Lack of Association Between Carotid Plaque Hematoma and Ischemic Cerebral Symptoms

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To investigate the association between carotid plaque hematoma and symptoms of cerebral ischemia a retrospective review of 200 consecutive carotid endarterectomies at the Neurological Institute of New York was carried out. Data analyzed included cerebral ischemic symptoms, angiographic findings, preoperative use of antithrombotic agents, and microscopic pathology of endarterectomy specimens. No association was found between ischemic symptoms ipsilateral to the endarterectomy and presence, size, or age of plaque hematomas. Plaque hematomas were less common among patients who took antithrombotic agents preoperatively than among those who did not. The presence of plaque hematoma was associated with angiographic carotid cross-sectional area stenosis of >75%. Patients with stenosis of <75% were more likely than those with stenosis of >75% to have ischemic symptoms ipsilateral to the endarterectomy, suggesting that criteria for surgical treatment of carotid atherosclerosis differ for those who are symptomatic vs. those who are asymptomatic. These results demonstrate the limitation of using a surgical series to extend causal inferences about the relation between plaque hematoma and cerebral ischemic symptoms to the general population of people with carotid atherosclerosis. (Stroke 1987;18:879–881)

Hemorrhage into atheromatous plaque is a common feature of large artery atherosclerosis.1−3 Some investigators have reported that carotid plaque hematomas occur significantly more often in symptomatic patients undergoing endarterectomy compared with those who are asymptomatic and that there is a correlation between age of the hematoma and timing of the symptoms.4−6 They postulate that plaque hematoma is an important precipitator of transient ischemic attack (TIA) and stroke, either by causing acute severe stenosis or by producing intimal disruption leading to overlying thrombus formation and consequent embolism. This argument provides a rationale for the role of endarterectomy in the prevention of stroke in people with atherosclerotic plaques or stenosis, both symptomatic and asymptomatic. Furthermore, it is suggested that the use of antithrombotic agents may obscure warning symptoms and may increase the risk of plaque hematoma.6 We conducted a study of all persons undergoing endarterectomy at the Neurological Institute of New York from October 1982 to May 1984 to further investigate the relation of carotid plaque hematoma to the occurrence of TIA and stroke in surgically treated patients and to determine if preoperative use of antithrombotic agents was associated with the presence of plaque hematoma.

Subjects and Methods

During the period under study, 200 carotid endarterectomies were performed. The study included those 198 endarterectomies about which clinical information could be found. Ninety-three men and 84 women with a mean age of 66 years comprised the study population; 156 had unilateral and 21 had bilateral endarterectomies. Clinical information was obtained by chart review to determine whether symptoms of focal cerebral ischemia in the territory of the treated carotid artery had occurred prior to surgery. The number of days before surgery of the initial and all subsequent neurologic symptoms was recorded, whether the symptoms were in the carotid territory of interest or not. In addition, data on timing and duration of the use of antithrombotic agents, both antiplatelet agents and anticoagulants, were obtained. The chart reviewer was blinded to the histologic characteristics of the surgical specimen and the angiographic findings.

Characterization of the pathology of endarterectomy specimens was based on microscopic examination of hematoxylin and eosin stained cross-sections. The pathologist had no knowledge of the clinical data on any patient. Plaque hematomas were recognized by the presence of degenerating blood or hemosiderin, and the age of the hematoma was estimated using standard histologic criteria of reaction to tissue injury7 to categorize the hemorrhages as acute, recent, of intermediate age, or old. An acute hematoma, estimated to be <1 week old, showed intact and degenerating red cells, many polymorphonuclear leukocytes and a few mononuclear cells, and little or no evidence of organization. A recent hematoma, estimated to be 1–4 weeks old, showed degenerating red cells, pigment-laden and foamy macrophages, developing organization tissue, and a predominance of mononuclear inflammatory
cells. A hematoma of intermediate age, estimated to be >4 weeks old, showed only residual degenerating blood, maturation of organization tissue with enlargement of vascular spaces, and loss of inflammatory cells except macrophages and a few plasma cells. An old hematoma, estimated to be months or years old, showed vascular, loose myxoid or collagenous tissue on hematoxylin and eosiin stain and varying numbers of hemosiderin-laden macrophages, confirmed on a Prussian blue stain for iron. Large hematomas were defined as those occupying ≥50% of the plaque cross-sectional diameter and contributing to high-grade stenosis or near-occlusion.

Angiograms were examined for 135 of the 198 endarterectomies. Determination of the degree of stenosis was made by measuring the minimal residual lumen and estimating the normal lumen diameter at that site in 2 planes. Severity of the stenosis was assessed based on a calculated percent reduction in cross-sectional area, with ≥75% reduction considered a critical or hemodynamically significant stenosis. The angiograms were reviewed without knowledge of the clinical or pathologic data.

Statistical analysis was performed using the χ2 and Mantel-Haenszel χ2 methods.8

Results

Symptoms of cerebral ischemia occurred in the territory of 122 (62%) of the treated carotid arteries, 38 (19%) had symptoms in some other vascular territory, 26 (13%) had nonlocalizing symptoms, and 12 (6%) had no neurologic symptoms. Of those 122 cases with ipsilateral symptoms, i.e., in the territory of the treated carotid artery, the timing of preoperative occurrence was 1–7 days in 8 (7%), 1–4 weeks in 32 (26%), 1–6 months in 57 (47%), and >6 months in 25 (20%).

All endarterectomy specimens had 1 or more histologic features of atherosclerosis. Ninety-six of the 198 specimens (48%) had evidence of plaque hematoma: 35 acute, 11 recent, 23 intermediate, and 27 old; 21 specimens (48%) had evidence of plaque hematoma: 35 acute, 11 recent, 23 intermediate, and 27 old; 21 large hematomas were identified. Among patients with plaque hematoma, 57% had ipsilateral symptoms. Of those without plaque hematoma, 65% had ipsilateral symptoms. Comparing these 2 groups, no association was found between plaque hematoma and ipsilateral symptoms (χ² = 1.47, p < 0.25). It was considered possible that only large hematomas are associated with ipsilateral symptoms, but in comparing the frequency of ipsilateral symptoms in the 3 groups with no hematoma (65%), small hematoma (56%), and large hematoma (62%), this association was not demonstrated (χ² = 1.72, p < 0.25).

A temporal association between plaque hematoma and the timing of symptoms was sought. It is unlikely that the estimate of the age of the hematoma was accurate when the plaque hematoma had occurred >4 weeks before surgery. Among cases with ipsilateral symptoms, a comparison was made between the group with acute or recent hematoma and the group with intermediate, old, or no plaque hematoma. In the former group, 9 of 31 (29%) had onset of ipsilateral symptoms within 4 weeks of surgery, whereas in the latter group 24 of 91 (26%) had onset of ipsilateral symptoms within that time period. These results show no association between hematoma < 4 weeks old and onset of ipsilateral symptoms in the 4 weeks prior to surgery (χ² = 0.08, p > 0.25). Of the 17 large hematomas with angiographically confirmed critical stenosis, 15 were dated as occurring within 4 weeks of surgery. Of these 15, 11 had neurologic symptoms in the territory of the treated carotid artery, and 5 (33%) had onset of these symptoms within the 4 weeks prior to surgery. The remainder included 6 with ipsilateral symptoms which began > 5 weeks before surgery and 4 with no symptoms or symptoms in another vascular territory.

Four additional cases had large hematomas, but we did not have their angiograms to determine the degree of stenosis. None of these cases had ipsilateral symptoms. These data document that, of the 198 endarterectomies, 5 were done in patients with both a large hematoma <4 weeks old and ipsilateral symptoms during the 4 weeks prior to surgery.

Of the 135 cases for which angiograms were reviewed, angiographically 97 (71.8%) had a critical stenosis. In the group with plaque hematoma, 83.3% had a critical stenosis on angiogram, while in the group with no plaque hematoma, only 58.7% had this degree of stenosis, showing an association between plaque hematoma and critical stenosis (χ² = 10.06, p < 0.01). Of the 21 cases classified as having large hematomas pathologically, 17 angiograms were reviewed and all showed stenosis of ≥75%. Fifty-one of 97 cases with critical stenosis (53%) had ipsilateral symptoms, and 32 of 38 cases without critical stenosis (84%) had ipsilateral symptoms. These proportions are significantly different (χ² = 15.66, p < 0.001), indicating an association between ipsilateral symptoms and the absence of critical stenosis. Since some authors have suggested that a plaque hematoma may disrupt the intimal surface and predispose to embolism from a nonstenotic artery, we did a stratified analysis based on the presence or absence of plaque hematoma. The stratified analysis demonstrated that the association between ipsilateral symptoms and noncritical stenosis was not explained by the presence of a plaque hematoma (Mantel-Haenszel χ² = 0.002, p > 0.25).

Concern has been raised that the use of antiplatelet agents or anticoagulants may increase the occurrence of plaque hematoma, thereby putting patients with atherosclerotic plaques at increased risk for ischemic events. To investigate this point, patients were classified as to whether they made daily use of an antithrombotic agent during the month prior to surgery. Data were obtained on use of antithrombotic agents for 148 of the 198 endarterectomies. Among the 97 users of antithrombotic agents, 25% had a plaque hematoma <4 weeks old, whereas among the 51 nonusers, 43% had a plaque hematoma <4 weeks old, a significant difference indicating no increased risk of plaque hematoma in users of antithrombotic agents (χ² = 5.28, p < 0.025).
Discussion

An important aspect of prevention of cerebral in-
farction is elucidating the pathogenesis of atheroscle-
rosis of the carotid bifurcation. Both perfusion failure
distal to a critical stenosis and embolism due to ulcer-
ation of an atherosclerotic plaque have been claimed as
causes of cerebral infarction. Some investigators who
have studied gross5 and microscopic46 pathologic
specimens of carotid plaques have concluded that hem-
orrhage within the plaque contributes to the develop-
ment of both stenosis and ulceration. They have also
reported that plaque hematoma is found more often in
symptomatic compared with asymptomatic patients
undergoing endarterectomy and concluded that plaque
hematoma has an important role in causing cerebral
ischemia. Others have not found carotid plaque he-
matoma to be associated with cerebral ischemic
symptoms.9

In agreement with these studies,4–6,9 we found that
hematoma is a common pathologic feature of carotid
plaques. However, we did not find an association be-
tween symptoms and hematomas, ipsilateral symp-
toms being as common among those with as those
without plaque hematoma. Among those patients with
large hematomas, that type presumed to be most likely
to cause symptoms because of a sudden and significant
reduction in lumen diameter, only 5 had onset of
symptoms ipsilateral to the hematoma, and within the
same period that the hematoma occurred. Thus, in only
5 of 198 cases can it be postulated that the hematoma
precipitated cerebral ischemia by causing a critical ste-
nosis. Among the remaining cases with ipsilateral
symptoms, plaque hematoma may have contributed to
the development of stenosis or ulceration but, given
the lack of a temporal association between hematoma
and symptoms, plaque hematoma cannot be identified
as a direct cause of cerebral ischemia. It is possible that
failure to recognize an association between the time of
occurrence of hemorrhage and the onset of symptoms
occurred because of inaccuracies in methods for deter-
mining the age of the hematoma. While our dating
criteria are based on standard histologic criteria includ-
ing the presence of degenerating blood, type of inflam-
matory response, and degree of organization,7 these
criteria define only the general sequence of events,
which may be altered by a variety of factors. For exam-
ple, because the atherosclerotic plaque is rather avas-
cular, the usual reaction to hemorrhage may be delayed
and slowed. In this study, an attempt was made to com-
pensate for such discrepancies by using broadly
defined time periods.

In the present study, plaque hematoma was positive-
ly associated with angiographically demonstrated criti-
 cal stenosis. Plaque hematoma is one of several fea-
tures of atherosclerosis contributing to the complexity
and thickness of the plaque.1–3,7 Our study found it to be
a marker of the severity of atherosclerosis. What is
perhaps surprising is that ipsilateral symptoms were no
more common among those with critical stenosis.
Rather, the noncritical stenosis group had the greater
proportion with ipsilateral symptoms. This result
seems to suggest that criteria for selecting patients for
surgery at our institution are different for those who
have ipsilateral symptoms than for those who do not. A
patient with TIA may have an endarterectomy on the
ipsilateral carotid for a noncritical stenosis, while a
patient who has no ipsilateral symptoms will not be
referred for endarterectomy unless the stenosis com-
promises flow. Since plaque hematoma is a marker for
stenosis severity, it is not surprising that hematoma
does not correlate with ipsilateral symptoms. These
results demonstrate the limitation of using a surgical
series to extend causal inferences about the relation
between plaque hematoma and cerebral ischemic
symptoms to the general population of people with
carotid atherosclerosis. Based on our results, the risk
of plaque hemorrhage causing an infarct due to embo-
lish or reduced flow in an asymptomatic person with
an atherosclerotic plaque is not a justification for pro-
phylactic endarterectomy.

Concern has been raised7 that antithrombotic agents
may increase the chance of intraplaque hemorrhage
and cause cerebral infarction or TIA. We demonstrated
no increased risk of plaque hematoma among those
patients taking antithrombotic medications during the
month before surgery.

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