Commentary

Should patients with lacunar stroke and severe carotid artery stenosis undergo endarterectomy?

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Introduction

The concept of lacunar infarction (LI) has been long recognized, but it was Fisher who first drew attention to the association with distinct clinical syndromes.1–4 In his original description, LIs were described as small subcortical infarcts affecting the basal ganglia, internal capsule, thalamus or pons, which occurred in association with occlusion of deep penetrating arterioles on a background of hypertensive small-vessel disease, chiefly lipohyalinosis and microatheroma.1–4

If this aetiopathogenetic description holds true for all patients, an associated severe ipsilateral carotid artery stenosis (CAS) would be regarded as coincidental rather than causative. Given that severe asymptomatic disease is often best managed medically, as the benefit of carotid endarterectomy (CEA) is marginal and cannot be recommended unless the perioperative complication rate is <3%,5–7 such a patient might be expected to gain little from surgery. However, recent National Stroke Guidelines recommend CEA for patients with non-disabling anterior circulation stroke and >70% ipsilateral CAS, irrespective of ischaemic stroke subtype.8 What, then, is the evidence that patients with LI are likely to benefit from this procedure?

To answer this question, we performed a search of Medline/PubMed databases, as well as the Cochrane Database of Systematic Reviews, entering the terms ‘lacunar stroke’, ‘lacunar infarction’, ‘lacunes’ and ‘carotid endarterectomy’. References arising from these articles were also searched and in some cases, authors of key articles were contacted directly.

The diagnosis of lacunar infarction

LI accounts for one quarter of all ischaemic strokes,9 and differentiation from other stroke subtypes is important, as the prognosis tends to be better in terms of mortality, disability and recurrence.10–12 Most patients present with one of five classical syndromes (see Table 1) which have a high positive predictive value for LI,1–4 though other entities such as primary intracerebral haemorrhage occasionally present in this way.13–15 Clinical features of cortical or vertebrobasilar involvement should be absent,13 and ideally, the diagnosis should be supported by the presence of an appropriate deep infarct <1.5 cm in diameter.2,3 However, the sensitivity of early CT for LI is only around 40%,9,11,13,16–18 increasing to 50–60% if repeated after the first few days,16,18 and 6–26% of lesions are missed by MRI, despite it being the imaging modality of choice.17,19–22 The combination of a classical syndrome and absence of an incongruous radiological lesion is therefore diagnostically acceptable.23

Can emboli cause lacunar infarction?

Although there is general agreement that localized disease affecting perforating arterioles is the most
important pathology underlying LI, there has been debate as to whether or not emboli might be responsible for an important minority of events\textsuperscript{11,12,14,24–35} and hence, whether the possibility of an embolic substrate need be investigated. The issue is of key importance when deciding whether an ipsilateral CAS is likely to be causal, but is difficult to resolve with certainty for two reasons. Firstly, there is a paucity of clinicopathological data because of the low short-term fatality rate,\textsuperscript{13,24} and arteriography cannot visualize small, penetrating arterioles. Secondly, multiple potential aetiologies for stroke often co-exist and an embolic cause cannot be proven \textit{in vivo} even when a source of embolism is the sole risk factor present,\textsuperscript{36} for example, over one third of unselected ischaemic strokes in patients with atrial fibrillation (AF) are likely to have a non-cardioembolic basis.\textsuperscript{37} However, several lines of evidence suggest that embolic LIs do, indeed, occur.

### Pathological studies

Animal research has clearly demonstrated that artificially introduced embolic material\textsuperscript{38} or platelet emboli produced \textit{in vivo} can enter deep penetrating arteries to cause LI, and human post-mortem (PM) data have shown LIs co-existing with ulcerated large artery plaque, with no other obvious cause for cerebral infarction.\textsuperscript{40} Histological analysis of carotid plaque from patients undergoing CEA whose CT scans have shown evidence of LI have also revealed fresh mural thrombus in some cases, suggesting recent embolization.\textsuperscript{41}

In a retrospective series of 2859 unselected PMs, 6% were found to have LI, most of which had not been associated with ante-mortem symptoms. Large-vessel disease was the sole identifiable cause in 17 (30%) of a subgroup of 56 patients who underwent an extensive pathological examination, in whom there was neither evidence of severe disease in the appropriate penetrating artery on microscopic examination, nor hypertension.\textsuperscript{35} Moreover, in a review of 20 clinically-studied patients who had LI and subsequently underwent a PM examination, four were thought to have resulted from embolism.\textsuperscript{42}

### Risk factor profiles

Although hypertension was almost universal in early reports of patients who had LI,\textsuperscript{1–3} later studies indicate that its prevalence is around 60%, and there is no convincing evidence that this is more common than in other subtypes of ischaemic stroke.\textsuperscript{30,31} This suggests the causative relationship with LI may be no stronger,\textsuperscript{31} and raises the possibility of mechanisms other than small-vessel disease in non-hypertensive patients.\textsuperscript{42} In addition, although AF in unselected patients with LI is considerably less common than in those with non-lacunar ischaemic stroke at 5–12%,\textsuperscript{26,28,37,43–45} it is more prevalent in the non-hypertensive subgroup, suggesting that embolism may be important in these patients.\textsuperscript{33,46}

### Case reports of probable embolic LI

LI occurring during cardiac catheterization has been reported,\textsuperscript{47,48} and in a series of 133 patients treated for native valve endocarditis, 8% of all strokes that occurred had the typical clinical and CT features of LI.\textsuperscript{49} In both these situations, an embolic substrate is highly likely.

### Imaging

Ay \textit{et al.}\textsuperscript{20} performed MR diffusion-weighted imaging in 62 patients with a classical lacunar syndrome within 3 days of presentation. This technique, which allows differentiation of new from old asymptomatic lesions, revealed that 16% of the patients had multiple areas of acute infarction, often in different vascular territories, and most were associated with a potential source of embolism. Furthermore, in a study of patients with hemispheric infarcts on CT and ipsilateral carotid disease but no history of stroke, lacunar as well as cortical infarcts were found to be more common with increasing severity of stenosis.\textsuperscript{50}

### Prevalence of an embolic source for LI

Several studies have sought evidence of a carotid or cardiac source of embolism in patients with

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Cases of lacunar infarction (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure motor hemiparesis</td>
<td>54</td>
</tr>
<tr>
<td>Sensorimotor syndrome</td>
<td>19</td>
</tr>
<tr>
<td>Ataxic hemiparesis</td>
<td>10</td>
</tr>
<tr>
<td>Pure sensory syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Dysarthria: clumsy hand</td>
<td>5</td>
</tr>
<tr>
<td>Other, e.g. hemiballismus, hemichorea</td>
<td>6</td>
</tr>
</tbody>
</table>

*In a series of 337 cases.\textsuperscript{9}
LI and are summarized in Table 2. At 1–28%, the frequency of moderate to severe ipsilateral carotid disease is lower in patients with non-lacunar ischaemic stroke, but probably exceeds the 1–5% of persons in the general population with a similar degree of ultrasonically-detectable disease in one or both sides, in addition, four of seven studies in which patients with LI were systematically screened reported that carotid disease was more common on the ipsilateral than contralateral side, and severe disease was more than twice as common ipsilaterally in a subgroup of 222 patients who had LI in the ECST trial.

Based on clinical criteria and transthoracic echocardiography, 5–20% of patients with LI have a potential cardiac source of embolism which is, again, less frequent than in patients with non-lacunar ischaemic stroke. In a case-controlled study in which patients with LI and healthy controls underwent transoesophageal echocardiography, the prevalence of a potential cardiac source of embolism was similar in both groups, although proximal aortic plaque was five times as frequent in those with LI at 20%.

### Transcranial Doppler ultrasound studies

Transcranial Doppler-detected microembolic signals (MES) indicate asymptomatic embolization in cerebral arteries, and a number of studies have investigated their frequency post stroke according to subtype. These have generally shown that MES are rare or absent following LI. In some of these studies, though, strokes were classified according to the likely aetiopathogenesis, so that patients who had symptoms or CT findings that suggested LI were not assigned to this diagnosis in the presence of a potential carotid or cardiac source of embolism, leaving a subgroup much less likely to have had emboli. In one of the studies, however, in which LI was defined radiologically, MES were equally common in those with LI and non-LI. An assessment of MES in patients who have sustained LI in association with an ipsilateral severe CAS, in comparison to other stroke subtypes, would help elucidate the likely causal importance of embolization in this subgroup.

An overview of these data indicates that embolic LIs can occur, and that around one third of patients have a potential large-artery or cardiac source of embolism, which was the only identifiable cause in 11%, in one study. Although the proportion in whom embolism is the genuine substrate for LI cannot be ascertained without pathological confirmation, it is evident that an ipsilateral severe CAS may be causal and should not be disregarded.

### Carotid endarterectomy in patients with lacunar infarction

The risk of stroke is considerably higher in patients with symptomatic severe CAS than in their asymptomatic counterparts, and in patients with non-disabling anterior circulation stroke and 70–99% stenoses, CEA reduces both the 2-year risk of ipsilateral stroke by up to 17%, and any major stroke or death by up to 10%. Moreover, the reduction in stroke risk is greatest in patients aged over 75 years. While patients with cardioembolic stroke were excluded from these studies, those who had LIs were included, although results in this subgroup were not presented separately. However, retrospective outcome data from the ECST and NASCET trials have now been reported according to stroke subtype. There were too few patients in the ECST with LI and severe ipsilateral CAS to draw conclusions on the effectiveness of surgery. However, in the NASCET study, the absolute risk reductions of recurrent ipsilateral stroke over 3 years following endarterectomy in patients with 50–99% CAS and either non-LI or probable LI (lacunar syndrome plus congruous CT lesion) or possible LI (lacunar syndrome and negative CT) were 15%, 9%, and 8.5%, respectively. It should, however, be noted that the numbers in the latter two groups were small, and their risk reductions did not achieve significance (Table 3). Further, a meta-analysis published in abstract form which included data from these two trials has shown that patients with LI and 70–99% CAS, but not 50–69% stenoses, benefited from surgery, although the degree was not stated. CEA also appears to reduce the subsequent risk of lacunar as well as large-artery stroke, suggesting that the observed benefit in patients presenting with LI is attributable to removal of an embolic source or, perhaps, improved perfusion. Compromised cerebral blood flow may underlie strokes occurring in association with severe carotid disease, and a haemodynamic mechanism of infarction in some patients who have small-vessel disease and severe CAS is both plausible on the basis of impaired autoregulation and supported by case studies. However, the relative importance of these two mechanisms is uncertain.
<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Any ipsilateral carotid disease (%)</th>
<th>Severe ipsilateral carotid disease (%)</th>
<th>Any contralateral carotid disease (%)</th>
<th>Severe contralateral carotid disease (%)</th>
<th>Source of cardioembolism (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salgado, 1996.12</td>
<td>37</td>
<td>1 (&gt;50% stenosis)</td>
<td>34</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Norvning, 1989.18</td>
<td>49</td>
<td>3 (&gt;50% stenosis)</td>
<td>48</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Kazui, 2000.57</td>
<td>NG</td>
<td>4 (&gt;60% stenosis)</td>
<td>NG</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Mead, 1998.53</td>
<td>NG</td>
<td>4 (&gt;70%)</td>
<td>NG</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Lindgren, 2000.90</td>
<td>NG</td>
<td>5 (&gt;50% stenosis)</td>
<td>NG</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Gan, 1997.14</td>
<td>NG</td>
<td>5 (&gt;60% stenosis)</td>
<td>NG</td>
<td>NG</td>
<td>5</td>
</tr>
<tr>
<td>Mead, 1999.34</td>
<td>NG</td>
<td>7 (&gt;70% stenosis)</td>
<td>NG</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Horowitz, 1992.28</td>
<td>23</td>
<td>8*</td>
<td>16</td>
<td>NG</td>
<td>18</td>
</tr>
<tr>
<td>Mead, 1997.52</td>
<td>NG</td>
<td>11 (&gt;50% stenosis)</td>
<td>NG</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Kappelle, 1988.29</td>
<td>31</td>
<td>13 (&gt;50% stenosis)</td>
<td>16</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Boiten, 1991.26</td>
<td>NG</td>
<td>13 (&gt;50% stenosis)</td>
<td>NG</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Tegeler, 1991.34</td>
<td>NG</td>
<td>13 (&gt;50% stenosis)</td>
<td>NG</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Loeb, 1986.31</td>
<td>NG</td>
<td>24*</td>
<td>NG</td>
<td>NG</td>
<td></td>
</tr>
<tr>
<td>Ghika, 1989.27</td>
<td>NG</td>
<td>28 (&gt;75% stenosis)</td>
<td>NG</td>
<td>NG</td>
<td>21</td>
</tr>
<tr>
<td>Pullicino, 1980.32</td>
<td>NG</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Sacco, 1991.51</td>
<td>159 patients with LI</td>
<td></td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Landi, 1992.31</td>
<td>85 patients with LI</td>
<td></td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Lindgren, 1994.50</td>
<td>49 patients with LI</td>
<td></td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Gosselink, 1984.62</td>
<td>83 patients with LI</td>
<td></td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

*Degree of stenosis not stated, but described as ‘haemodynamically significant’. US, ultrasound; NG, not given. Studies in which carotid imaging was used selectively are not included.
Table 3  Three-year risk of ipsilateral ischaemic stroke according to medical or surgical treatment in patients presenting with lacunar or non-lacunar stroke and 50–99% carotid stenosis in the NASCET study.22,80

<table>
<thead>
<tr>
<th>Stroke subtype at presentation</th>
<th>Stroke over 3 years with medical treatment (%)</th>
<th>Lacunar stroke over 3 years with medical treatment (%)</th>
<th>Stroke over 3 years with surgery (%)</th>
<th>Absolute risk reduction (%) of all stroke with surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable lacunar ($n = 210$)</td>
<td>25.5</td>
<td>9.2</td>
<td>16.5</td>
<td>9 (NS)</td>
</tr>
<tr>
<td>Non-lacunar ($n = 665$)</td>
<td>24.9</td>
<td>2.9</td>
<td>9.7</td>
<td>15.2 ($p = 0.002$)</td>
</tr>
</tbody>
</table>

NS, not significant: NB: the risk of perioperative major stroke and death in this trial was only 2.1%.

Conclusion

Although data are limited, current evidence suggests that patients with recent LI and severe CAS will, on balance, benefit from surgical intervention. However, it is important to realize that this benefit is probably confined to a relatively small subgroup, with no effect in most of the remainder, and net harm in the occasional patient. Further research should focus on prognostic modelling to enable patient stratification in terms of their likely risk:benefit ratio, which would allow targeted use of carotid endarterectomy, perhaps incorporating data on sonographically-detected MES and a qualitative assessment of plaque to reflect embolicigenic potential, together with clinical factors.

In the interim, clinicians should remain mindful that the absolute benefit derived from surgery following LI appears to be greater than in patients with asymptomatic disease, but less than that in non-lacunar stroke, consistent with the concept that lesions are causal in some, but not all cases. A particularly careful assessment of local perioperative complication rates, and co-morbidities which may influence this, is therefore mandatory when considering surgical intervention in individual patients.

Acknowledgements

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References


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