Mechanisms of second and further strokes

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Abstract

Objectives—The mechanisms underlying recurrent stroke may be complex and multifactorial, but they have not been studied systematically. The aim was to analyse the different patterns and pathophysiological mechanisms of second and further strokes.

Methods—Recurrent stroke patterns and mechanisms were studied in 102 patients admitted with second or further strokes to the stroke centre in Lausanne University Hospital.

Results—The patients with an initial cardioembolic stroke experienced recurrent stroke of the same type most often, followed by those with initial non-lacunar non-cardioembolic stroke, brain haemorrhage, and lacunar stroke (77%, 65%, 58%, and 48% respectively). Forty two per cent of the recurrent strokes in patients with an initial brain haemorrhage were ischaemic, whereas patients with ischaemic stroke only occasionally suffered brain haemorrhage (5%). In patients with brain haemorrhage, the lobar location predominated in both the first and all episodes (66% and 78% respectively), suggesting a small, occult arteriovenous malformation or cerebral amyloid angiopathy rather than hypertensive small artery disease. The functional disability of patients after an initial lacunar stroke was significantly better than in patients with other stroke subtypes (p<0.001), but the difference became non-significant after recurrent stroke (p=0.26).

Conclusions—Most of the recurrent strokes were of the same type as the first episode for both cardioembolic and non-lacunar non-cardioembolic stroke, however, about half of the patients with an initial brain haemorrhage or a lacunar stroke experienced other types of stroke recurrently. The findings suggest that the coexistence of multiple aetiologies may play a major part in determining the mechanism of stroke recurrence. The study is an important step in understanding the patterns of stroke recurrence, which may be critical for better prevention.

Keywords: cerebral infarction; intracerebral haemorrhage; recurrence

Despite many successful efforts at stroke prevention,1 stroke recurrence remains common.2 Epidemiological studies have identified risk factors for recurrent stroke, such as hypertension or raised blood sugar.3 4 It remains unclear, however, how the management of these risk factors can prevent stroke recurrence,2 4 probably because the mechanisms underlying recurrent stroke are complex and multifactorial. Moreover, a precise aetiological classification of recurrent stroke may be difficult in such epidemiological studies with many patients (cardioembolic infarction after lacunar stroke or brain haemorrhage after large artery disease, etc). For example, in the Stroke Data Bank,5 6 ischaemic strokes are subdivided into six aetiologies: lacunar stroke, cardiac embolism, large artery atherosclerosis, tandem pathology, other unusual causes, and undetermined cause. Although a predominance of same type recurrence after large artery atherosclerosis has been reported, about half of the patients with stroke recurrence of the same type are in fact classified into the group with strokes of undetermined cause. Understanding the pathophysiological mechanisms of stroke recurrence is mandatory for effective secondary prevention. The aim of this study was to analyse the different aetiological patterns and underlying mechanism of recurrence after an initial stroke.

Methods

From January 1990 to November 1995 we studied patients admitted to the stroke centre at Lausanne University Hospital with recurrent stroke (acute brain infarction or intracerebral haemorrhage) after a well identified initial stroke. Lausanne University Hospital is the only public hospital in the Lausanne area and is located in a city of 250 000 people. Most acute patients in this area are referred to the stroke centre at Lausanne University Hospital. We excluded patients: (1) without detailed medical records or without CT or MRI in the acute stage of the first stroke, so that the type of stroke could be differentiated; (2) with stroke after medical procedures (carotid endarterectomy, angiography, etc) or trauma; (3) with cerebral haemorrhage which was intratumorous or caused by a ruptured cerebral aneurysm, or vascular malformation; and (4) with subarachnoid haemorrhage or subdural haemorrhage. We also excluded patients with a recurrence of only transient ischaemic attacks (TIAs) because it was difficult to determine the aetiology of the TIA episodes from limited information. Information about the first strokes of patients who had not been admitted in our service was collected from their families, home doctors, and hospitals where they were admitted during their first episodes. Systematic investigations were performed following the standard protocol of the Lausanne Stroke Registry,11 including brain CT, carotid ultrasound, transcranial Doppler, 12 lead ECG, three lead ECG monitoring (24 to 70 hours), and standard blood and urine tests, including...
venous packed cell volume and fasting blood cholesterol. Cerebral angiography, brain MRI, two dimensional transthoracic and transoesophageal echocardiography with or without a microbubble test, and 24 hour ECG (Holter) monitoring were performed in selected patients.

Strokes were classified into three main groups based on the definitions of the Lausanne Stroke Registry13: (1) lacunar infarction (infarct with a lacunar syndrome (pure motor hemiparesis, pure sensory stroke, sensory-motor stroke, and ataxic hemiparesis) and a normal CT or small (<15 mm), deep infarct on CT); (2) non-lacunar infarction (infarct with neurological findings not compatible with lacunar syndrome and a normal CT or a hypodense area>15 mm, corresponding to the clinical picture); and (3) brain haemorrhage (stroke with a hyperdense area suggesting primary bleeding corresponding to the clinical picture, excluding haemorrhagic transformation of ischaemic stroke). The presumed causes of non-lacunar infarction included13: (1) large artery atheroma with >50% stenosis of the corresponding artery (extracranial or intracranial); (2) atherosclerosis, but without >50% stenosis of the corresponding large artery; (3) cardiac embolic sources (mitral or aortic valve diseases including mitral valve prolapse, prosthetic valves, recent myocardial infarction, infective or non-infective endocarditis, non-ischaemic dilated cardiomyopathy, left ventricular ischaemic dyskinesia, left ventricular thrombus, atrial myxoma, atrial fibrillation, sick sinus syndrome, and patent foramen ovale with or without atrial septal aneurysm, with presumed paradoxical embolism); and (4) other causes, which were not compatible with large artery atheroma or cardiac embolic sources, or which remained undetermined. In the present study, non-lacunar infarctions were subdivided according to the presence or absence of cardiac embolic sources. However, infarcts occurred in the internal carotid artery area of the occluded side, and infarcts in the border zone suspected of a haemodynamic mechanism because of an associated decrease in blood pressure were classified as non-cardioembolic infarcts. Infarct topography was classified as: (1) anterior circulation (including superficial and deep territories); (2) posterior circulation; and (3) border zone according to reported guidelines.14 Brain haemorrhage was subdivided into two aetiologic subtypes: (1) hypertensive and (2) non-hypertensive according to history of hypertension. We considered two topographic forms of haemorrhage: (1) lobar (supratentorial) and (2) non-lobar, including the thalamus, basal ganglia, and infratentorial. The classification was performed independently by the two authors in a non-blind fashion to the subtypes of the patients’ other stroke episodes. If different classifications were made, we discussed these differences until agreement was achieved.

The following risk factors were considered15: (1) hypertension (blood pressure >160/90 mm Hg at least twice before the stroke); (2) diabetes mellitus (known fasting hyperglycaemia before the stroke); (3) current or former cigarette smoking; (4) hypercholesterolaemia (cholesterol concentration >6.5 mmol/l).

For evaluating the functional disability after the acute state (activities of daily living, ADL), which was evaluated at the time of discharge, we used a five level classification; 1 for no disability, 2 for mild disability (return to all activities but with some difficulty), 3 for moderate disability (return to most main activities but with difficulty), 4 for severe disability (impossible to return to most activity), and 5 for death.16 The medication at the time of recurrence was also investigated.

Statistical comparisons among the groups were performed using the Kruskal-Wallis test for continuous variables, as well as the χ2 and Fisher’s exact tests for categorical variables. Intergroup comparisons were performed with Bonferroni’s method. A two tailed probability value<0.05 was considered significant.

Table 1 shows the stroke subtypes. There was no significant difference in age between men and women or among cardioembolic infarction, non-lacunar non-cardioembolic infarction, lacunar infarction, and brain haemorrhage. The mean interval between the first and last stroke tended to be longer in patients with initial lacunar infarction than in other groups.

### Results

#### General Features

During the study period, 102 patients (77 males and 25 females, mean age (SD): 63.7 (13.2) years) had 121 episodes of recurrent stroke (one recurrence in 86 patients, two in 14 patients, three in one patient, and four in one patient). Table 1 shows the stroke subtypes. There was no significant difference in age between men and women or among cardioembolic infarction, non-lacunar non-cardioembolic infarction, lacunar infarction, and brain haemorrhage. The mean interval between the first and last stroke tended to be longer in patients with initial lacunar infarction than in other groups.

#### Risk Factors

In the patients who had experienced a cardioembolic infarction as their first stroke, the frequency of cardiac ischaemia was significantly higher than in patients with an initial lacunar or haemorrhagic stroke (p<0.05). No patient with an initial brain haemorrhage had a potential cardiac source of embolism, which
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Table 2 Risk factors and the first stroke type

<table>
<thead>
<tr>
<th></th>
<th>NL-CE</th>
<th>NL-NE</th>
<th>LI</th>
<th>BH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>65.0</td>
<td>39</td>
<td>83.0</td>
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<tr>
<td>Diabetes mellitus</td>
<td>5</td>
<td>25.0</td>
<td>7*</td>
<td>14.9</td>
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<tr>
<td>Smoking</td>
<td>7</td>
<td>35.0</td>
<td>29</td>
<td>61.7</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>7</td>
<td>35.0</td>
<td>18</td>
<td>38.3</td>
</tr>
<tr>
<td>Cardiac ischaemia</td>
<td>10</td>
<td>50.0</td>
<td>12</td>
<td>25.5</td>
</tr>
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<td>PCS</td>
<td>20</td>
<td>100</td>
<td>16‡</td>
<td>34.0</td>
</tr>
</tbody>
</table>

*p<0.05; lower than LI.
‡p<0.01; higher than BH.
†p<0.001; lower than NL-CE.
NL-CE=non-lacunar cardioembolic infarction; NL-NE=non-lacunar non-cardioembolic infarction; LI=lacunar infarction; BH=brain haemorrhage; PCS=potential cardiac source.

Table 3 Change in stroke type between first and recurrent stroke (number of episodes)

<table>
<thead>
<tr>
<th>Recurrence/1st</th>
<th>NL-CE</th>
<th>NL-NE</th>
<th>LI</th>
<th>BH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>NL-CE</td>
<td>15*</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NL-NE</td>
<td>4</td>
<td>33*</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>LI</td>
<td>1</td>
<td>7</td>
<td>14*</td>
<td>5</td>
</tr>
<tr>
<td>BH</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>11*</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>51</td>
<td>29</td>
<td>19</td>
</tr>
</tbody>
</table>

*p<0.001; recurrence of the same type of stroke more often than other types.
NL-CE=non-lacunar cardioembolic infarction; NL-NE=non-lacunar non-cardioembolic infarction; LI=lacunar infarction; BH=brain hemorrhage; 1st and recurrence=the first and recurrent stroke type, respectively. Bold numbers indicate recurrent episodes of the same type of stroke as the first.

was a significantly lower occurrence than in the other groups (p<0.01). Patients with an initial lacunar infarction were significantly more likely to have diabetes mellitus than those with non-lacunar non-cardioembolic infarction (p<0.05, table 2). Some patients had multiple risk factors: 30% of the patients with initial cardioembolic infarction, 26% of those with initial non-lacunar non-cardioembolic infarction, 37% of those with initial lacunar infarction, and 6% of those with initial brain haemorrhage had three or more risk factors.

RECURRENT PATTERNS

In general, recurring strokes were always more often of the same type as the first stroke. The patients with an initial cardioembolic infarction had the highest same type recurrence rate, followed by those with initial non-lacunar non-cardioembolic infarction, those with initial brain haemorrhage, and those with initial lacunar infarction (table 3). Seven (44%) of 16 patients with initial non-lacunar non-cardioembolic infarction and five (56%) of nine patients with initial lacunar infarction who had a potential cardiac source of embolism developed cardioembolic infarcts. The recurring strokes of patients with an initial brain haemorrhage included non-lacunar non-cardioembolic infarction in 16%, lacunar infarction in 26%, and cardioembolic infarction in none, whereas no patient with initial cardioembolic infarction, 8% with initial non-lacunar non-cardioembolic infarction, and 4% with initial lacunar infarction developed brain haemorrhage. Among the 14 patients who had three strokes, one repeated two cardioembolic infarcts, six repeated two non-lacunar non-cardioembolic infarcts, five repeated two lacunar infarcts, one repeated two brain haemorrhages, and one experienced three different types of stroke (one non-lacunar non-cardioembolic infarct, one lacunar infarct, and one brain haemorrhage). The two patients who had more than three recurrences had experienced a lacunar infarction as their first stroke. One patient had four strokes which were all lacunar infarcts, and the other with five strokes had one non-lacunar non-cardioembolic infarct and four lacunar infarcts.

CARDIOEMBOLIC INFARCTION

In the 17 recurrent episodes of cardioembolic infarction, 10 (76%) were located in the anterior circulation. Eight (80%) of 10 patients with initial lesions in the anterior circulation and five (71%) of seven patients with initial lesions in the posterior circulation developed recurrent episodes in the anterior circulation. No cardioembolic infarct was located in a border zone. Two of three patients who developed recurrent non-lacunar non-cardioembolic infarcts had a border zone infarction associated with carotid artery stenosis.

NON-LACUNAR NON-CARDIOEMBOLIC INFARCTION

In all 84 patients with non-lacunar non-cardioembolic infarcts, the most frequent cause was large artery atheroma, followed by atherosclerosis without more than 50% stenosis, and other causes (39%, 37%, and 24% respectively). Of the 12 patients with first stroke due to other causes, four patients had an embolic stroke from an undetermined source. Three of them developed embolic strokes from an undetermined source. The fourth patient developed a cardioembolic infarction. Two patients with internal carotid artery dissection did not have dissection as the cause of recurrent stroke: one patient had a non-lacunar non-cardioembolic infarct in the posterior circulation and the other a brain haemorrhage. Of the remaining six patients, one had positive anticardiolipin antibodies and one had hypertension as a sole risk factor.

Overall, infarcts most often involved the anterior circulation, followed by the posterior circulation and the border zone (66%, 24%, and 11% respectively). There was no significant relation between the involved territory and the presumed cause of the non-lacunar non-cardioembolic infarction, except that border zone infarcts were typically associated with large artery stenosis or occlusion (91.7%). Eighty-nine per cent of initial episodes located in the anterior circulation, 83% of those located in the posterior circulation, and 50% of those located in the border zone resulted in repeated recurrent episodes in the same territory (p<0.01 for the anterior circulation infarction, p<0.05 for the posterior circulation and the border zones). There were too few patients with subcortical versus superficial infarction to perform a meaningful analysis.

LACUNAR INFARCTION

The first stroke was a supratentorial lacunar infarct in 13 patients, and an infratentorial lacunar infarct in four patients. The other two patients showed multiple lacunar infarcts on CT. The recurrent episodes were essentially the same between the patients with diabetic
mellitus as a sole risk factor and other patients: the eight patients with diabetes mellitus as a sole risk factor developed three cardioembolic infarcts, four non-lacunar non-cardioembolic infarcts, one brain haemorrhage, and repeated four lacunar infarcts, whereas the other 11 patients developed three cardioembolic infarcts, four non-lacunar non-cardioembolic infarcts, and repeated 10 lacunar infarcts.

BRAIN HAEMORRHAGE
In the patients with an initial brain haemorrhage, 11 (69%) had a lobar and five (31%) a non-lobar location. Of all episodes of haemorrhage, 21 (77.8%) were lobar. No infratentorial haemorrhage occurred in either the initial or recurrent episodes. No patient with an initial brain haemorrhage was undergoing anticoagulation therapy when any brain haemorrhage occurred. Three patients with a lobar haemorrhage as the first stroke had a new haemorrhage in the same region without visible vascular malformation. Of all episodes of haemorrhage, 52% of the lobar haemorrhages and 67% of the non-lobar haemorrhages occurred in hypertensive patients. Ten patients with a hypertensive brain haemorrhage as the first stroke had 12 recurrent episodes, including five haemorrhages (42%), three non-lacunar non-cardioembolic infarcts (25%), and four lacunar infarcts (33%). Six patients with a non-hypertensive brain haemorrhage as the first stroke had seven recurrent episodes, including six haemorrhages (86%) and one lacunar infarct (14%).

PREVENTIVE TREATMENT
Among the 86 patients with a first ischaemic stroke, 58 patients (67%) received antiplatelet drugs, 12 patients (14%) received anticoagulant drugs (including those given for reasons other than stroke, such as the secondary prevention of pulmonary embolism), five patients (6%) had surgical treatments, and 11 patients (13%) had no special treatment for secondary prevention after the first episode. Only one patient developed a brain haemorrhage while on anticoagulation. Among the 16 patients who had at least two cardioembolic infarcts, 13 did not receive anticoagulant drugs at the time of recurrence. Of the two patients who had a carotid endarterectomy after a first non-lacunar non-cardioembolic infarction, one had a new stroke contralateral to the endarterectomy, and the other repeated a same type stroke on the ipsilateral side, associated with restenosis of the internal carotid artery. Among the 16 patients with a first brain haemorrhage, two patients (13%) received antiplatelet drugs, one patient (6%) underwent a surgical treatment, and 13 patients (81%) had no treatment after the first episode.

PROGNOSIS
After the first stroke, all but one of the patients (95%) with an initial lacunar infarction were completely independent (level 1), whereas 65% of the patients with an initial cardioembolic infarction, 49% of those with an initial non-lacunar non-cardioembolic infarction, and 69% of those with brain haemorrhage were mildly to severely dependent (level 2–4). This difference in ADL between initial lacunar infarction and the other three subtypes was highly significant (p<0.001). After a recurrent stroke, however, this difference disappeared (p=0.26). The ADL was not significantly different between the patients with recurrence ipsilateral to the initial stroke and those with contralateral recurrence.

Discussion
Although there have been several prospective studies which have identified specific risk factors, aetiological features, and prognostic characteristics for recurrent strokes, the results are heterogeneous and remain controversial. Identification of the underlying mechanisms for recurrence is the key to effective secondary prevention. However, a precise aetiological classification of recurrent episodes in a large number of patients has not been available from hospital or community based stroke registries, although there are scarce smaller studies, which primarily focused on lacunar stroke. The present study is not an epidemiological study evaluating the frequency and risk of stroke recurrence, but an attempt at better analysing the different pathophysiological patterns of first versus second and further strokes.

Our findings show that despite preventive treatment, patients with first stroke may not only experience a repeat of the same type of stroke, but may also develop other kinds of strokes. Previous hospital or community based follow up studies did not emphasise the potential changes in recurrent stroke subtypes, and our study provides a first attempt at analysing the patterns of recurrent stroke and delineating the factors associated with recurrence in each subtype.

The present study has inevitable limitations. Firstly, because this is not a prospective study, it is difficult to determine the true recurrence rate in patients with each subtype of stroke. Patients might neglect very mild symptoms, which may decrease the apparent rate of recurrence of lacunar stroke. Fatal recurrence episodes might not have been referred to our service, which might be a cause of the apparent lack of pontine haemorrhage. Secondly, the whole group of selected patients might have some bias because of the strict exclusion criteria. A mean age of 64 years seems slightly lower than that of other studies, which may decrease the apparent rate of recurrence of lacunar stroke. Finally, the present study has inevitable limitations. Firstly, because this is not a prospective study, it is difficult to determine the true recurrence rate in patients with each subtype of stroke. Patients might neglect very mild symptoms, which may decrease the apparent rate of recurrence of lacunar stroke. Fatal recurrence episodes might not have been referred to our service, which might be a cause of the apparent lack of pontine haemorrhage. Secondly, the whole group of selected patients might have some bias because of the strict exclusion criteria. A mean age of 64 years seems slightly lower than that of other studies, which may decrease the apparent rate of recurrence of lacunar stroke. Finally, the present study has inevitable limitations.
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...reported that 32%-40% of the patients with lacunar infarction may develop non-lacunar non-cardioembolic stroke. 
Cerebral amyloid angiopathy (CAA) and angiomas are known aetiologies of non-hypertensive haemorrhage, usually in a lobar location. Three of our patients had recurrent lobar haemorrhage at the same site, which might be explained by a small, hardly visible angioma. Because lobar haemorrhage...
recurred in different sites in many patients, CAA may also play a part, although no histological proof was available.

Our findings show that recurrence of stroke need not be of the same type, aetiology, and location as the first episode. Many patients in the present study had multifactorial risk factors and coexisting potential causes of stroke, explaining in part why the patterns of stroke recurrence may be so heterogeneous. An improved understanding of the patterns of recurrence of stroke may allow for the development of more accurate prediction and better prevention of recurrence in individual patients.

We thank Drs S Blecic and JP Neu for their help in selecting the patients.