Plaque Hemorrhage Is a Marker of Thromboembolic Activity in Patients with Symptomatic Carotid Disease[1]

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Purpose: To assess whether carotid plaque hemorrhage depicted with magnetic resonance (MR) imaging was associated with thromboembolic activity as assessed with transcranial Doppler imaging.

Materials and Methods: The local research ethics committee approved the study, and all patients gave informed written consent. Between April 2005 and December 2006, patients with high-grade symptomatic carotid stenosis were prospectively recruited. All underwent MR imaging of the carotid arteries for plaque hemorrhage and diffusion-weighted imaging of the brain. Transcranial Doppler imaging of the symptomatic carotid artery was performed over 1 hour to assess the presence of microembolic signal. To determine the relationship between the presence of plaque hemorrhage and diffusion-weighted imaging–positive signal and presence of microembolic signal, a logistic regression analysis was performed.

Results: Fifty-one patients (23 women and 28 men; mean age ± standard deviation, 72 years ± 11) underwent complete MR imaging; 46 (86%) of these patients underwent complete transcranial Doppler imaging. In 32 (63%) patients, there was plaque hemorrhage in the index carotid artery. The presence of plaque hemorrhage increased the risk for ipsilateral abnormalities at diffusion-weighted imaging (odds ratio, 6.2 [95% confidence interval: 1.7, 21.8]; $P < .05$). Multiple diffusion-weighted imaging–depicted abnormalities of multiple ages were present exclusively in patients with plaque hemorrhage shown at MR imaging (12 of 32 [38%] patients with plaque hemorrhage versus none of 19 patients without plaque hemorrhage; $P < .05$). The presence of plaque hemorrhage also increased the presence of microembolic signal (odds ratio, 6.0 [95% confidence interval: 1.8, 19.9]; $P = .003$).

Conclusion: In patients with carotid plaque hemorrhage demonstrated at MR imaging, there was increased spontaneous microembolic activity at transcranial Doppler imaging and cerebral ischemic lesion patterns suggestive of recurrent embolic events; these findings suggest that plaque hemorrhage shown at MR imaging might be a marker of thromboembolic activity and further validate the usefulness of carotid imaging in identifying patients with active carotid arterial disease.

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Thromboembolism is the predominant mechanism causing ischemic strokes in patients with carotid artery disease. Large randomized controlled trials of symptomatic carotid artery disease have shown that carotid endarterectomy is highly beneficial in preventing stroke in patients with high-grade carotid stenosis, especially when performed early (1). The risk for recurrent events decreases with time, and subsequently the majority of patients with carotid disease will not have any recurrent events (1). Therefore, the identification of high- and low-risk patients would be helpful for initiating timely and appropriate management.

Carotid plaque hemorrhage is increasingly being recognized as an important feature in plaque instability (2–4). It is thought to arise from disruption of fragile neovessels within the carotid plaque and contributes to the necrotic core of the plaque, thereby increasing the size of plaque (3,5).

Plaque hemorrhage can be accurately identified by using a T1-weighted gradient-echo fat-suppressed magnetic resonance (MR) imaging technique (6,7). Plaque hemorrhage depicted with MR imaging was shown to predict increased risk for recurrent events in patients with symptomatic (8,9) and those with asymptomatic (10) carotid disease. Moreover, the presence of plaque hemorrhage at MR imaging was associated with the extent of chronic cerebral ischemic lesion load (11). These studies strongly support an association between carotid plaque hemorrhage and cerebral ischemia but do not provide information about the nature of the association. For plaque hemorrhage to be pathophysiologically relevant, direct evidence of a link between this hemorrhage and spontaneous thromboembolic activity is needed.

The most widely used technique to assess thromboembolism is transcranial Doppler imaging. The depiction of microembolic signals with transcranial Doppler imaging is an accepted marker of thromboembolic plaque activity, and microembolic signals in patients with carotid disease were found to be associated with recurrent clinical events (12).

Diffusion-weighted imaging offers an alternative and complementary tool to detect the consequences of macroscopic cerebral thromboemboli. This type of imaging is the most sensitive technique to depict acute and subacute cerebral ischemia, whether clinically apparent or silent. Presence of multiple acute lesions at diffusion-weighted imaging was closely associated with carotid disease (13) and recurrent strokes (14). In a recent study, the presence of multiple diffusion-weighted imaging–depicted lesions with varying ages, reflecting recurrent ischemic events, was particularly sensitive for predicting recurrent strokes (14).

The aim of this study was to assess whether plaque hemorrhage at MR imaging was associated with thromboembolic activity as assessed with transcranial Doppler imaging.

Advances in Knowledge

- Carotid plaque hemorrhage in symptomatic patients is associated with acute and subacute ischemic cerebral lesions (prevalence in patients with plaque hemorrhage, 12 of 32 [38%]).
- Carotid plaque hemorrhage is associated with spontaneous embolization as detected with transcranial Doppler imaging (odds ratio, 6.0 [95% confidence interval: 1.8, 19.9]).

Materials and Methods

Recruitment

Between April 2005 and December 2006, 51 symptomatic patients (23 women and 28 men; mean age ± standard deviation, 71.6 years ± 10.5) with high-grade carotid stenosis were prospectively and consecutively recruited into this study. Patients were included if they presented within 6 weeks of an anterior circulation event (stroke or transient ischemic attack) or amaurosis fugax in the presence of a high-grade stenotic (60%–99%) lesion of the carotid arteries. The degree of stenosis was determined according to duplex scanning criteria, as used in the North American Symptomatic Carotid Endarterectomy Trial.

The local research ethics committee approved the study, and all patients gave informed written consent. Exclusion criteria were any contraindication for MR imaging or a situation in which waiting for MR imaging or transcranial Doppler imaging would have delayed carotid endarterectomy.

MR Imaging Studies

MR imaging was performed with a 1.5-T imager (Signa; GE Medical Systems, Waukesha, Wis) by using an eight-channel neurovascular coil.

Carotid imaging was performed by using a coronal T1-weighted, magnetization-prepared, three-dimensional gradient-echo sequence with a water excitation pulse that excludes signal from fat. The following parameters were used: relaxation time msec/echo time msec, 5.9/1.5; flip angle, 15°; inversion time, 19 msec; acquisition matrix, 320 × 320 × 36, and voxel size, 1.07 × 1.07 × 2.00 mm (interpolated to 512 × 512 × 72, voxel

Implication for Patient Care

- By helping identify patients with unstable carotid plaques, this MR imaging technique has the potential to improve selection of patients with carotid stenosis for carotid intervention.

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Abbreviations:
ADC = apparent diffusion coefficient
CI = confidence interval
ROI = region of interest

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size of 0.58 × 0.58 × 1.00); frequency encoding direction, feet to head; number of signals acquired, 1.5; acquisition time, 255 seconds. No spectral fat saturation was applied.

Diffusion-weighted MR imaging was performed by using an axial fat-suppressed single-shot double-spin-echo echo-planar imaging sequence with 15 diffusion gradient directions, a *b* factor of 1000 sec/mm^2, and one image without diffusion-weighted imaging (b = 0 sec/mm^2). Other parameters were as follows: 10000/105; acquisition matrix, 112 × 112; field of view, 220 mm (interpolated to matrix of 256 × 256, pixel size of 0.86 × 0.86 mm); number of sections, 40; section thickness, 3 mm with 0.3-mm gap; number of signals acquired, two; acquisition time, 240 seconds.

Postprocessing was performed by using the manufacturer's proprietary software to calculate average b = 1000 sec/mm^2 image and apparent diffusion coefficient (ADC) maps.

Image Analysis

Image analysis was performed offline by using standard image reconstruction techniques, as provided by JAVA Imaging software (Xinapse Systems, Aldwincle, England), to assess axial reformats and assess intensity of the plaque hemorrhage signal. Two investigators (N.A. and D.P.A., with 2 and over 15 years of experience in image analysis, respectively) were blinded to the clinical and transcranial Doppler data.

Plaque hemorrhage was identified if the maximum signal intensity within the carotid plaque was greater than 150% of the maximum intensity of the adjacent muscle, as described elsewhere (8). The presence or absence of high signal intensity was recorded in both the symptomatic artery and the asymptomatic arteries; the reviewers were blinded to the microembolic findings. Intraobserver and interobserver variabilities were tested in a random set of 30 patients (60 carotid arteries) selected by another investigator (P.S.M.). This testing demonstrated excellent agreement (Cohen κ = 0.88 for one reviewer and 0.81 for the other reviewer).

By using a Sun workstation (Oracle, Redwood Shores, Calif), the b = 1000 sec/mm^2 averaged diffusion-weighted images were jointly interpreted by two investigators (N.A. and D.P.A., with over 6 months of experience interpreting images jointly) who were blinded to all clinical information, including the symptomatic side and whether MR imaging showed plaque hemorrhage. The diffusion-weighted images were assessed 3 months after the carotid images were assessed.

A diffusion-weighted image was considered positive if the b = 1000 sec/mm^2 image demonstrated an area of hyperintensity (Fig 1). Thresholds were assigned to the images according to the signal intensity of normal-appearing white matter for each respective hemisphere and each axial diffusion-weighted imaging section. A circular region of interest (ROI) of a standard size (50 mm^2) was placed by one author (N.A.) in the middle of each hemisphere of each section on normal-appearing white brain matter. The mean and the standard deviation of the intensity were calculated for the ROI. A cutoff threshold was chosen to be the mean + 3 standard deviations, and the images were windowed at this threshold of signal intensity. At this cutoff threshold, all areas of hyperintensities were considered to be areas of ischemia (diffusion-weighted imaging positive). These lesions were further classified as single lesions or multiple lesions. Multiple lesions were defined as lesions that were topographically distinct (separated in space in-plane or through-plane).

By using the edge-detection ROI function with JAVA Imaging software, ROIs were semi-automatically drawn if the threshold intensity was greater than the mean + 3 standard deviations of the hemisphere.

To determine the age of the diffusion-weighted imaging–positive lesions, the ADCs were calculated for each lesion. The initial ROI drawn around each of the lesions was saved. The analysis software used in the study allowed simultaneous placements of the matching ROIs onto the ADC maps. Mirror images of ROIs were projected onto the ADC maps of the contralateral hemispheres to create a control ROI for each patient. In some cases, the contralateral side had to be manually resited to exclude sulcal cerebrospinal fluid and other areas of ischemia that would distort the control ADCs. The ADCs were calculated within the ROIs (Fig 2).

To control for any variations in ADC between patients, an ADC ratio was calculated (14) by dividing the mean ADC of the ischemic lesion by the mean ADC of the mirror contralateral image (ADC ischemia/ADC contralateral). Normalized and elevated relative ADC lesions were classified together and defined as being greater than 0.95.

Lesions depicted at diffusion-weighted imaging were further classified into four groups according to multiplicity and age: single lesion with a low ADC ratio, single lesion with a normalized ADC ratio, multiple lesions with the same ADC ratios, and multiple lesions with different ADC ratios.

All the diffusion-weighted images and MR images showing plaque hemorrhage were analyzed at different times, with investigators blinded to the clinical details.

Detection of Microemboli with Transcranial Doppler Imaging

The ipsilateral (to the side of the symptomatic carotid artery) middle cerebral artery was insonated by using a 2-MHz probe (EmboDop; Compumedics DWL, Singen, Germany) by a transtemporal route continuously over an hour after the MR imaging. A sample volume 8 mm long and a low gain provided a setting optimal for discriminating emboli from the background setting. The contralateral middle cerebral artery was not insonated.

The waveforms were recorded onto a compact disc and were analyzed at a later date, offline. All analyses were performed with the investigators blinded to the clinical information and to whether MR images showed plaque hemorrhage.

Emboli were identified according to the Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium (15) by listening to the raw signal acquired from the Doppler

Figure 1

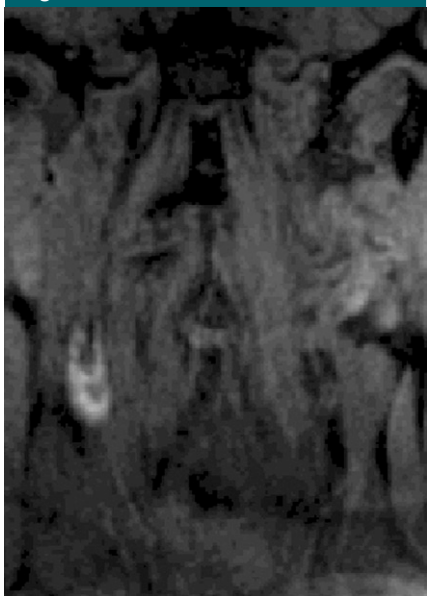
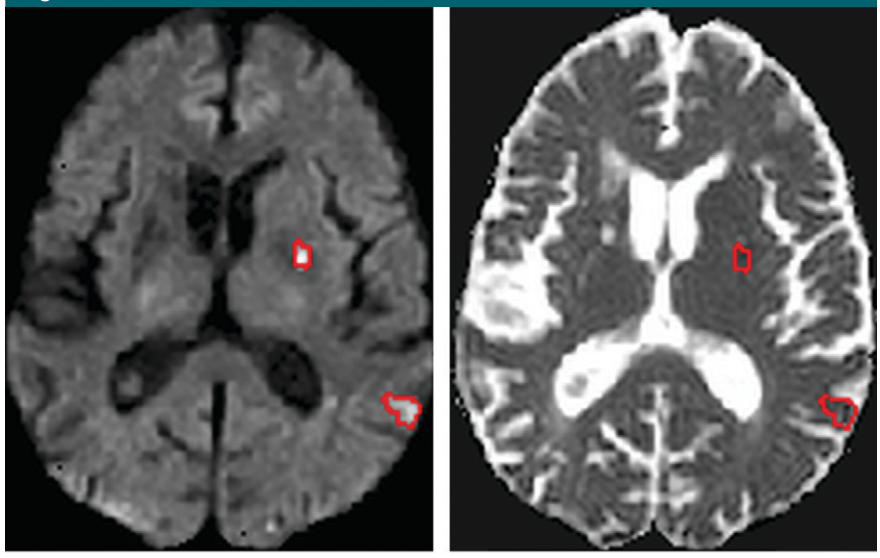


Figure 1: Diffusion-weighted image shows hyperintensity of right carotid plaque, indicating plaque hemorrhage.

Figure 2



a. b.

Figure 2: **(a)** Diffusion-weighted image demonstrates lesions, with ROI markings (red). **(b)** ADC map with superimposed ROIs (red).

device and simultaneously watching the post–fast Fourier transform signal on the screen of the device.

Microembolic signals were identified as high-intensity signals that were unidirectional within the velocity spectrum, lasted less than 300 milliseconds, had intensity greater than 7 dB above the background velocity spectrum, and were associated with a characteristic "chirping" sound.

The plaque was considered to be positive for microembolic signal when one or more microemboli were detected in the ipsilateral middle cerebral artery during the recording. The total number of microembolic signals was also calculated over the hour.

Statistical Analysis

We used χ^2 and Mann-Whitney tests to compare categorical and continuous demographic and risk factors, respectively, between the group with and the group without plaque hemorrhage.

To determine the relationship between the presence of plaque hemorrhage and diffusion-weighted imaging–positive signal and presence of a microembolic signal, a logistic regression analysis was performed. To further control for confounding factors, a multivariate logistic regression model was used.

Statistical calculations were made by using statistical software (SPSS version 15.0; SPSS, Chicago, Ill), and $P < .5$ was used to indicate a statistically significant difference. Odds ratios and 95% confidence intervals (CIs) are reported.

Results

Patients

Of the 59 patients who fulfilled the inclusion criteria and agreed to participate in the study, 51 (86%) underwent successful MR imaging examinations. Eight patients (16%) were excluded: two because of carotid occlusion, five because of claustrophobia, and one because further clinical evaluation suggested that the patient was asymptomatic. Symptoms were as follows: stroke in 12 patients (24%), transient ischemic attacks in 26 (51%), and amaurosis fugax in 13 (26%). The median delay between the presenting symptom and MR imaging was 19 days (interquartile range, 12–27 days).

All the MR images were of adequate quality for analysis. Among the 51 patients who underwent MR imaging of the carotid arteries, images of the ipsilateral carotid arteries in 32 (62.7%) patients showed evidence of plaque hemorrhage at MR imaging and in 19 (37.3%) did not. Clinical presentation and age did not significantly differ between the patients with plaque hemorrhage shown at MR imaging and those without; however, there was a male predominance among patients with plaque hemorrhage shown at MR imaging (Table 1). Age distributions did not significantly differ by sex (mean age, 69 years ± 11 in men and 74 ± years in women; $P = .09$). There were no other significant differences in the demographic and risk factors between men and women.

Abnormalities at Diffusion-weighted Imaging and Plaque Hemorrhage at MR Imaging

Twenty-seven of 51 patients (53%) had evidence of at least one diffusion-weighted imaging–depicted abnormality on the MR image. Twenty-two (69%) patients with plaque hemorrhage at MR imaging had lesions shown on the diffusion-weighted image, but only five patients (26%) without plaque hemorrhage had lesions depicted at diffusion-weighted imaging.

Ischemic lesions were of similar size in patients with and those without

Table 1

Demographic Characteristics and Clinical Risk Factors of Patients with and Those without Plaque Hemorrhage at MR Imaging

Variable	Plaque Hemorrhage Shown at MR	Plaque Hemorrhage Not Shown at MR	*P* Value
Patients	32 (62.7)	19 (37.3)	
Age (y)*	73 ± 10	70 ± 12	.3
No. of women	10 (31)	13 (68)	.01
Hypertension	25 (78)	14 (73)	.7
Ischemic heart disease	9 (28)	6 (32)	.8
Previous myocardial infarction	6 (19)	5 (26)	>.99
Diabetes mellitus	5 (11)	2 (7)	.7
Smoker	10 (31)	11 (58)	
Statin use	21 (66)	13 (68)	.4
Presenting symptom			
Stroke	9 (28)	3 (16)	
Transient ischemic attack	18 (56)	8 (42)	.1
Amaurosis fugax	5 (16)	8 (42)	
Median time between last symptom and MR imaging (d)†	17 (10–24)	22 (15–28)	.2

Note.—Unless otherwise noted, data are numbers of patients, with percentages in parentheses.

* Data are mean ± standard deviation.

† Numbers in parentheses are the interquartile range.

Table 2

Logistic Regression Analysis Showing Odds Ratios of Factors That Affect the Presence of Abnormalities Shown at Diffusion-weighted Imaging

Variable	Odds Ratio*	*P* Value
Age	1.0 (0.9, 1.0)	.7
Female sex	0.5 (0.1, 1.5)	.2
Hypertension	1.8 (0.5, 6.7)	.4
Ischemic heart disease	1.0 (0.3, 3.4)	>.99
Diabetes mellitus	0.9 (0.1, 15.1)	.9
Smoker	1.9 (0.6, 5.8)	.3
Degree of stenosis	1.0 (0.5, 1.9)	.9
Stroke presentation	9.4 (1.1, 84.1)	.04
Time between last symptom and diffusion-weighted imaging	0.99 (0.96, 1.0)	.5
Presence of plaque hemorrhage	6.2 (1.7, 21.8)	.005

* Numbers in parentheses are 95% CIs.

plaque hemorrhage (median size, 1.2 mL [range, 0.8–3.8 mL] vs 2.1 mL [range, 1.1–11.1 mL], respectively; $P = .3$). Two patients (4%) had atrial fibrillation. Both these patients had plaque hemorrhage shown at MR imaging, and one of these patients had an ischemic lesion depicted at diffusion-weighted imaging.

Of the 27 patients with lesions shown at diffusion-weighted imaging, 23 (81%) had lesions in the anterior circulation territory and four (19%) had multiple lesions in both the anterior and the posterior circulation.

The presence of plaque hemorrhage increased the risk for diffusion-weighted imaging abnormalities (odds ratio, 6.2 [95% CI: 1.7, 21.8]; $P < .05$). The only other factor that increased the presence of lesions depicted at diffusion-weighted imaging was stroke (odds ratio, 9.4 [95% CI: 1.1, 84.1]; $P < .05$) (Table 2). After adjustment for age, sex, stroke presentation, and the time delay between the presenting symptom and MR imaging, the presence of plaque hemorrhage increased the risk for diffusion-weighted imaging–depicted lesions (odds ratio, 5.8 [95% CI: 1.0, 32.8]; $P < .05$).

Patients with plaque hemorrhage also had more acute and subacute ischemic lesions than did patients without plaque hemorrhage (mean number of lesions, 3.8 ± 4.7 vs 0.6 ± 0.1, respectively; $P < .05$).

The ADCs were calculated for 134 lesions seen on the diffusion-weighted images among 27 patients (range of ratio, 0.7–1.4). All six patients with single lesions seen at diffusion-weighted imaging had normalized relative ADCs; none of these patients had low relative ADCs. Of the 21 patients with multiple lesions depicted at diffusion-weighted imaging, nine (43%) had only normalized or low relative ADCs; 12 of the 21 patients (57%) were considered to represent lesions of multiple ages (both low and normalized ADCs). Of note, multiple diffusion-weighted imaging–depicted lesions of multiple ages were seen only in patients with plaque hemorrhage shown at MR imaging; the difference in frequency was significant (12 of 32 [38%] vs 0 of 19, respectively; $P < .05$) (Table 3).

Microembolic Signals and Plaque Hemorrhage at MR Imaging

Of the 51 patients who underwent MR imaging, five (10%) did not have an adequate window for transcranial Doppler imaging. Twenty of 46 remaining patients (44%) had microembolic signals detected from the symptomatic ipsilateral middle cerebral artery. Seventeen (59%) of the 29 patients with plaque hemorrhage shown at MR imaging had microembolic signals compared with only three (18%) of the 17 patients without plaque hemorrhage shown at MR imaging ($P < .05$). This resulted in an odds ratio of 6.0 (95% CI: 1.8, 19.9; $P = .003$) for the presence of carotid plaque hemorrhage to be predictive of microembolic signal (Table 4).

Table 3

Frequencies of Lesions Shown at Diffusion-weighted Imaging and Relative ADCs in Patients with and Those without Plaque Hemorrhage

Variable	Plaque Hemorrhage Shown at MR	Plaque Hemorrhage Not Shown at MR
Single lesion at diffusion-weighted imaging with decreased relative ADC	0	0
Single lesion at diffusion-weighted imaging without decreased relative ADC	3	3
Multiple lesions at diffusion-weighted imaging with decreased relative ADC or normalized relative ADC (single age)	7	2
Multiple lesions at diffusion-weighted imaging+ lesion with decreased relative ADC and normalized relative ADC (different ages)	12	0
Total	22	5

Note.—Data are numbers of patients. $\chi^2 = 6.8$; $P = .034$ for totals.

Table 4

Logistic Regression Analysis Showing Odds Ratios of Factors That Affect the Presence of Microembolic Signals

Variable	Odds Ratio*	*P* Value
Age	1.0 (1.0, 1.1)	.4
Female sex	0.6 (0.2, 2.1)	.5
Hypertension	1.1 (0.3, 4.2)	.9
Ischemic heart disease	1.2 (0.4, 4.2)	.8
Diabetes mellitus	1.3 (0.1, 22.4)	>.99
Smoker	0.4 (0.1, 1.5)	.2
Degree of stenosis	1.2 (0.6, 2.4)	.6
Time between last symptom and diffusion-weighted imaging	0.98 (0.95, 1.02)	.3
Presence of plaque hemorrhage	6.6 (1.6, 28.2)	.01

* Data in parentheses are 95% CIs.

Microembolic Signal and Diffusion-weighted Imaging

There was no overall association between the presence of a lesion shown at diffusion-weighted imaging and the presence of microembolic signals; of the patients with microembolic signal, approximately equal numbers showed the presence and the absence of lesions at diffusion-weighted imaging ($n = 46$; 12 of 22 [55%] had lesions shown at diffusion-weighted imaging and had a microembolic signal; eight of 24 [33%] did not have lesions shown at diffusion-weighted imaging and had a microembolic signal; $\chi^2 = 2.1$; $P = .2$). In contrast, nine of 10 patients (90%) with multiple diffusion-weighted imaging–depicted lesions of multiple ages showed microembolic signal compared with 20 of 46 (44%) in the total patient group ($\chi^2 = 9.3$; $P < .005$).

Discussion

This study investigated a hypothesized link between carotid plaque hemorrhage as a marker of instability and thromboembolic activity in patients with symptomatic high-grade carotid stenosis. By using combined carotid plaque imaging to depict plaque hemorrhage and both transcranial Doppler imaging and cerebral diffusion-weighted imaging approximately 19 days after the event, we demonstrated a strong association between carotid plaque hemorrhage and thromboembolic activity. Patients with plaque hemorrhage showed increased spontaneous microembolic activity at transcranial Doppler imaging (more frequently acute or subacute cerebral ischemic lesions), and these were more often considered recurrent as indexed by multiple lesions of multiple ages.

Intraplaque hemorrhage has been implicated in the destabilization of atherosclerotic plaques by contributing to the necrotic core of the plaque (2,3) and subsequent rupture of the plaque (16), which may result in thrombosis. By detecting this important pathophysiologic factor with MR imaging, we observed a strong association between microembolic signal and carotid plaque hemorrhage. Atherothrombotic emboli dislodging from the carotid plaque can be identified with transcranial Doppler imaging as a microembolic signal, and these emboli were associated with histologic features indicating instability of carotid plaque (17,18). Hence, the more frequent microembolic signal recordings in patients with carotid plaque hemorrhage provide evidence that increased spontaneous thromboembolic activity is associated with plaque hemorrhage. This finding agrees with and substantially extends those of a previous study that plaque hemorrhage seen at MR imaging helps predict microembolization during the dissection phase of carotid endarterectomy (19). That previous study was confounded by the fact that surgical manipulation of the carotid artery probably triggered emboli, which may have led to false-positive results.

Embolism is a dynamic process that depends not on the embolus itself but the target vascular bed, including collateral supply and perfusion. Studies of both microembolic signal and diffusion-weighted imaging have demonstrated that diffusion-weighted imaging is not sensitive to every microembolic signal, but lesions depicted at diffusion-weighted imaging are associated with an increased microembolic signal load (20,21). Furthermore, in the presence of carotid disease, microembolic signal helps predict the development of lesions visible on diffusion-weighted images (22).

In addition, small asymptomatic lesions shown at diffusion-weighted imaging are also associated with microembolic signal in patients with carotid disease (23). Diffusion-weighted imaging complements monitoring with transcranial Doppler imaging because it allows visualization of events that have occurred over weeks rather than only during the monitoring period.

Multiple emboli or break-up of a single embolus is thought to be responsible for multiple ischemic lesions seen at diffusion-weighted imaging (24,25). In fact, multiplicity of diffusion-weighted imaging–depicted lesions indicates that the lesions are embolic because they are associated with presence of carotid disease (13). In this study, we found an association between multiple ischemic lesions detected with diffusion-weighted imaging and carotid plaque hemorrhage shown at MR imaging. This finding further supports the notion that plaque hemorrhage in symptomatic carotid disease is a valid biomarker of plaque instability and thromboembolic activity.

Previous studies have shown that ADC maps are useful in determining the age of ischemic lesions (26). In the first few days after an ischemic event, the high signal at diffusion-weighted imaging is caused by a low ADC. After about 10 days, the ADC normalizes and then increases in the chronic phase (26,27). The high signal seen in lesions shown at diffusion-weighted imaging in the subacute and the chronic phases is thought to be caused by T2 shine-through. In our study, all the patients who had diffusion-weighted imaging–depicted lesions with both low and normalized ADCs had evidence of plaque hemorrhage at MR imaging. This finding suggests that these patients, in addition to their clinical events, had subclinical recurrent ischemic events at one or more time points.

Patients with multiple lesions of varying ages are already known to be at increased risk for recurrent clinical ischemic events (14), most likely indicating a persistent active embolic source. Therefore, the sensitivity of diffusion-weighted imaging–depicted lesions of multiple ages for predicting ongoing embolic activity is supported by our finding of a selective association of those lesions with microembolic signal. However, ADC normalization may not always indicate a subacute lesion because it also reflects tissue reperfusion occurring acutely after stroke (< 3 hours) (28). In our recruitment, we did not assess patients at least 10 days after an event (Table 1), and no patients had thrombolysis.

Because embolization is not expected to be constant, recording of Doppler signals over an hour may not be adequate (29). Increasing recording times or repeating recordings does increase the proportion of patients and subsequently may increase the positive predictive value of MR imaging. However, 1-hour recordings (30,31) have been thought to be sufficient to ascertain whether embolization is occurring.

Although plaque hemorrhage shown at MR imaging was found to depict most plaques that embolize, its positive predictive value is limited. We did not use multisequence MR imaging to assess other plaque features, such as rupture of the fibrous cap, which have also been implicated in plaque destabilization (10). In particular, there was no discrimination between intraplaque hemorrhage and juxta-plaque hemorrhage. Such features would have different pathophysiologic implications. The inability to differentiate these two different entities may explain the moderate specificity for identifying plaques that were embolizing. Nevertheless, the detection of methemoglobin by this MR imaging sequence has high negative predictive value in detecting plaque instability. The ongoing instability may be pathologically explained by ongoing rebleeding in the carotid plaque or the ongoing inflammation perpetuated by the presence of plaque hemorrhage in the carotid plaque (32).

Our study is limited by its cross-sectional design and the delay between presenting symptom and MR imaging. Some acute lesions may have been missed because of the delay in imaging. However, diffusion-weighted imaging has demonstrated ischemia up to 10 weeks after an ischemic insult (33), and in our study there were no significant differences in delay between the two groups of patients. We also did not assess patients with asymptomatic carotid disease, who are known to have a moderate prevalence of plaque hemorrhage; these patients may not have cerebral ischemic lesions.

In conclusion, the results of this study suggest that the detection of plaque hemorrhage with MR imaging is a useful biomarker with which to index thromboembolic activity related to instability of carotid plaque in symptomatic patients with high-grade carotid disease.

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