The correlation between carotid plaque ulceration and cerebral infarction seen on CT scan

Andrew J. Zukowski, M.D., Andrew N. Nicolaides, F.R.C.S.,
Ronald T. Lewis, F.R.C.S.(C), Averil O. Mansfield, F.R.C.S.,
Michael A. Williams, F.R.C.S., Epaminondas Helmis, M.D.,
G. Mark Malouf, F.R.C.S., David Thomas, M.D., Aghiad Al-Kutoubi, M.D.,
Pantelis Kyprianou, M.D., and Harry H. G. Eastcott, F.R.C.S.,
London, England

The purpose of the study was to determine the association between cerebral infarction seen on CT scan and macroscopic ulceration of atheromatous carotid plaques in patients undergoing carotid endarterectomy. Following carotid endarterectomy in 65 patients, specimens were examined for the presence of ulceration without knowing the result of the preoperative CT brain scan. The 65 patients thus investigated underwent 68 carotid endarterectomies: 36 for a history of transient ischemic attacks (TIAs), 13 for amaurosis fugax, and six for prior strokes; 13 asymptomatic patients had prophylactic carotid endarterectomy prior to coronary bypass. A macroscopic ulcer was present in 42 specimens. Twenty-six (62%) of the patients with ulceration had one or more ipsilateral cerebral infarcts on CT scan. Only two (8%) of the 26 patients without an ulcer had cerebral infarcts. Of the 36 patients who presented with TIAs, 26 (72%) had carotid plaque ulcers and 23 (88%) of these had cerebral infarcts on CT scan also. In contrast, only three of 13 asymptomatic patients had plaque ulcers and only one of these had a cerebral infarct. There is a high incidence of cerebral infarction seen on CT scan in patients presenting with TIAs. These infarcts occur predominantly in patients with ulcerated atheromatous carotid lesions. (J VASC SURG 1984; 1:782-786.)

Although it has been established for several decades that symptoms of cerebral ischemia are often associated with carotid atherosclerosis,1-3 attention has only recently been directed to changes in carotid plaques that produce symptoms.4,5 There is now increasing evidence that transient ischemic attacks (TIAs) are more frequently embolic than hemodynamic events. Dixon et al.6 have recorded an increased risk of TIAs and strokes in patients with nonstenotic ulcerative lesions of the carotid bifurcation. The strongest evidence for embolization from the atheromatous carotid artery has been derived in the 1960s from the demonstration of Hollenhorst plaques in the retinal vessels of patients with ipsilateral amaurosis fugax.7 More recent evidence is the association of TIAs and carotid plaque ulceration.1 The present study provides further evidence in support of the embolic theory by examining the association between macroscopic ulceration of atheromatous carotid plaques and cerebral infarction identified on preoperative CT brain scans in patients having carotid endarterectomy.

PATIENTS AND METHODS

Seventy-eight consecutive patients admitted for carotid endarterectomy were classified as having

Table I. Clinical presenting symptoms in 65 patients who underwent 68 carotid endarterectomies

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIAs</td>
<td>36</td>
<td>53</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Nil</td>
<td>13</td>
<td>19</td>
</tr>
</tbody>
</table>

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Fig. 1. Incidence of end-organ effects, that is, cerebral infarction and/or amaurosis fugax, in patients with and without plaque ulcers.

Table II. Incidence of cerebral infarction and amaurosis fugax

<table>
<thead>
<tr>
<th>With ulceration</th>
<th>Without ulceration</th>
<th>Fisher's exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Ipsilateral infarcts</td>
<td>26</td>
<td>62</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Neither</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

hemispheric TIAs, amaurosis fugax, or prior strokes or as being symptomatic. All patients had duplex Doppler examination of the carotid and vertebral arteries, and all but three underwent biplane carotid angiography. CT brain scans without enhancement were requested before operation and carotid endarterectomy specimens were retrieved at operation for examination. The CT brain scans were examined for presence or absence of infarcts in the “carotid territory” of the ipsilateral cerebral hemisphere. The presence of contralateral infarcts was also noted.

Eighty-one consecutive carotid endarterectomy specimens were obtained from 78 patients. An attempt was made by the surgeons to remove the specimens in one piece. The specimens were washed in saline solution and were then studied by two vascular surgeons who did not know the result of the CT brain scan. The examination was performed in bright light with optical loops that produced two times magnification.

RESULTS

CT brain scans were not obtained for technical reasons in 10 patients, and three specimens removed piecemeal were unsuitable for study. Thus complete data were available for analysis on 68 carotid specimens from 65 patients. Our population included 38 males and 27 females whose mean age was 70 ± 6.3 years (mean ± SD). Table I lists the presenting symptoms in these 65 patients who had 68 carotid endarterectomies. The majority had hemispheric TIAs; but 13 had ipsilateral amaurosis fugax, and six had made good recovery from stroke. In 13 asymptomatic patients with severe carotid stenosis, prophylactic carotid endarterectomy was performed prior to aortic coronary bypass.

All 65 patients had more than 50% stenosis of the involved internal carotid artery shown by duplex Doppler examination; this was confirmed further by angiography. CT evidence of ipsilateral brain infarcts was found in 28 patients. Contralateral infarcts were found only in nine patients, all of whom had symptomatic disease of the corresponding internal carotid artery; four had carotid occlusion and prior stroke; and five had significant stenosis (>50%) and TIAs.

Table II shows the incidence of cerebral infarction and amaurosis fugax in the 42 sides with and 26 sides without plaque ulceration. There is a higher incidence of both ipsilateral infarcts and amaurosis fugax in the group with ulceration than in the group without ulceration. One patient with ulceration had
both a cerebral infarct and amaurosis fugax; thus 35 (83%) of the 42 with plaque ulcers had CT evidence of cerebral infarct or amaurosis fugax. Fig. 1 summarizes these findings and shows the striking difference in the incidence of total end-organ effects, that is, cerebral infarct and/or amaurosis fugax, between patients with and without carotid plaque ulcers (p < 0.0001).

Fig. 2 shows the incidence of plaque ulcers and cerebral infarction in the 36 patients with TIAs and the 13 who were asymptomatic. There is a higher incidence of both plaque ulcers and cerebral infarcts in the group with TIAs than in the group of asymptomatic patients. Of the 36 patients with TIAs, only one had a cerebral infarct without carotid plaque ulceration. One patient of the six who had presented with a history of stroke had a cerebral infarct without evidence of carotid plaque ulceration also. In this patient the carotid endarterectomy had been performed when the patient had recovered 3 months after the stroke.

DISCUSSION

The embolic theory of TIAs has been difficult to prove because the majority of patients presenting with symptoms have a hemodynamically significant carotid stenosis. There is no doubt that a number of patients with TIAs have decreased cerebral perfusion, as shown by xenon-133 and positron emission tomography measurements. However, in a large number of patients with TIAs the regional cerebral perfusion is normal and a different mechanism should be responsible for their symptoms.

If embolization occurs, a source of emboli should be present and the end-organ effects of embolization such as cerebral infarction and amaurosis fugax should be closely associated with this source. Our study yields just these findings. Macroscopic carotid plaque ulcers were found in almost three fourths of patients presenting with TIAs; and ipsilateral cerebral infarcts were present on CT scans of 88% of these patients. In contrast to these findings, carotid plaque ulceration and CT evidence of brain infarcts were both infrequent in the asymptomatic patients.

The results do not imply that carotid plaque ulcers are the only source of TIAs. A variety of other pathologic lesions in the heart and extracranial cerebrovascular supply are additional sources. Hertzer et al. hypothesized that ultramicroscopic ulcerations and thrombi at the carotid bifurcation might also be present in atheroma that appears smooth on gross inspection and could form a source of emboli. Only two of 10 such specimens examined in his study by scanning electron microscopy did not show an ulcer. In our study only two patients, one with TIAs and the other with a history of stroke, had CT evidence of cerebral infarcts but did not have macroscopic carotid ulcers on inspection of the specimen. However, they might have had microscopic ulcers. Alternatively, a macroscopic ulcer might have been present when the patients had symptoms but healed in the interval before operation. As yet we have not examined our specimens histologically, but we plan to do so in the second phase of this study.

Histologic examination will be required to throw light on the present controversies surrounding the pathogenesis of plaque ulcers.
patients presenting without a history of stroke had evidence of a cerebral infarction on their CT scan, and we have presented the term "silent" cerebral infarction to describe this entity, which to my knowledge has not been previously described in the literature.

In our series there was a suggestion that these patients with a "silent" cerebral infarction might have a higher incidence of perioperative neurologic deficits, and I would like to know if you found a similarly increased incidence of perioperative neurologic deficits, and I would like to know if you found a similarly increased incidence of postoperative neurologic deficit in these patients.

We also correlated the preoperative angiographic finding of an ulcer with the preoperative CT result. In our series 119 carotid arteries were found to have smooth stenoses, and of these, 22% were found to have an ipsilateral cerebral infarction on CT scans prior to operation. Ninety-five

et al. and Lusby et al. attribute these ulcers to the breakdown of endothelium overlying sites of intraplaque hemorrhage. In our study macroscopic intraplaque hemorrhages were visible in many specimens with ulcers, but further evaluation must await microscopy.

The significance of the cerebral infarcts so commonly identified on CT scans of patients presenting with TIAs only is uncertain. Vorstrup et al. found similar infaracts in patients with recent TIAs. With emission tomography they also showed that ischemic brain tissue damage persisted even after successful carotid endarterectomy. Our study suggests as well that these infaracts may be "markers" of concomitant ulceration in stenosed internal carotid arteries. The fact that contralateral infarcts occurred only in the presence of significant disease of the corresponding internal carotid artery supports this interpretation.

If CT evidence of cerebral infaracts in patients with TIAs does imply associated carotid plaque ulceration, this would be a valuable observation, for, unlike carotid stenosis that is easily diagnosed by noninvasive studies macroscopic carotid ulcers are difficult to identify even by selective carotid angiography. Moreover, carotid ulceration even in the absence of stenosis may affect patient prognosis. It has been found that large ulcers are associated with an annual stroke rate of 5% to 7%. Studies of the natural history of patients with asymptomatic carotid stenosis, now in progress in several centers, should include CT brain scans in their protocol, as these may prove to be the key to identifying a high-risk group.

REFERENCES

DISCUSSION

Dr. Jack N. Graber (Minneapolis, Minn.). In your study you have noted that nearly 30% of those patients who present without symptoms of stroke, that is, transient ischemic attack or asymptomatic bruit, had the unexpected finding of a cerebral infarction on their CT scan. At the Vascular Service at the Tufts University-Boston Veterans Administration Medical Center we have recently reported similar data in which we found that 18% of 78 patients presenting without a history of stroke had evidence of a cerebral infarction on their preoperative CT scan, and we have presented the term "silent" cerebral
carotid arteries were found to have ulcerative disease, and of these, 19% were found to have an ipsilateral infarction on CT scans. The ulcers were not a preponderant finding in the patients who presented with a "silent" cerebral infarction. These data suggest caution in accepting the premise that the presence of an ulcer alone predicts an increased incidence of cerebral infarction.

I would like to know if your patients with ulcer disease had an increased risk of perioperative neurologic deficit. In our series, they did not. Last, did you perform arteriograms prior to your operations and, if so, how did the arteriograms correlate with the macroscopic finding of ulcer?

Dr. Andrew Carney (Oak Park, Ill.). The significance of this article is that the focus is shifting from the carotid arteriogram to the brain. This study addresses the structural changes in the brain but does not address the perfusion changes that occur. Specifically, patients who have acute embolism to the brain may not have a demonstrable infarct on a static scan. However, contrast infusion may be able to demonstrate luxuriant perfusion surrounding the "infarcted" area. The CT scan has the capability of measuring brain perfusion. Since that modality is more widely applied, I expect we will see more studies discussing the relationship of carotid lesions to brain perfusion.

I would like to ask what the timing was of the CT scans and whether the patients had infusion or dynamic CT scans?

Dr. William C. Mackey (Boston, Mass.). Dr. Zukowski and his colleagues are to be commended for presenting a timely study that helps to confirm many of our prejudices regarding the pathogenesis of cerebrovascular symptoms. These findings support a long-held impression of our group at the Tufts University-New England Medical Center. We have maintained that it is the character of the plaque, not just the patient's symptoms at the time of presentation, that determines the risk of cerebral vascular events and therefore should determine the need for endarterectomy.

We have carried out a similar study in 89 patients with signs or symptoms of cerebrovascular disease. In evaluating their 178 hemispheres by CT scanning we found that 36 of 178, or 20%, have CT evidence of infarction. Of note is that 61% of the patients with CT scan evidence of hemispheric infarction were symptomatic, whereas 68% of the patients with negative CT scans were symptomatic. In the CT-positive group, however, nearly 75% had complex plaques, which we define as plaques with ulceration, severe stenosis, or occlusion, whereas in the CT-negative group only about 50% had complex plaques. Also, 15% of the CT negative group and 27% of the CT positive group had intraoperative EEG changes requiring shunting. There was, however, no difference in postoperative neurologic morbidity rates between the CT-positive and CT-negative groups with our technique for selective shunting on the basis of EEG criteria.

From our data we strongly concur with Dr. Zukowski that a CT scan positive for hemispheric infarction in a patient with carotid disease is a marker for the unstable plaque and may by itself be considered an indication for endarterectomy.

I would like to ask the authors several questions. First, was plaque morphology examined preoperatively with B-mode ultrasound? Second, were the plaques examined for the presence of intraplaque hemorrhage, which Dr. Imparato and others have suggested as a precursor lesion to ulceration? Third, were peripheral infarcts, which we have often attributed to emboli, differentiated in your study from more central infaracts usually attributed to hypertension?

Dr. Anthony M. Imparato (New York, N.Y.). Dr. Zukowski, could you tell from looking at those plaques exactly what embolized from the carotid plaque?

Dr. Zukowski (closing). Dr. Imparato, I must say that that is a difficult question. As we are all aware, the embolic material in complex plaques may be blood clot or atheromatous debris. The latter may result from breakthrough of subintimal hemorrhage in the plaque. In several of these plaques we saw evidence of intraplaque hemorrhage with a thrombus at the ulcer. In others, there was just an ulcer. I presume that in those cases the thrombus may have already embolized.

Dr. Graber, I agree that there are several "silent" infarctions in patients with carotid plaque ulceration, and that is in agreement with our findings. We have not observed any increase in postoperative neurologic deficit in patients with preoperative CT evidence of brain infarcts. In fact, the overall incidence of postoperative neurologic deficit has been nil.

As far as angiography used alone is concerned, we performed such studies in almost all of the patients with the exception of three who were asymptomatic and who had duplex Doppler studies only. We operated on the basis of these findings. Although angiograms were performed in two views, including cerebral views as well, I can only say that if the ulcer is small, it is very difficult to see. I do not think that we can rely on angiographic findings to identify small plaque ulcers.

Dr. Carney, we did not do any perfusion scans to measure regional blood flow in these patients. Unfortunately, we did not have the facilities to perform such scans. I would also like to add that all our CT scans were without enhancement, and perhaps that reflected a slightly lower incidence of cerebral infarction. With enhancement perhaps even smaller infarcts can be detected, and the incidence will be therefore increased.

Dr. Mackey, we did not examine our patients with high-resolution B-mode imaging. They all had duplex scans, but the resolution of our instrument does not allow us to study the plaque pathology fully. Most of the CT infarcts seen on CT scans were in fact peripheral, but I cannot tell you precisely how many were central.