The Infarct Shape Predicts Progressive Motor Deficits in Patients with Acute Lacunae-sized Infarctions in the Perforating Arterial Territory

Yong-Peng Yu\textsuperscript{1} and Lan Tan\textsuperscript{2}

Abstract

Objective This study was performed to analyze the lesion patterns of lacunae-sized infarctions on diffusion-weighted imaging (DWI) findings in the perforating arterial territory, and to determine whether this pattern of satellite lesions affected progressive motor defect (PMD).

Methods Seventy-five patients with acute lacunae-sized infarctions in the perforating arterial territory (pons or territory of the lenticulostriate arteries), which was confirmed by cranial magnetic resonance image (MRI), were enrolled in this study. These patients were divided into PMD (n=30) and non-progressive motor defect (NPMD) (n=45) groups according to the dynamic scores of the National Institutes of Health Stroke Scale (NIHSS) within 7 days after stroke. The lesion patterns of lacunae-sized infarctions were divided into single oval or satellite lesions signs based on DWI. The risk factors of stroke and the clinical characteristics of all the subjects, including neurological deficits, infarction lesion patterns in image, and the condition of the basilar artery, were comparatively analyzed.

Results The constituent ratio of satellite lesions signs [20/30 (66.7%)] in the PMD group was higher than that [10/45 (22.2%)] of the NPMD group ($\chi^2=6.1$, $p=0.013$). Mean NIHSS scores in the PMD group on admission were higher than that of the NPMD group (4.60±1.40 vs. 3.75±1.2, $t=2.81$, $p=0.003$). A logistic regression analysis showed that the pattern of satellite lesions was associated with PMD. [odds ratio (OR): 3.0, 95% confidence interval (CI) 1.25-7.17, $p=0.014$].

Conclusion Satellite lesions are one of the features of lacunae-sized infarctions patterns, which might be an independent predictor in DWI findings for PMD in patients with lacunae-sized infarctions in the perforating arterial territory.

Key words: cerebral infarction, penetrating artery, satellite lesions, progressive motor deficits, MRI

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Introduction

Lacunar infarction is defined as an infarction that is caused by the occlusion of a single penetrating artery that measures less than 15-20 mm maximum in diameter (1, 2). In recent years, the concept of “perforating artery disease (PAD)” was proposed in the Chinese ischemic stroke sub-classification (CISS) in 2011 (3). Acute isolated infarction in the territory of a single penetrating artery, which is caused by atherosclerosis at the proximal segment of the penetrating arteries or lipohyalinotic degeneration of arterioles, is called PAD, which can be presented with a giant lacunar infarction. Lacunar infarction is a subtype of ischemic stroke that accounts for approximately 25% of all ischemic stroke cases with a higher prevalence in the south Asian population (4-6). Diverse morphologic patterns of lacunae-sized ischemic infarction could be detected by diffusion-weighted imaging (DWI) scans in the perforating arterial territory. Lacunar infarction is generally considered to have a fair clini-
Materials and Methods

The subjects enrolled in this study consisted of 75 consecutive patients who visited our hospitals between October 2011 and June 2013 and were diagnosed by DWI as having lacunae-sized infarctions in the territory of the penetrating artery [brainstem or deep perforating branches of middle cerebral artery (MCA)]. There included 36 men and 39 women with a mean age of 68.5±11.6. Medical histories of all subjects were checked carefully. All patients underwent a standardized neurological examination, carotid duplex and magnetic resonance angiography (MRA) or computed tomography angiography (CTA). The hospital’s institutional review committee on human research approved this study protocol.

Clinical assessment

Clinical assessments included relevant medical history, medications administered during hospitalization, and neurological examinations, which were performed by a neurologist. The definitions of the vascular risk factors adopted for this study were as follows: hypertension was diagnosed in patients who had ≥2 readings of systolic blood pressure ≥160 mmHg or diastolic pressure ≥90 mmHg documented before the onset of stroke, or a clinical history of hypertension with the use of antihypertensive medication at any time before or at the time of stroke. Diabetes was diagnosed in patients who had a history of diabetes, were taking insulin or an oral hypoglycemic agent, or had a fasting blood glucose level ≥126 mg/dL on at least 2 occasions. Regarding the smoking status, patients were classified as having never smoked or smoked (including current smokers and ex-smokers). Hypercholesterolemia (serum total cholesterol ≥220 mg/dL, or use of antihypercholesterolemic medications). Smoking habits, alcohol consumption, and atrial fibrillation were evaluated on admission. All patients underwent a conventional 12-lead electrocardiograph (ECG) examination and echocardiography. The severity of neurological impairments of the index stroke was measured using the National Institutes of Health Stroke Scale (NIHSS). Early neurologic deterioration was defined as any increase in the NIHSS score at discharge compared with that at admission. The scores were checked by the board-certified neurologists. The neurologists checked the scale very two hours and immediately when the motor deficits progressed in the patients. PMD is defined as the deterioration of a NIHSS motor score ≥1 during the first 7 days after stroke onset (13, 18, 19). There were thirty cases of lacunae-sized infarctions in patients with PMD (PMD group) and 45 cases of patients with NPMD (NPMD group) in this study. All patients were treated with antiplatelet therapy (Aspirin 100 mg/d) and atorvastatin (20 mg/d) in the hospital.

Imaging evaluation

All patients completed cranial MRI within 72 hours of
Table 1. Baseline Clinical Characteristics in the PMD and NPMD Groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PMD (n=30)</th>
<th>NPMD (n=45)</th>
<th>t or χ² value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year, M±SD)</td>
<td>70.4±12.0</td>
<td>67.0±11.5</td>
<td>1.237</td>
<td>0.110</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>14 (46.7%)</td>
<td>22 (48.9%)</td>
<td>0.013</td>
<td>0.909</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>7 (23.3%)</td>
<td>5 (11.1%)</td>
<td>1.423</td>
<td>0.231</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>18 (60%)</td>
<td>33 (73.3%)</td>
<td>0.285</td>
<td>0.593</td>
</tr>
<tr>
<td>Hyperlipemia (n, %)</td>
<td>19 (63.3%)</td>
<td>9 (20%)</td>
<td>6.344</td>
<td>0.012</td>
</tr>
<tr>
<td>Coronary heart disease (n, %)</td>
<td>2 (15%)</td>
<td>3 (6.7%)</td>
<td>0.220</td>
<td>0.639</td>
</tr>
<tr>
<td>Auricular fibrillation (n, %)</td>
<td>2 (15%)</td>
<td>3 (6.7%)</td>
<td>0.220</td>
<td>0.639</td>
</tr>
<tr>
<td>History of stroke (n, %)</td>
<td>6 (20%)</td>
<td>12 (26.7%)</td>
<td>0.272</td>
<td>0.601</td>
</tr>
<tr>
<td>Current smoking (n, %)</td>
<td>9 (23.3%)</td>
<td>17 (37.8%)</td>
<td>0.236</td>
<td>0.627</td>
</tr>
<tr>
<td>Alcohol drinking (n, %)</td>
<td>5 (16.7%)</td>
<td>10 (22.2%)</td>
<td>0.234</td>
<td>0.628</td>
</tr>
<tr>
<td>Initial NIHSS score, (M±SD)</td>
<td>4.60±1.40</td>
<td>3.75±1.2</td>
<td>2.810</td>
<td>0.003</td>
</tr>
<tr>
<td>Maximal diameter, (mm, M±SD)</td>
<td>16.20±3.8</td>
<td>13.8±3.5</td>
<td>2.811</td>
<td>0.003</td>
</tr>
<tr>
<td>Maximal diameter, &gt;15mm</td>
<td>22 (73.3%)</td>
<td>15 (33.3%)</td>
<td>3.772</td>
<td>0.052</td>
</tr>
<tr>
<td>Satellite lesions shape (n, %)</td>
<td>20 (66.7%)</td>
<td>10 (22.2%)</td>
<td>6.100</td>
<td>0.013</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA or ipsilateral MCA stenosis</td>
<td>19 (63.3%)</td>
<td>12 (26.7%)</td>
<td>4.688</td>
<td>0.030</td>
</tr>
<tr>
<td>ICAS (n,% )</td>
<td>14 (36.7%)</td>
<td>7 (20%)</td>
<td>4.699</td>
<td>0.030</td>
</tr>
<tr>
<td>ECAS (n,% )</td>
<td>7 (23.3%)</td>
<td>4 (11.1%)</td>
<td>2.186</td>
<td>0.139</td>
</tr>
</tbody>
</table>


onset, and conventional spin-echo sequences for cross-sectional and sagittal T1WI, T2WI, DWI were performed. “Infarct size” was measured as the maximal diameter of the lesion. Whether the infarction was located in the territory brainstem or MCA could be determined based on the cross-sectional imaging of T1WI, T2WI or DWI. MRI was performed on a 3.0-T system (GE MR Discovery 750 3.0T General Electric Company, Fairfield, USA). DWI was conventionally scanned. The parameters of DWI were as follows: slice thickness of 4-5 mm, interslice gap of 1-2 mm, field of view of 240 mm, repetition time of 7,000 msec, echo time of 85.3 msec, matrix number of 128×128, and b value of 1,000 sec/mm². The parameters of the T2-weighted image were as follows: repetition time of 4,000 msec, echo time of 100 msec, slice thickness of 5 mm, and interslice gap of 2 mm. The patients in the hospital would complete CTA or MRA within one week. Artery stenosis was divided into normal, mild stenosis (<50%), or moderate to severe stenosis (≥50%). Previous studies had shown that any degree of disease of MCA can lead to perforating artery stenosis and occlusion, which may be the main cause of lacunar-size infarction (20). Although the relationship between brainstem infarction and stenosis, and occlusion of vertebral basilar artery still remains controversial, increasing evidence still supports the association between these conditions (21). In addition, the assessment on other intracranial atherosclerotic stenosis (ICAS) and extracranial atherosclerotic stenosis (ECAS) was performed.

Lacunar-size infarction inclusion criteria were based on the following

1. Acute infarction which coincided with the occurrence of clinical symptoms in the brain stem or the perforating artery territory of MCA. The maximal diameter of the lesion was confined to less than 20 mm in supratentorial lesions or less than 15 mm in infratentorial lesions. 2. Infarction lesions showed a single oval or satellite lesion sign in DWI. MRI was performed on a 3.0-T system (GE MR Discovery 750 3.0T General Electric Company, Fairfield, USA). DWI was conventionally scanned. The parameters of DWI were as follows: slice thickness of 4-5 mm, interslice gap of 1-2 mm, field of view of 240 mm, repetition time of 7,000 msec, echo time of 85.3 msec, matrix number of 128×128, and b value of 1,000 sec/mm². The parameters of the T2-weighted image were as follows: repetition time of 4,000 msec, echo time of 100 msec, slice thickness of 5 mm, and interslice gap of 2 mm. The patients in the hospital would complete CTA or MRA within one week. Artery stenosis was divided into normal, mild stenosis (<50%), or moderate to severe stenosis (≥50%). Previous studies had shown that any degree of disease of MCA can lead to perforating artery stenosis and occlusion, which may be the main cause of lacunar-size infarction (20). Although the relationship between brainstem infarction and stenosis, and occlusion of vertebral basilar artery still remains controversial, increasing evidence still supports the association between these conditions (21). In addition, the assessment on other intracranial atherosclerotic stenosis (ICAS) and extracranial atherosclerotic stenosis (ECAS) was performed.

Statistical analysis

The measurement data were analyzed using a univariate analysis with Student’s t-test or Chi-square test. Logistic regression analysis was used to evaluate the relationship between PMD and the independent risk factors. All statistical analyses were performed with SPSS software package for Windows version 11.5. (Statistical Product and Service Solutions, Chicago, USA) Data were expressed as the mean ± SEM and statistical significance was set at p<0.05.

Results

There were 75 cases of patients with lacunar-size infarction which were divided into the PMD group (n=30) and the NPMD group (n=45). A univariate analysis showed that
there was a significant difference in the lesion diameter (p=0.003), lesion diameter greater than 15 mm (p=0.003), hyperlipidemia (p=0.012) and ipsilateral MCA trunk or basilar artery stenosis (p=0.03) between the PMD and NPMD groups. The constituent ratio of ICAS and ECAS in the PMD group was higher than that of the NPMD group (Table 1).

The number of patients with the satellite lesions shaped pattern of the lacunae-sized infarct was 20 (66.7%) and those with the single oval shape was 10 (33.3%) (Table 1). The satellite lesions shaped pattern of the lacunae-sized infarct was more commonly observed in the PMD group than in the NPMD group [20 (66.7%) vs. 10 (22.2%)], respectively, p=0.013). The presence of BA or ipsilateral MCA stenosis was also different between the two groups [19 (63.3%) in the PMD group vs. 12 (26.7%) for the NPMD group, p=0.03]. The baseline characteristics were not different between patients with the satellite lesions shape pattern and those with the single oval shape pattern except for hyperlipemia, maximal diameter, and the NIHSS score (Table 2). After adjusting for risk factors (the initial NIHSS score and maximal diameter) the significant association of the satellite lesions shape with PMD still remained (OR: 3.0, 95% CI 1.25-7.17, p=0.014). However, the maximal diameter of the lesion was not significantly larger in the satellite lesions shape group (16.20±3.8 mm vs. 13.8±3.5 mm, p=0.052). A logistic regression analysis showed that satellite lesions sign in DWI was a risk factor for predicting PMD.

**Discussion**

Progressing stroke is a special type of acute ischemic stroke, however, the concepts and definitions remain controversial. Most scholars have defined it as neurological symptoms and signs, but still underwent the gradual stepwise progression or aggravation despite an active intervention that was performed in the first 6 hours to 7 days after ischemic stroke onset. PMD is defined as the deterioration of the NIHSS motor score ≥1 during the first 7 days after stroke onset (13, 18, 19). The predication and management of progressing stroke has been a major clinical problem. The factors that cause neurological deterioration can be due to the central nervous system itself or systemic factors. In recent years, there are more and more studies on predictors of progressive stroke in view of an infarction lesion. Some studies have suggested that subcortical infarcts, especially infarction in the striatum and internal capsule, displayed a higher percentage of PMD, which mainly resulted from a deep perforating artery occlusion (22). Perforating artery disease may be an important mechanism of progressive stroke (23). It was reported that lacunar infarction type in the corona radiata was an independent predictor of PMD (10). Early neuroimaging findings showed that scattered distribution of lesions in DWI may contribute to predicting the occurrence of early neurological deterioration (END) (24).

Previous studies reported that giant infarct size in acute lacunar infarctions was associated with PMD (11, 25). Only a limited number of studies have investigated the association between DWI findings and PMD in acute lacunar-size infarction (9, 11, 12, 26). A previous study suggested that posterior type infarct was the independent predictor in DWI findings for PMD in patients with lacunar infarction in the lenticulostriate artery territory (9). Nagakane et al. reported that patients with supratentorial lacunar infarctions with a corona radiata lesion on DWI was significantly more frequent in the PMD group. However, the association between the lacunar infarction shape in the perforating arterial territory and PMD is still a new problem in the clinical practice. In the present study, the infarct size did not independently correlate with PMD. We could not confirm a similar result described in previous study (11, 25). This might be due to the differences in the time from the onset to MRI detection between the present study and theirs, 8 hours and nearly 40 hours, respectively. We speculated that if DWI was evaluated within 24 hours after the onset of infarctions, it might only reveal partial or initial lesions, which can subsequently enlarge into giant infarcts, and also underestimate the role of the infarct size factor in PMD, which is usually based on the DWI finding at a different time point. Furthermore, it seems reasonable that infarct size was not found to be predictors for PMD in this study. In previous studies, higher age (9) and female sex (9, 11, 12) were often reported to be associated with PMD. However, in the present study, we could not conclude that age and gender were independent predictors for PMD. The reason for such findings remains unexplained and further investigation is required.

The present study found that different patterns of lacunar infarction were associated with PMD. In addition, we also found that the size of the lesion diameter (>15 mm) in the PMD group was higher than that in the NPMD group. The diameter of infarction lesions that showed the satellite lesions shape was larger than that of the single oval lesion, and was more prone to progress. We speculated that the imaging of lacunar size infarction in the perforating arterial territory that showed the satellite lesions shape is due to the involvement of the proximal segment of the penetrating arteries or its parent arteries. The possible mechanisms might be as follows: 1) Atherosclerosis extension at the proximal segment of the penetrating arteries leads to occlusion at more than two branches of penetrating artery; 2) Disease in the parent artery of the perforating artery leads to occlusion in its several terminal branches; or 3) Unstable plaque in the

### Table 2 Logistic Regression Analysis on the Independent Risk Factors for PMD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR value</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipemia</td>
<td>3.17</td>
<td>1.29-7.76</td>
<td>0.012</td>
</tr>
<tr>
<td>Initial NIHSS score ≥ 4 points</td>
<td>3.0</td>
<td>1.01-8.90</td>
<td>0.048</td>
</tr>
<tr>
<td>Maximal diameter &gt; 15mm</td>
<td>2.2</td>
<td>0.99-4.87</td>
<td>0.052</td>
</tr>
<tr>
<td>Satellite lesions shape</td>
<td>3.0</td>
<td>1.25-7.17</td>
<td>0.014</td>
</tr>
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<td>BA or ipsilateral MCA stenosis</td>
<td>2.37</td>
<td>1.08-5.17</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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artery falls off and blocks the proximal segment of the penetrating arteries (26, 27). All of these conditions mentioned above could cause infarction in the territory of more than one small artery. Due to relatively more involved vessels, vasogenic edema consequent to infarction, an inflammatory reaction, and a series of cascades resulted in the progress of a neurological deficit. An isolated small infarction that occurred in the brainstem tended to be located in the interior of the brainstem, which almost resulted from occlusion in the terminal of a single perforating artery. The lesion diameter was relatively small and radiographic patterns presented an oval shape. When occlusion occurred at the proximal segment of the penetrating arteries, the infarction lesion almost displayed the satellite lesions shape, which could injure the corticospinal tract in the ventral part of pons, which promoted deterioration under this condition.

There are several limitations associated with the present study. First, this study was a retrospective study with a small sample size. Therefore, further prospective studies with a larger number of patients are needed to confirm these results. Second, although there is a similar detection sensitivity for the MRA and CTA in an atherosclerotic lesion, inconsistent methods of angiography may still lead to some bias. Because of the relative difficulty in repeating MRI in these patients, we have not investigated the change in the shape of the satellite lesions using DWI, however, we hypothesize that some lesions may be integrated into giant lacunar lesions as time progresses. However, this hypothesis requires further study.

In summary, the results of this study indicated that the satellite lesions shape in DWI is one of the characteristics of lacunar infarction imaging patterns, which may be an independent factor for predicting occurrence of PMD. Recognizing this special form of cerebral infarction would be useful in identifying high-risk patients with progressive stroke and facilitating the start of early individualized treatment for preventing PMD. The intrinsic correlation between the satellite lesions sign pattern and PMD should be confirmed by large-scale prospective studies in the future.

The authors state that they have no Conflict of Interest (COI).

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References