Variation in Risk Factors for Recent Small Subcortical Infarcts With Infarct Size, Shape, and Location

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Background and Purpose—Lacunar infarction is attributable to a perforating arteriolar abnormality. Possible causes include embolism, atheromatosis, or intrinsic disease. We examined whether the size, shape, or location of the lacunar infarct varied with embolic sources, systemic atheroma, or vascular risk factors.

Methods—We examined data from 3 prospective studies of patients with clinical and diffusion-weighted imaging–positive symptomatic lacunar infarction who underwent full clinical assessment and investigation for stroke risk factors. Lacunar infarct sizes (maximum diameter; shape, oval/tubular; location, basal ganglia/centrum semiovale/brain stem) were coded blind to clinical details.

Results—Among 195 patients, 48 infarcts were tubular, 50 were 15 to 20 mm in diameter, and 97 and 74 were located in the basal ganglia and the centrum semiovale, respectively. There was no association between infarct size or shape and any of the risk factors. Centrum semiovale infarcts were less likely to have a potential relevant embolic source (4% versus 11%; odds ratio, 0.16; 95% confidence interval, 0.03–0.83) and caused a lower National Institute of Health Stroke Scale score (2 versus 3; odds ratio, 0.78; 95% confidence interval, 0.62–0.98) than basal ganglia infarcts. There were no other differences by infarct location.

Conclusions—Lacunar infarcts in the basal ganglia caused marginally severer strokes and were 3 times more likely to have a potential embolic source than those in the centrum semiovale, but the overall rate of carotid or known cardiac embolic sources (11%) was low. We found no evidence that other risk factors differed with location, size, or shape, suggesting that most lacunar infarcts share a common intrinsic arteriolar pathology. (Stroke. 2013;44:3000-3006.)

Key Words: pathogenesis • pathology • stroke • stroke, lacunar

In 1982, Fisher described 2 possible arteriolar pathologies that led to recent small subcortical infarction: lipohyalinosis, associated with smaller infarcts, and arteriolosclerosis, associated with larger ones. Atheroma of the parent artery, for example, middle cerebral artery, could also affect the perforating arteriole and might cause larger basal ganglia lacunar infarcts, for example, if several perforating arterioles were affected simultaneously.1 However, these pathological examinations were mostly performed late after the stroke, making it difficult to determine the cause of the index event. The recent wider availability of sagittal and coronal views on diagnostic imaging has increased the recognition that some recent lacunar infarcts may be long or tubular, leading to the suggestion that such infarcts comprise a distinct subgroup of lacunar stroke recognizable by their tubular shape1 and location in the basal ganglia, which may have a different pathogenesis (Figure 1). This subgroup of lacunar stroke has also been associated with progressive subacute neurological deterioration after initial presentation.4,5

In general, patients with lacunar ischemic stroke have a different risk factor profile than other nonlacunar stroke subtypes,6 with fewer ipsilateral embolic sources (eg, cardioembolic or carotid stenosis) and less evidence of large artery atheroma elsewhere (eg, ischemic heart disease).

An association between the larger, tubular lacunar infarcts in the basal ganglia and a risk factor profile similar to other atheromatous conditions would imply that such infarcts were atheromatous in nature. However, studies that examined whether lacunar infarcts of varying size, shape, and locations had different risk factors or potential stroke causes have produced inconsistent or incomplete results (Table 1).7–11 Hence, we investigated patients with a clinical and magnetic resonance diffusion-weighted imaging (DWI) confirmed diagnosis of lacunar ischemic stroke to determine whether clinical features and risk factors varied with the size, shape, or location of the lacunar infarct.

Methods

Patient Recruitment

We examined data from 3 existing prospective stroke studies and identified all patients with a symptomatic magnetic resonance DWI–confirmed lacunar infarction, who had both an ECG and a carotid-
ECG tape if there was any suspicion of arrhythmia. We defined including patent foramen ovale, in addition to recording by 24-hour imaging. In addition, we performed echocardiography in younger patients and in patients with any suspected cardiac abnormality, in- tes mellitus; hypercholesterolemia (a previous diagnosis or a fasting history, including the following conditions: hypertension (a previous diagnosis of hypertension or blood pressure ≥140/90 mm Hg); diabetes mellitus; hypercholesterolemia (a previous diagnosis or a fasting total cholesterol level >5 mmol/L); and smoking (current or within the previous 12 months). All patients had a 12-lead ECG and carotid ultrasonogram. We included 2 prospective observational studies from a regional Stroke Service in Edinburgh (1 published,1 now completed recruiting) and consecutive patients with lacunar stroke admitted to the Stroke Unit of Careggi University Hospital, Florence, in our analysis. All studies were approved by the relevant research ethics committee. Patients were recruited in Edinburgh from 2005 to 2007 and 2010 to 2012 and in Florence from 2007 to 2011.

Patient Assessment
All patients were assessed at presentation with a structured full clinical assessment by a stroke specialist and by MRI at 1.5 T, including DWI, T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and T2*-weighted images. The clinical assessment included the National Institutes of Health Stroke Scale score; if symptoms were improving by the time of presentation, we estimated the worst National Institutes of Health Stroke Scale score from the history. We recorded medical history, including the following conditions; hypertension (a previous diagnosis of hypertension or blood pressure ≥140/90 mm Hg); diabetes mellitus; hypercholesterolemia (a previous diagnosis of a fasting total cholesterol level >5 mmol/L); and smoking (current or within the previous 12 months). All patients had a 12-lead ECG and carotid Doppler ultrasound performed blind to stroke subtype and brain imaging. In addition, we performed echocardiography in younger patients and in patients with any suspected cardiac abnormality, including patent foramen ovale, in addition to recording by 24-hour ECG tape if there was any suspicion of arrhythmia. We defined ≥50% carotid stenosis as clinically significant using the North American Symptomatic Carotid Endarterectomy Trial criteria.1,3 We defined a lacunar infarct on DWI on the basis of focal hyperintense signal in the deep grey or white matter of the cerebral hemispheres or brain stem, not extending to the cerebral cortex and not >20 mm in maximum axial diameter. We recognize that the 20 mm cutoff is arbitrary, but it is a widely used definition and we considered that infarcts with maximum axial diameter >20 mm were likely to be striatocapsular infarcts (attributable to transient middle cerebral artery embolic occlusion or persistent middle cerebral artery occlusion with good peripheral collateral arteries, as described by Donnan et al4). Of the 518 patients recruited into the 2 studies in Edinburgh, 154 had a lacunar lesion on MRI, but the remainder had a cortical infarct (205), no infarct on imaging (n=142), or were recruited in an early pilot phase and lacked complete risk factor data (n=17). Of the 879 consecutive patients with acute ischemic stroke admitted to the Stroke Unit in Florence, 79 had a lacunar stroke syndrome; of these, 41 had a lesion on DWI-MRI. There was no statistically significant difference in demographics or risk factors between the included and nonincluded lacunar stroke patients. All patients gave written informed consent, and the studies were approved by the local Research Ethics Committee.

Statistical Analysis
We performed univariate analysis using Fisher exact test for dichoto- mous variables and the Mann–Whitney test for continuous, non-parametric variables (age, National Institutes of Health Stroke Scale score, and lesion size). We first assessed the variables individually; then we assessed 2 combined variables: extracranial atherosclerotic; one or more of carotid stenosis, peripheral vascular disease, and ischemic heart disease; and any potential embolic source which consisted of either or both of atrial fibrillation and ipsilateral carotid stenosis. We used binary logistic regression for multivariable analysis using preselected parameters and those that were significant on univariate analysis. We then analyzed the relationship between size, shape, and location of the infarct. To visually examine whether lesion size was normally distributed, we plotted a Kernel density plot. We examined the distribution of lesion size by the location and shape of lesions, the presence of a potential embolic source, and the presence of large artery atheromatous disease.

Results
We identified 195 suitable patients (Table 2). The infarct was <15 mm in axial diameter in 145 of 195 (74%) patients and 15 to 20 mm in 50 patients (26%); tubular in 48 of 195 (25%) and oval in 147 of 195 (75%); located in the basal ganglia in 97 of 195 (50%), in the centrum semiovale in 74 of 195 (38%), and in other locations in 24 of 195 (12%). Furthermore, 70% (137/195) of patients were men, with a median age of 68 years (interquartile range, 59–75). Most patients (73%) were hypertensive, 38% had hypercholesterolemia, and 45% were smokers.

Figure 1. Examples of lacunar infarcts of varying sizes and shapes. A, A tubular lacunar infarction on images obtained from coronal T1-weighted (left) and axial diffusion-weighted imaging (right), B) a small ovoid infarction in the right basal ganglia, and C) a larger ovoid infarction in the right centrum semiovale.
Univariate Analysis of Size, Shape, Location, Risk Factors, and Clinical Features

On univariate analysis (Table 2), there was no association between infarct size, or shape, and risk factor profiles. Lacunar strokes located in the basal ganglia caused severer strokes than those in the centrum semiovale: median initial National Institutes of Health Stroke Scale score was 3 in the basal ganglia and 2 in the centrum semiovale (P=0.04). The association between basal ganglia location and the presence of a relevant embolic source (11% versus 4%) did not reach statistical significance (P=0.099). There were no other differences by infarct location. We examined the location of lesions in the basal ganglia and found that 6 of 41 (14%) thalamic infarcts had an embolic source compared with 5/56 (9%) lesions elsewhere in the basal ganglia (internal capsule and medial lentiform; P=0.0519). Conversely, 6 of 11 basal ganglia infarcts with an embolic source were in the lateral thalamus.

There was no significant difference in the median size of lesion in the basal ganglia, centrum semiovale, or posterior circulation locations (all 10 mm, P=0.767; Figure 2A). Tubular lesions were larger (median, 17.5 mm) than oval lesions (median, 10 mm; P<0.001; Figure 2B). There was no statistically significant relationship between infarct shape and location: 23 of 97 (24%) of basal ganglia infarcts were tubular against 16 of 74 (22%) of centrum semiovale infarcts. Therefore, there was a subset of larger, tubular infarcts, but they did not occur consistently in any particular part of the brain.

To explore lesion topography further, we plotted the distribution of lesion size (mm) for both tubular and oval-shaped lesions (Figure 2). Although oval lesions were normally distributed, tubular lesions were nonnormally distributed (Figure 2B), implying that these may be the tail of a larger normally distributed group of lesions. There was no difference in the distributions of the size of lesions with and without an
Multivariable Analysis of Size, Shape, Location, Risk Factors, and Clinical Features

Multivariable analysis demonstrated that patients with a centrum semiovale infarct were less likely to have a potential embolic source (atrial fibrillation or ipsilateral carotid stenosis) than those with a basal ganglia infarct (odds ratio, 0.16; 95% confidence interval, 0.03–0.83; Table 3). However, patients with an embolic source or extracranial large vessel disease were not more likely to have a larger lesion than those without embolic sources or extracranial large artery disease (Table 3) in this series.

Discussion

Our study showed little association between clinical risk factors and the size, shape, or location of a lacunar stroke except for an association between basal ganglia infarcts and a potential relevant embolic source, for example, ipsilateral carotid stenosis or atrial fibrillation. However, most patients did not have a potential carotid or cardioembolic source, as detected on carotid ultrasonogram or ECG in all, or on echocardiography (performed where indicated), whether the lesion was in the basal ganglia (89%) or the centrum semiovale (96%). There was also no significant difference in overall infarct sizes between the centrum semiovale and basal ganglia.

Six other studies (Table 1) have examined associations between risk factors and size, shape, or location of lacunar infarcts, but the present study is the only one to examine the relationship with and between all 3 factors, in addition to including patients with recent lacunar infarction in all perforating arteriolar territories. The present study is also nearly twice as large as previous studies, except for one, but this latter compared risk factors in patients with basal ganglia and pontine infarcts only, not those with centrum semiovale infarcts, nor did it compare infarct size or shape. Some studies only examined the centrum semiovale and included the deep border zone and lacunar infarcts if in white matter. Others found that patients with a small centrum semiovale embolic source or in the same with or without extracranial large vessel disease (Figure 3).
infarct were more likely to have an embolic source than patients with a similar lesion in the basal ganglia, although they included intracranial stenosis, which is rare in our population and excluded the thalamus and all other territories supplied by the basilar and posterior cerebral arteries. A pathology study in Edinburgh found a potential embolic source in 10 of 12 subjects with centrum semiovale lacunar infarcts at autopsy who presented with, and died of, various conditions. However, only half of these had a history of symptomatic stroke, of uncertain relationship to the infarct seen at postmortem, at some point before death. We found no association between the size of infarcts and risk factors, although Ohara et al found an association between larger infarcts and women and between intracranial stenosis and thrombin/antithrombin complex. Ashdaghi et al (published in abstract) examined the shape of lacunar lesions in 2264 patients with DWI-proven lesions; classifying the lesion as of slab, stick, oval, or multiple type. They found that diabetes mellitus was more common in patients with oval lesions; however, investigation of other risk factors is limited as patients were excluded if they had a potential source of embolism. Our finding that shape was not linked to different risk factors was similar to the findings of Ryu et al, who described infarcts shaped like conglomerated beads but did not find these to have different risk factors compared with oval infarcts.

The strengths of our study include a large group of prospectively recruited stroke patients subtyped using risk factor–free methods, thus avoiding expectation bias or confounding of the process. The use of acute DWI–MRI allowed accurate diagnosis of lacunar infarction and assessment of infarct characteristics. The risk factors were assessed in a standardized manner blind to all clinical data, reducing potential for confounding from the belief of the assessing clinician about the stroke pathogenesis. Including both inpatients and outpatients avoided any bias toward severer stroke as many patients with lacunar stroke are only mildly affected and may not be admitted to hospital.

The cutoff of 20 mm may have complicated the results and been influenced by the time of imaging, as recent lesions are larger than those at a later stage. Previous studies used imaging at a later stage after stroke. Future studies should consider the shape of all subcortical lesions regardless of size because this may help to determine the cutoff of lacunar

Figure 2. Kernel density plot demonstrating the distribution of lacunar infarction size by shape and location of lesion (area under the curve=1, irrespective of sample size).

Figure 3. Histograms of lacunar lesion size, by the presence of a potential embolic source and by large vessel (LV) disease elsewhere.
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versus striatocapsular infarcts in future. A major weakness is that we were not able to examine for intracranial artery stenosis or aortic arch atheroma in the patients nor for cardioembolic sources with echocardiography or 24-hour ECG in all patients, although these were performed wherever indicated. However, in the context of intracranial stenosis, we did perform intracranial arterial imaging in all 120 patients in a previous study (half with recent small subcortical infarction) in a similar population in Edinburgh and did not find any intracranial stenoses at all, although there were cervical carotid stenoses (which we would have detected with carotid ultrasonography); many of these 120 patients overlapped with the present population.11 With reference to aortic arch atheroma, diagnostic standards for clinically relevant atheroma are not yet established and it would be difficult to examine all patients with transesophageal echocardiography or magnetic resonance angiography of the aortic arch. We did not gather data on the speed of onset of the infarct, whether sudden or progressive, although previous studies have reported an association between basal ganglia infarcts and progressive symptoms. We had fewer of the larger, tubular, basal ganglia infarcts, which limited the associations that could be tested in multivariable analysis without overfitting. We measured the maximum diameter on acute DWI, which may overestimate the true infarct size through blooming effects; however, this may have underestimated the maximum dimensions of some tubular basal ganglia infarcts. Future studies should describe the lesions’ maximum longitudinal and axial dimensions and evaluate the rapidity of change in visible infarct dimensions on different sequences over time.

We found no evidence of differences in risk factors by lacunar infarct location, size, or shape, except for the association between having a potential embolic source and infarcts in the basal ganglia. The low absolute proportion of patients with a relevant carotid or known cardioembolic source (11%) should be compared with the much higher proportion of patients with nonlacunar stroke who have either ipsilateral (22%) or contralateral (8%) carotid stenosis or cardioembolic sources (26%) detected by the same means.4 The size distribution of tubular lesions demonstrated in Figure 2 raises the possibility that these lesions classed as small subcortical are actually the lower tail of a distribution of larger deep infarcts, for example, striatocapsular,14 and should encourage further measurement of lesions in other data sets and reexamination of the current size limits and risk factor associations.

This work provides further evidence that most lacunar infarcts are attributable to an intrinsic arteriolar pathology regardless of their morphology and should be tested in other populations using risk factor–free clinical subtyping and DWI to be certain of the stroke subtype and location on imaging. Future research should concentrate on defining the pathogenesis of lacunar ischemic stroke, avoiding risk factor–based subtyping, and developing treatments.

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