the Edge Group (on the edge of the WMH). Those outside the edge of the WMH were the Non-edge Group. Vascular risk factors, clinical data, baseline infarct size, infarct sites, and severity of WMH (by Fazekas scale) were recorded. Cavity formation was identified by MR follow-up imaging. Risk factors for cavity formation were also investigated.

Results: There were 37 (38.5%) subjects in the Edge Group and 59 (61.5%) in the Non-edge Group; 55 (57.3%) subjects had cavity formation in follow-up imaging. Subjects in the Edge Group had higher risk of developing cavities than those in the Non-edge Group (78.4% vs. 44.1%, $p < 0.05$). In univariate analysis, subjects with cavity formation had larger infarct size and their infarcts were more often located in subcortical white matter. Vascular risk factors, clinical data, and WMH did not differ between subjects with cavity formation and those without. In logistic regression analysis, DWI infarct size and being in the Edge Group were independent risk factors for cavity formation.

Conclusions: Lacunar infarcts on the edge of WMH are more likely to develop cavities, suggesting that WMH penumbra affects cavity formation.

MeSH Keywords: **Cerebral Small Vessel Diseases • Leukoencephalopathies • Stroke, Lacunar**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/896324>

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Background

Cerebral small vessel disease (SVD) can cause severe problems; it is responsible for about one-fifth of all strokes [1,2], doubles the future risk of stroke [3], and contributes to cognitive impairment [4,5]. The most common neuroimages of SVD include white matter hyperintensities (WMH) and lacunes [6]. WMH are areas of increased signal intensity on T2-weighted and FLAIR and decreased on T1-weighted MR imaging with respect to normal brains, and are considered to be caused by chronic ischemia resulting from SVD. In earlier studies, WMH have been identified as an independent risk factor for lacune formation. However, the possible mechanistic links are not fully understood.

A lacune is a cerebrospinal fluid-filled cavity consistent with a previous acute infarction [7]. However, not all lacunar infarcts progress to lacunes or cavities [8]. It has been hypothesized that imaging evolution of acute infarcts may be affected by their locations. A previous study has found that there is penumbra on the edge of WMH, which is normal-appearing white matter (NAWM) tissue surrounding WMH. Cerebral blood flow (CBF) in WMH penumbra is significantly lower than the total brain NAWM [9]. Consequently, infarcts that occur in WMH penumbra may much more easily develop cavities because of secondary ischemic attack. In subjects with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), 90% of new lacunes preferentially localize to the edge of WMH because of WMH penumbra [10]. However, the relationship between cavity formation and WMH penumbra in the general population has never been investigated.

Therefore, our aim was to investigate whether cavity formation is different between infarcts on the edge of WMH and those away from the edge. We intended to identify the impact of WMH penumbra on the formation of lacunes or cavities. We hypothesized that acute lacunar infarcts on the edge of WMH have higher risk of developing cavities. We also investigated independent risk factors for cavity formation.

Material and Methods

Subject population

All subjects with acute lacunar infarct admitted to Beijing Chaoyang Hospital affiliated to Capital Medical University from Jan 2011 to May 2015 were retrospectively identified. We only included subjects with a single acute lacunar infarct who underwent MRI examination no more than 7 days after onset and had a repeat MRI examination at 3 or more months later. Lacunar infarct was defined as an acute round or ovoid lesion of increased signal intensity on axial diffusion-weighted imaging

(DWI) ≤ 25 mm and coronal fluid-attenuated inversion recovery (FLAIR) ≤ 25 mm in the distribution of a small penetrating artery. We recruited subjects with a larger-size cutoff than typically used for lacunar infarction (15 mm) because DWI likely overestimates final infarct size and because an absolute size cutoff has remained controversial, as in a previous study [8]. Because our study mainly focused on the relationship between different types of SVD, only subjects with infarcts associated with SVD were included, according to TOAST criteria [1]. The Institutional Review Board of Beijing Chaoyang Hospital affiliated to Capital Medical University approved the study and all subjects provided informed consent to participate in this study.

We collected the following data at baseline: age, sex, and vascular risk factors (including history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, stroke or transient ischemic attack (TIA), smoking, and alcohol use). At admission, we recorded results of clinical data, including level of hemoglobin (HGB), triglyceride (TG), total cholesterol (CHOL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), hemoglobin A1c (HbA1c), homocysteine (Hcy), blood urea nitrogen (BUN), serum creatinine (Cr), and uric acid (UA). Stroke severity at admission was determined by using the NIH Stroke Scale (NIHSS).

MR measure at baseline and follow-up

MR imaging at baseline and follow-up was acquired on the same 3.0 T Siemens scanner (Erlangen, Germany). The parameters of MR examination were: axial T1-weighted imaging (repetition time, 2000 ms; echo time, 9.2 ms), axial T2-weighted (repetition time, 4500 ms; echo time, 93 ms), axial diffusion-weighted imaging (repetition time, 3300 ms; echo time, 91 ms), and coronal fluid-attenuated inversion recovery sequences (repetition time, 8000 ms; echo time, 86 ms). All these sequences had 5-mm slice thickness and 1.5-mm interslice gap.

Baseline infarct size was defined as the largest diameter on axial DWI and coronal FLAIR. Baseline infarct size on T1 and T2 were also recorded. Infarct sites were recorded as subcortical white matter, thalamus, basal ganglia, and infratentorial region. Formation of a cavity was defined as presentation of a CSF-like lesion on follow-up T1, T2, and FLAIR within the original area of acute DWI abnormality, as in a prior study [8]. Follow-up imaging was obtained as a routine examination if patients had nonspecific clinical complaints, worsening of existing deficits, or recurrent stroke symptoms.

To precisely identify the borderline of a lacunar infarct, the pixilated method was used. Using image reading software (GE Medical Systems, centricity enterprise web 3.0), infarct region was amplified ($\times 8$) and pixilated. The value of each pixel on the borderline of a lacunar infarct was obtained. We then defined

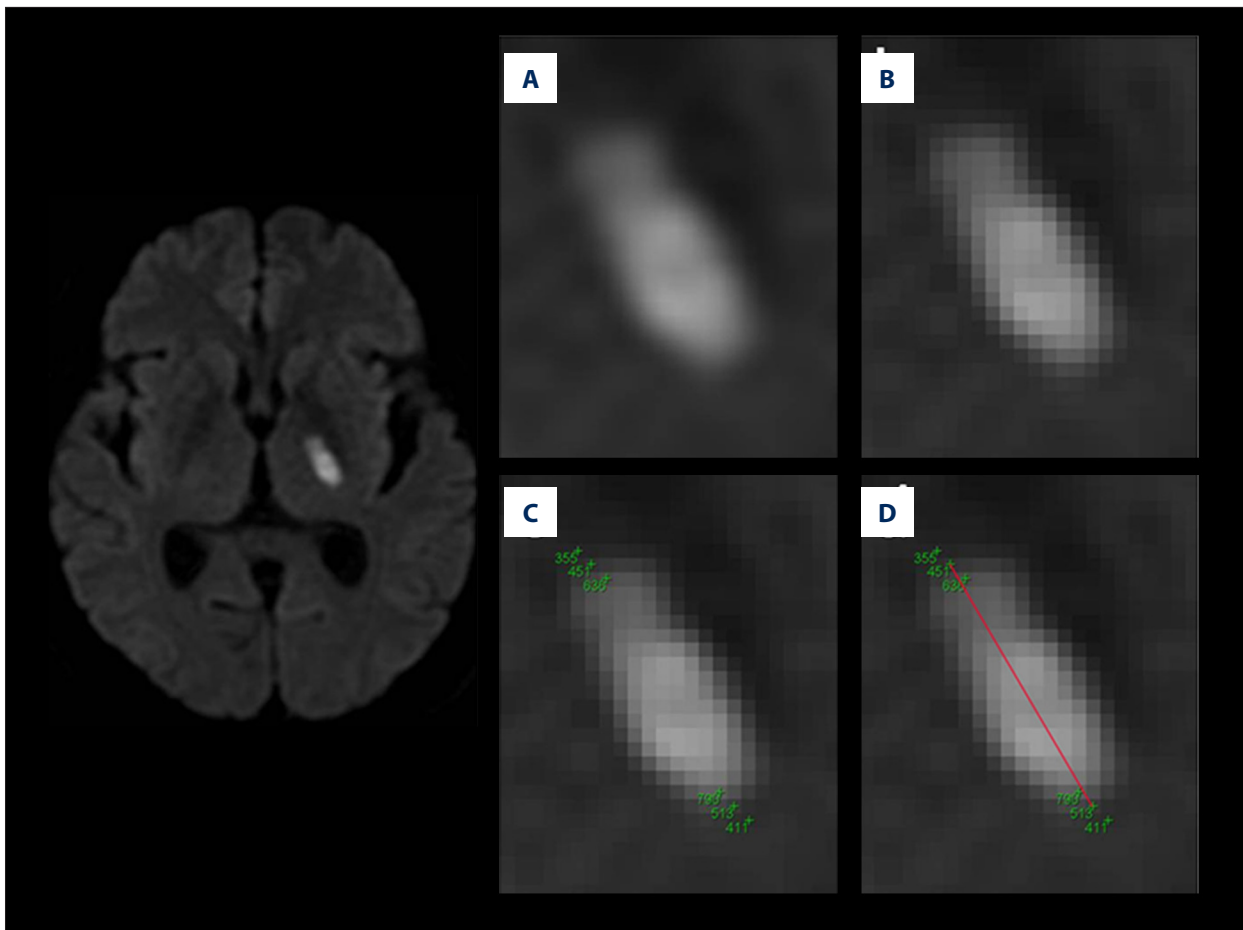


Figure 1. Pixilated method used to measure infarct size. Infarct region was amplified and pixilated (A, B). Pixel value of each pixel on the borderline of a lacunar infarct was obtained (C). We defined the sites with the most changed pixel values as the borderline of lacunar infarction in the direction of largest diameter and measured the infarct size (D).

the sites with the most changed pixel values as the borderline of the lacunar infarction in the direction of its largest diameter (Figure 1). Cavity size was also calculated by pixilated method. More precise definition and greater interrater agreement were found by pixilated method. The intraclass correlation coefficient for baseline DWI, T1, T2, and FLAIR lesion size were 0.97, 0.98, 0.98, and 0.93, respectively (n=26), and follow-up T1, T2, and FLAIR cavity sizes were 0.97, 0.91, and 0.86, respectively (n=10).

Spatial relationship between acute lacunar infarcts and WMH

Spatial relationships between lacunar infarcts and WMH were identified by using a visual rating scale used to assess relationships between new lacunes and pre-existing WMH in a previous study [10]. The 4 situations were: grade 0, lacunar infarcts have no contact with WMH; grade Ia, contact without overlap between lacunar infarcts and WMH; grade Ib, partial overlap between lacunar infarcts and WMH; and grade II, lacunar

infarcts completely overlap with pre-existing WMH (Figure 2). The assessment was conducted on T2 and FLAIR. Lacune was defined as presentation of a decreased signal (CSF-like lesion) on T2 and FLAIR within the original area of acute DWI abnormality. Two raters made the decisions and conflicting results were resolved by discussion. Subjects with infarcts in grade Ia or Ib were considered as infarcts on the edge of WMH (Edge Group), while those in grade 0 or II were infarcts outside the edge of WMH (Non-edge Group).

The Fazekas scale was used to assess severity of WMH [11]. Periventricular WMH and deep WMH were evaluated separately and totaled together as Fazekas scores. The degree of WMH severity was rated by Fazekas scores (mild: 0–2; moderate: 3–4; severe: 5–6).

Statistical analysis

All data are presented as mean and SD for continuous variables with normal distribution, interquartile range for continuous

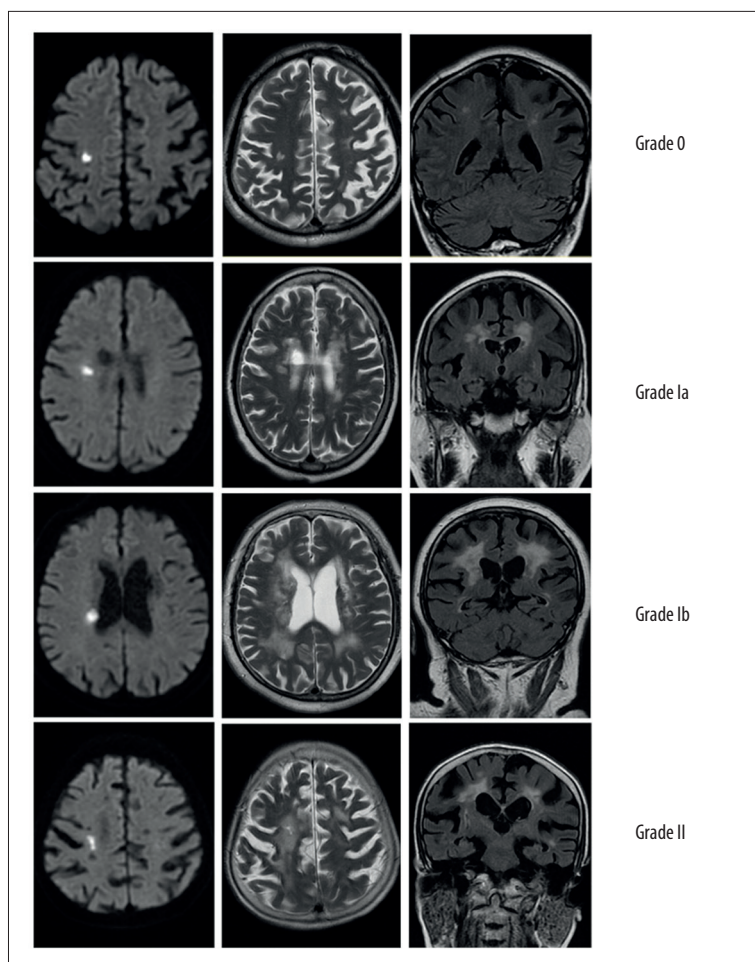


Figure 2. Spatial relationship between acute lacunar infarct and WMH. Grade 0, no contact between acute lacunar infarct and WMH; Grade Ia, contact without overlap between acute lacunar infarct and WMH; Grade Ib, partial overlap between acute lacunar infarct and WMH; and Grade II, acute lacunar infarct appeared complete within a pre-existing white matter hyperintensities (grade II imaging was from a subject without follow-up imaging).

variables with non-normal distribution, and frequency and percentages for categorical variables. Continuous variables with normal distribution were compared using the *t* test with significance set at $p < 0.05$, while the Wilcoxon rank-sum test was used for continuous variables with non-normal distribution. Categorical variables were compared by means of the chi square test. We performed logistic regression analysis to determine independent predictors for cavity formation, with age, sex, vascular risk factors (significant by univariate analysis), clinical data (significant by univariate analysis), infarct sites, infarct size (on DWI and FLAIR), being in the Edge Group, time to follow-up, periventricular WMH, and deep WMH in the model. Analysis was performed using the Statistical Package for Social Sciences (SPSS version 16).

Results

During the study period, 266 subjects with lacunar infarcts were identified and 96 subjects with follow-up imaging were included. We found no significant difference in age, sex, vascular risk factors, clinical data, or imaging characteristics between

subjects with follow-up imaging and those without (Table 1). Of the 96 included subjects, 8 subjects had recurrent stroke. The mean age was 64.81 ± 10.69 years and 67 (69.8%) were male. The infarct site was in subcortical white matter in 45 (46.9%), in basal ganglia in 11 (11.5%), in the thalamus in 15 (15.6%), and in the infratentorial region in 25 (26%). The mean infarct size was 12.74 ± 4.46 mm on DWI, 11.63 ± 4.45 mm on T1, 12.55 ± 4.27 mm on T2, and 12.62 ± 3.84 mm on FLAIR. Considering the spatial relationship between infarct and WMH, 37 (38.5%) subjects were in the Edge Group (grade Ia=24 and grade Ib=13) and 59 (61.5%) were in the Non-edge Group (grade 0=59 and grade II=0).

The mean time interval from baseline MR to follow-up was 13.07 ± 8.3 months and 55 (57.3%) infarcts progressed to cavities. The size of cavities was about half that of the original infarcts, with 7.11 ± 3.16 mm on T1, 7.93 ± 3.56 mm on T2, and 5.83 ± 2.88 mm on FLAIR. Furthermore, risk of cavity formation varied in different cerebral regions. The highest risk of cavity formation was in subcortical white matter (73.33%), followed by the thalamus (53.33%) and infratentorial region (48%), and the lowest risk of cavity formation was in basal ganglia (18.2%).

Basic characteristics and cavity formation between subjects in the Edge Group and Non-edge Group are presented in Table 2. Subjects in the Edge Group had higher risk of cavity formation than those in the Non-edge Group (78.4% vs. 44.1%, $p<0.05$). Subjects in the Edge Group also had more severe periventricular WMH, but not total WMH or deep WMH. Vascular risk factors and clinical data did not differ between the 2 groups except for hypertension, with marginal difference (51.4% vs. 71.2%, $p=0.049$).

Basic characteristics between subjects with cavity formation and no cavity formation are given in Table 3. Univariate analysis showed that the 2 groups did not differ in terms of age, sex, vascular risk factors, clinical data, WMH (total WMH, periventricular WMH, and deep WMH), or time to follow-up. However, infarct sites and size were significantly different. In subjects with cavity formation, infarcts were more often located in subcortical white matter and presented with larger lesion size. Subjects with cavity formation were more frequently in the Edge Group. In logistic regression analysis, DWI infarct size (OR=1.13, 95% CI 1.01–1.25) and being in the Edge Group (OR=4.30, 95% CI 1.65–11.19) were independent risk factors for cavity formation after adjustment for age, sex, infarct sites, periventricular WMH, and deep WMH in the model (Table 4).

Discussion

This is the first study to mainly focus on comparing cavity formation in acute lacunar infarcts on vs. outside the edge of WMH. Results showed that about 40% of acute lacunar infarcts appeared on the edge of WMH, which were more likely to progress to lacunes or cavities. DWI infarct size and being in the Edge Group were predictors for cavity formation.

Studies on the spatial relationship between lacunes and WMH are rare and show controversial results. In the LADIS study, 34% of lacunes appeared in pre-existing WMH [12]. However, about 90% of lacunes were found on the edge of WMH in CADASIL subjects [10]. Because of differences in included subjects and spatial categories, it is difficult to compare these results. As lacunes are mainly from acute infarcts, our finding of 38.5% of lacunar infarcts on the edge of WMH at baseline is much lower than that in CADASIL subjects. This may be because CADASIL subjects have higher risk of suffering ischemic stroke and developing severe WMH [13], which could increase the contact or overlap possibility between lacunes and WMH. Furthermore, subjects with silent infarcts were not included in our study, which may have underestimated the results. Incidence of silent infarcts is about 20% in healthy elderly people and up to 50% in stroke patients, and some of them are located in subcortical white matter [14].

Our finding of no lacunar infarcts in pre-existing WMH is novel. In pathological studies, vascular density decreases in WMH [15], which may reduce the occurrence of infarcts. However, the vascular density does not fall below a level that could cause infarcts, and WMH rarely convert completely to infarcts. Results from positron emission tomography (PET) showed that there is a reduction of cerebral glucose metabolism in WMH [16]. This suggests that a metabolic equilibrium develops in WMH, and neurocytes in WMH may be more tolerant of ischemic attack. Further studies are needed to confirm this hypothesis. Exploring the exact mechanisms may provide new strategies to prevent lacunar infarcts.

We found that lacunar infarcts on the edge of WMH were more likely to develop cavities and that being in the Edge Group was an independent risk factor for cavity formation. These results support the hypothesis that WMH penumbras affect cavity formation. WMH penumbra, considered as regions on the edge of WMH, was first detected in a DTI study [17]. Their results showed that WMH may represent foci of more widespread and subtle white matter changes. Another study found that cerebral blood flow in WMH penumbra is significantly lower than the total brain NAWM, extending approximately 12 mm from both periventricular WMH and deep WMH [9]. Furthermore, it had been reported that normal molecular organization of axons, which is essential for long-term survival of neurocytes, is disrupted in adjacent region of microinfarcts [18]; these finding may be applicable to WMH. Therefore, changes in cerebral blood flow and microstructures on the edge of WMH may be vulnerable to and increase the possibility of cavity formation. It is of clinical importance to understand the exact mechanisms of WMH penumbra because effective treatment of WMH penumbra may stop WMH progression and cavity formation and thereby prevent cognitive deterioration.

The incidence of cavity formation varies among studies, from 28% to 94% [8,19]. In the present study, 58.2% of lacunar infarcts progressed to cavities, which is consistent with a previous study [8]. Many factors had been reported to be associated with cavity formation, including history of hypertension, stroke, periventricular WMH, deep WMH, time to follow-up, and even MRI sequence [8,12,20]. We found that baseline DWI infarct size was also an independent risk factor for cavity formation. This may be because larger infarcts are more likely to capsulate and develop cavities because of complete necrosis.

There are several potential limitations in our study. First, the main limitation is that there might be selective biases in our study because subjects with follow-up imaging may have higher risk of recurrent stroke and concomitant diseases than those without. It was difficult for us to remedy this limitation because this was a retrospective observational study. We compared baseline characteristics between subjects with

Table 1. Basic characteristics between subjects with follow-up imagings and without follow-up imagings.

	Subjects with follow-up imagings (n=96)	Subjects without follow-up imagings (n=170)	p value
Demographics			
Age, years	64.81±10.69	63.75±10.96	0.446
Sex, male	67 (69.8%)	123 (72.4%)	0.657
Vascular risk factors			
Hypertension	61 (63.5%)	111 (65.3%)	0.774
Diabetes	43 (44.8%)	61 (35.9%)	0.153
Hyperlipidemia	28 (29.2%)	35 (20.6%)	0.114
Coronary artery disease	18 (18.8%)	19 (11.2%)	0.086
Stroke or TIA	29 (30.2%)	45 (26.5%)	0.514
Smoking	56 (58.3%)	90 (52.9%)	0.396
Alcohol use	43 (44.8%)	61 (35.9%)	0.153
Laboratory tests			
Hemoglobin, g/L	138.34±14.84	140.24±15.60	0.335
Triglyceride, *mmol/L	1.37 (1.00, 2.18)	1.31 (0.92, 1.91)	0.143
Cholesterol, mmol/L	4.84±1.29	4.68±1.01	0.256
Low density lipoprotein, mmol/L	2.73±0.79	2.66±0.66	0.467
High density lipoprotein, mmol/L	1.23±0.36	1.23±0.33	0.966
Hemoglobin A1c, *%	6.30 (5.70, 7.90)	6.10 (5.60, 7.20)	0.165
Homocysteine, *μmol/L	16.00 (13.25, 19.75)	17.00 (14.00, 20.00)	0.432
Blood urea nitrogen, *mmol/L	4.30 (3.60, 5.28)	4.60 (3.90, 5.60)	0.168
Serum creatinine, *μmol/L	77.80 (68.25, 93.18)	80.40 (64.90, 93.10)	0.925
Uric acid, μmol/L	293.72±88.86	364.20±92.10	0.367
NIHSS at admission*	3 (1, 5)	3 (1, 5)	0.759
Sites of acute lacunar infarcts			
Subcortical white matter	45 (46.9%)	80 (47.1%)	0.442
Basal ganglia	11 (11.5%)	31 (18.2%)	
Thalamus	15 (15.6%)	24 (14.1%)	
Infratentorial region	25 (26.0%)	35 (20.6%)	
Infarct size at baseline (mm)			
DWI	12.74±4.46	13.11±4.67	0.524
T1	11.63±4.45	11.82±4.47	0.737
T2	12.55±4.27	13.08±4.41	0.342
FLAIR	12.62±3.84	13.40±3.98	0.123
Total WMH (Fazekas scale)*	3 (2, 4)	3 (2, 4.25)	0.786
Mild (0–2)	41 (42.7%)	79 (40.6%)	
Moderate (3–4)	32 (33.4%)	59 (34.8%)	
Severe (5–6)	23 (23.9%)	42 (24.8%)	
Periventricular WMH (Fazekas scale)*	2 (1, 2)	2 (1, 3)	0.932
Subcortical WMH (Fazekas scale)*	1 (1, 2)	1 (1, 2)	0.756
Edge group	37 (38.5%)	56 (33.0%)	0.358

TIA – transient ischemic attack; NIHSS – NIH Stroke Scale; DWI – diffusion-weighted imaging; FLAIR – fluid-attenuated inversion recovery; WMH – white matter hyperintensities. * Continuous variables with non-normal distribution are expressed as median (interquartile range).

Table 2. Basic characteristics and cavity formation between subjects in edge group and non-edge group.

	Edge group (n=37)	Non-edge group (n=59)	p value
Age, years	64.11±10.89	65.25±10.63	0.271
Sex, male	26 (70.3%)	41 (69.5%)	0.936
Hypertension	19 (51.4%)	42 (71.2%)	0.049**
Diabetes	15 (40.5%)	28 (47.5%)	0.507
Hyperlipidemia	11 (29.7%)	17 (28.8%)	0.923
Coronary artery disease	4 (10.8%)	14 (23.7%)	0.115
Stroke or TIA	12 (32.4%)	17 (28.8%)	0.707
Smoking	23 (62.2%)	33 (55.9%)	0.547
Alcohol use	13 (35.1%)	30 (50.8%)	0.132
Hemoglobin, g/L	137.95±13.83	138.59±15.55	0.565
Triglyceride, *mmol/L	1.46 (0.90, 2.63)	1.36 (1.05, 2.06)	0.332
Cholesterol, mmol/L	4.95±1.43	4.77±1.20	0.442
Low density lipoprotein, mmol/L	2.70±0.68	2.74±0.85	0.893
High density lipoprotein, mmol/L	1.20±0.36	1.25±0.37	0.129
Hemoglobin A1c, %	6.76±1.56	7.21±2.04	0.632
Homocysteine, *µmol/L	17.00 (14.00, 18.50)	16.00 (13.00, 20.00)	0.782
Blood urea nitrogen, *mmol/L	4.10 (3.40, 5.75)	4.50 (4.00, 5.20)	0.055
Serum creatinine, *µmol/L	74.80 (68.60, 92.55)	81.00 (68.00, 94.60)	0.740
Uric acid, µmol/L	275.09±90.56	305.41±86.50	0.417
NIHSS at admission	3.68±3.17	3.17±2.25	0.434
Sites of acute lacunar infarcts			
Subcortical white matter	35 (94.6%)	10 (16.9%)	
Basal ganglia	0	11 (18.6%)	
Thalamus	1 (2.7%)	14 (23.7%)	
Infratentorial region	1 (2.7%)	24 (40.7%)	
Infarct size at baseline (mm)			
DWI	13.55±4.49	12.23±4.40	0.831
T1	12.40±4.69	11.14±4.26	0.896
T2	13.47±4.39	11.97±4.13	0.536
FLAIR	13.38±3.42	12.15±4.04	0.205
Total WMH (Fazekas scale)*	4 (2, 5)	2 (1, 4)	0.059
Mild (0–2)	11 (29.7%)	30 (50.8%)	
Moderate (3–4)	10 (27.0%)	22 (37.2%)	
Severe (5–6)	16 (43.2%)	7 (11.9%)	
Periventricular WMH (Fazekas scale)*	2 (1, 3)	2 (1, 2)	0.046**
Subcortical WMH (Fazekas scale)*	2 (1, 2.5)	1 (1, 2)	0.163
Cavity formation	29 (78.4%)	26 (44.1%)	0.001**

TIA – transient ischemic attack; NIHSS – NIH Stroke Scale; DWI – diffusion-weighted imaging; FLAIR – fluid-attenuated inversion recovery; WMH – white matter hyperintensities. * Continuous variables with non-normal distribution are expressed as median (interquartile range); ** $p < 0.05$ between subjects in edge group and non-edge group.

Table 3. Baseline characteristics between subjects with cavity formation and without cavity formation.

	Cavity formation (n=55)	No cavity formation (n=41)	p value
Age, years	64.64±11.38	65.05±9.82	0.853
Sex, male	38 (69.1%)	29 (70.7%)	0.863
Hypertension	31 (56.4%)	30 (73.2%)	0.091
Diabetes	22 (40.0%)	21 (51.2%)	0.274
Hyperlipidemia	15 (27.3%)	13 (31.7%)	0.636
Coronary artery disease	12 (21.8%)	6 (14.6%)	0.372
Stroke or TIA	14 (25.5%)	15 (36.6%)	0.240
Smoking	31 (56.4%)	25 (61.0%)	0.650
Alcohol use	22 (40.0%)	21 (51.2%)	0.274
Hemoglobin, g/L	137.44±14.95	139.56±14.80	0.491
Triglyceride, * mmol/L	1.36 (0.98, 2.12)	1.42 (1.06, 2.42)	0.844
Cholesterol, mmol/L	4.86±1.41	4.81±1.12	0.870
Low density lipoprotein, mmol/L	2.72±0.80	2.73±0.78	0.928
High density lipoprotein, mmol/L	1.23±0.37	1.24±0.35	0.908
Hemoglobin A1c, *%	6.10 (5.70, 7.10)	7.00 (5.70, 8.95)	0.076
Homocysteine, * μmol/L	16.00 (13.00, 19.00)	16.00 (14.00, 23.00)	0.730
Blood urea nitrogen, mmol/L	4.68±2.02	4.81±1.69	0.738
Serum creatinine, μmol/L	82.02±31.67	85.83±23.61	0.519
Uric acid, μmol/L	299.27±99.12	286.79±78.62	0.482
NIHSS at admission	3.60±2.51	3.05±2.79	0.313
Sites of acute lacunar infarcts			
Subcortical white matter	33 (60.0%)	12 (29.2%)	0.006**
Basal ganglia	2 (3.6%)	9 (22.0%)	
Thalamus	8 (14.5%)	7 (17.1%)	
Infratentorial region	12 (21.8%)	13 (31.7%)	
Infarct size at baseline (mm)			
DWI	13.72±4.48	11.42±4.13	0.012**
T1	12.52±4.56	10.43±4.04	0.021**
T2	13.41±4.35	11.39±3.92	0.021**
FLAIR	13.37±3.57	11.62±4.00	0.026**
Total WMH (Fazekas scale)	3 (2, 5)	2 (1, 4)	0.082
Mild (0–2)	20 (36.4%)	21 (51.2%)	
Moderate (3–4)	18 (32.8%)	14 (34.2%)	
Severe (5–6)	17 (30.9%)	6 (14.7%)	
Periventricular WMH (Fazekas scale)*	2 (1, 3)	1 (1, 2)	0.257
Subcortical WMH (Fazekas scale)*	1 (1, 2)	1 (1, 2)	0.050
Edge group	29 (52.7%)	8 (19.5%)	0.001**
Time to follow-up (months)	11.78±7.76	14.80±9.01	0.077

TIA – transient ischemic attack; NIHSS – NIH Stroke Scale; DWI – diffusion-weighted imaging; FLAIR – fluid-attenuated inversion recovery; WMH – white matter hyperintensities. * Continuous variables with non-normal distribution are expressed as median (interquartile range). ** $p < 0.05$ between subjects with cavity formation and those without cavity formation.

Table 4. Baseline predictors for cavity formation.

Baseline variables	n	Cavity formation		
		β	p value	Exp(B) 95% CI
Infarct size on DWI	96	0.118	0.032	1.126 (1.010, 1.254)
Edge group	96	1.458	0.003	4.298 (1.651, 11.188)

DWI – diffusion-weighted imaging. Logistic regression were performed to determine independent predictors for lacune formation after adjustment for age, sex, infarct sites, periventricular WMH and deep WMH in model.

and without follow-up imaging. The results showed no difference, which enabled us to provide valuable information. However, this limitation may reduce the external validity of our study, and standard cohort studies are needed in the future. Second, it may be not be sufficiently precise to visually define infarcts in grade Ia and Ib as infarcts on the edge of WMH or WMH penumbra. Regions of WMH penumbra defined by cerebral blood flow may be much more reasonable to use in future studies. Third, the time intervals between baseline and follow-up imaging were not consistent, but time interval did not differ between subjects with cavity formation and those without. In addition, 3 months may be long enough for cavity formation to occur because it has been reported that nearly all cases of acute lacunar infarction reveal evidence of cavitation at 90 days on T1-weighted imaging [20]. It may be better to calculate the infarct volume and cavity volume, but some

of them were too small for us to identify their borderline on MR imaging. Other potential limitations included the single-center study design and missing subjects with silent infarcts.

Conclusions

Our data show that 40% of lacunar infarcts appear on the edge of WMH in the general population and that these are more likely to develop cavity formation. Infarct size and being in the Ege Group are independent risk factors for cavity formation, suggesting that WMH penumbra affects cavity formation.

Disclosure of conflicts of interest

None.

References:

- Kolominsky-Rabas PL, Weber M, Gefeller O, Neundorfer B, Heuschmann PU: Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. *Stroke*, 2001; 32: 2735–40
- Schneider AT, Kissela B, Woo D et al: Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. *Stroke*, 2004; 35: 1552–56
- Debetto S, Markus HS: The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMI*, 2010; 341: c3666
- van der Flier WM, van Straaten EC, Barkhof F et al: Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. *Stroke*, 2005; 36: 2116–20
- Pavlovic AM, Pekmezovic T, Tomic G et al: Baseline predictors of cognitive decline in patients with cerebral small vessel disease. *J Alzheimers Dis*, 2014; 42(Suppl.3): S37–43
- Pantoni L: Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*, 2010; 9: 689–701
- Gouw AA, Seewann A, van der Flier WM et al: Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *J Neurol Neurosurg Psychiatry*, 2011; 82: 126–35
- Koch S, McClendon MS, Bhatia R: Imaging evolution of acute lacunar infarction: leukoariosis or lacune? *Neurology*, 2011; 77: 1091–95
- Promjunyakul N, Lahna D, Kaye JA et al: Characterizing the white matter hyperintensity penumbra with cerebral blood flow measures. *Neuroimage Clin*, 2015; 8: 224–29
- Duering M, Csanadi E, Gesierich B et al: Incident lacunes preferentially localize to the edge of white matter hyperintensities: Insights into the pathophysiology of cerebral small vessel disease. *Brain*, 2013; 136: 2717–26
- Pantoni L, Basile AM, Pracucci G et al: Impact of age-related cerebral white matter changes on the transition to disability – the LADIS study: rationale, design and methodology. *Neuroepidemiology*, 2005; 24: 51–62
- Gouw AA, van der Flier WM, Pantoni L et al: On the etiology of incident brain lacunes: longitudinal observations from the LADIS study. *Stroke*, 2008; 39: 3083–85
- Rutten JW, Haan J, Terwindt GM et al: Interpretation of NOTCH3 mutations in the diagnosis of CADASIL. *Expert Rev Mol Diagn*, 2014; 14: 593–603
- Vermeer SE, Longstreth WT Jr., Koudstaal PJ: Silent brain infarcts: a systematic review. *Lancet Neur*, 2007; 6: 611–19
- Brown WR, Thore CR: Review: Cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol Appl Neurobiol*, 2011; 37: 56–74
- Takahashi W, Takagi S, Ide M et al: Reduced cerebral glucose metabolism in subjects with incidental hyperintensities on magnetic resonance imaging. *J Neurol Sci*, 2000; 176: 21–27
- Maillard P, Fletcher E, Harvey D et al: White matter hyperintensity penumbra. *Stroke*, 2011; 42: 1917–22
- Hinman JD, Lee MD, Tung S et al: Molecular disorganization of axons adjacent to human lacunar infarcts. *Brain*, 2015; 138: 736–45
- Loos CM, Staals J, Wardlaw JM, van Oostenbrugge RJ: Cavitation of deep lacunar infarcts in patients with first-ever lacunar stroke: a 2-year follow-up study with MR. *Stroke*, 2012; 43: 2245–47
- Moreau F, Patel S, Lauzon ML et al: Cavitation after acute symptomatic lacunar stroke depends on time, location, and MRI sequence. *Stroke*, 2012; 43: 1837–42