Plaque Features Associated With Increased Cerebral Infarction After Minor Stroke and TIA

A Prospective, Case-Control, 3-T Carotid Artery MR Imaging Study

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OBJECTIVES The goal of this study was to determine whether a 3-T magnetic resonance imaging (MRI) protocol combining carotid atherosclerotic plaque and brain imaging can identify features of high-risk acutely symptomatic plaque that correlate with brain injury.

BACKGROUND It has previously been demonstrated that, in asymptomatic patients, MRI can identify features of carotid plaque that are associated with stroke, such as the presence of a large lipid core. We hypothesized that the early phase (<7 days) after a cerebrovascular event, when risk of recurrence is highest, may be associated with particular plaque characteristics that associate with cerebral injury.

METHODS Eighty-one patients (41 presenting acutely with transient ischemic attack [TIA] or minor stroke and 40 asymptomatic controls) underwent multicontrast carotid artery MRI on 2 separate occasions, each accompanied by diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) imaging of the brain.

RESULTS Complex (American Heart Association [AHA] type VI) plaques were seen in 22 of 41 patients (54%) in the symptomatic group versus 8 of 40 (20%) in the asymptomatic group (p < 0.05). They were caused by intraplaque hemorrhage (34% vs. 18%; p = 0.08), surface rupture (24% vs. 5%; p = 0.03), or luminal thrombus (7% vs. 0%; p = 0.24). Noticeably, 17 of 30 (57%) cases of AHA type VI plaque were in vessels with <70% stenosis. At follow-up scanning (>6 weeks later), only 2 cases of symptomatic AHA type VI plaque showed evidence of full healing. The presence of fibrous cap rupture was associated with increases in DWI and FLAIR lesions in the brain. Combined carotid plaque and brain MRI may aid risk stratification and treatment selection in acute stroke and TIA.

CONCLUSIONS Early carotid wall MRI in patients experiencing minor stroke or TIA showed a higher proportion of “complex” plaques compared with asymptomatic controls; a majority were in arteries of <70% stenosis. Fibrous cap rupture was associated with increases in DWI and FLAIR lesions in the brain. Combined carotid plaque and brain MRI may aid risk stratification and treatment selection in acute stroke and TIA. (J Am Coll Cardiol Img 2012;5:388–96) © 2012 by the American College of Cardiology Foundation
Stroke is a major cause of mortality and disability (1). After an initial transient ischemic attack (TIA) or minor stroke secondary to large artery atherosclerosis, patients remain at a particularly high risk of disabling stroke within the first 7 days (2). Patients with severe (70% to 99%) ipsilateral carotid stenosis on carotid ultrasound are currently treated with early carotid endarterectomy, and some patients with moderate (50% to 69%) symptomatic stenosis may also benefit from surgery (3,4). However, determination of individual patient risk and selection of optimal therapy remain challenging. The association between carotid artery stenosis and stroke risk was originally demonstrated using x-ray arteriography (5,6). This technique is invasive, relatively expensive, has limited availability, and has largely been replaced by noninvasive imaging with Doppler ultrasound, computed tomography (CT) angiography, and magnetic resonance (MR) angiography (7). However, because atherosclerotic plaques accumulate within the vessel wall and are heterogeneous in both composition and morphology, angiographic techniques cannot reveal the full complexity of plaque disease, and opportunities for more precise diagnosis and stratification of risk, based on appreciation of plaque characteristics, may be overlooked (8). This limitation of conventional angiography may be of particular importance in moderately sized plaques with modest impingement on the vessel lumen (9).

Magnetic resonance imaging (MRI) is noninvasive, does not involve harmful ionizing radiation, provides high-resolution images, and is widely available for clinical use. The ability of MRI to accurately identify potential features of “high-risk” or “unstable” plaque such as hemorrhage (10), surface rupture (11), lipid-rich necrotic core (10), and thrombus (12) has now been extensively validated by comparison of imaged plaques with histological examination of carotid endarterectomy samples (10,12–15).

A MR classification of plaque, modified from the American Heart Association (AHA) grading system has been developed. Type IV/V plaque describes “vulnerable” plaque with a large lipid core, whereas AHA type VI plaque exhibits features consistent with acute events, as suggested by intra-plaque hemorrhage, cap rupture, or thrombus (16).

A number of studies have evaluated carotid plaque with MRI after stroke, but recruitment to the majority of these studies was extended up to 3 to 12 months after the index event so that plaque features very early after the event (relating to the time of greatest risk and possibly the source of infarction) remain largely unexplored (17–21). Alternatively, carotid arteries may have been imaged early after an acute event but without a control group or follow-up scan for comparison (22) or in small numbers without quantification of the extent of brain injury (23).

Accordingly, the present study investigated the ability of high-resolution MRI at 3-T to characterize carotid plaques of patients early after minor stroke or TIA. To determine the natural history of symptomatic plaque, patients were re-examined with carotid MRI after 6 weeks. MRI-derived plaque characteristics were compared with a stable matched population of asymptomatic patients. Lastly, to test whether “acute” carotid plaque characteristics related to cerebral infarction, diffusion-weighted imaging (DWI) (for acute lesions) (24) and fluid-attenuated inversion recovery lesions (FLAIR) (for established infarcts) (25) in the brain on MRI were quantified in both populations.

METHODS

Patient recruitment. This was a single-center study in a tertiary hospital. The protocol was approved by the local research ethics committee, and all patients provided written informed consent.

Potential study participants were identified from patients presenting with symptoms of a first TIA or stroke to the Acute Stroke Service at the John Radcliffe Hospital, Oxford, United Kingdom. All participants had the diagnosis of a cerebrovascular event confirmed by 2 independent physicians. Consecutive patients with an ipsilateral carotid artery

ABBREVIATIONS AND ACRONYMS

<table>
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<th>Abbreviation</th>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<td>DWI</td>
<td>diffusion-weighted imaging</td>
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<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
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<td>MR</td>
<td>magnetic resonance</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>PDW</td>
<td>proton density-weighted</td>
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<td>TE</td>
<td>echo delay time</td>
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<td>TIA</td>
<td>transient ischemic attack</td>
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<td>TOF</td>
<td>time of flight</td>
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<td>TR</td>
<td>repetition time</td>
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Acute 3-T MRI of Carotid Plaque in Stroke

Lindsay et al.

All turbo spin echo images were obtained with a repetition time (TR) of 1 R-R interval, echo delay (TE) of 14 ms; for TOF, TR/TE 72/4.1 ms. To correct for intersubject variability and coil-related signal inhomogeneities, all images were manually thresholded so that all lesions were confirmed as described by Hatsukami et al. (11). In all cases of surface disruption, breach of integrity of the fibrous cap was confirmed as described by Hatsukami et al. (11). Wall measurements were obtained using semiautomated image quantification software developed at the University of Oxford and Osirix imaging software (26).

Plaques were assigned a grade of I to VIII according to the modified AHA plaque grading system for MRI (11). In all cases of surface disruption, breach of integrity of the fibrous cap was confirmed as described by Hatsukami et al. (11). Wall measurements were obtained using semiautomated image quantification software developed at the University of Oxford and Osirix imaging software (26).

All brain imaging analysis was performed using Osirix and Jim 5.0 imaging analysis software (Xinapse Systems Ltd., Aldwincle, United Kingdom) by a single reader who was blinded to plaque imaging results and clinical symptoms (A.C.L.). Outlining of all pathological lesions seen on axial DWI and FLAIR imaging of the brain was performed for each slice and converted into a total lesion volume for each hemisphere. To correct for intersubject variability and coil-related signal inhomogeneities, all images were manually thresholded so that all lesions were compared with the signal intensity of white matter with normal appearance in each hemisphere and for each axial section.

Statistical analysis. The Fisher exact test was used to test the baseline characteristics between the acutely symptomatic group and the control cohort. In addition, comparison of plaque grades between cohorts was conducted by using the Wilcoxon signed rank test in addition to the Fisher exact test. DWI data were nonparametrically distributed, and a Mann-Whitney U test was used to compare cerebral injury values between groups that were divided by carotid plaque characteristics.

RESULTS

Eighty-two patients were recruited. Of the 42 symptomatic patients, 1 was unable to tolerate the entire scan procedure; therefore, images were available from 41 symptomatic patients for analysis. Full imaging data were obtained in all 40 patients in the asymptomatic cohort. The groups were well

Brain MRI. After carotid wall imaging, MR brain imaging data were collected using a 12-channel head receive coil. After an initial localizer sequence, all patients underwent DWI (TR/TE = 4,436/93 ms, b values = 0.1000 s/mm², 27 slices 4.5 mm apart, voxel size 1.6 × 1.6 × 3 mm) and FLAIR (TR/TE/inversion time = 13,970/94/2,500 ms; FA = 150 degrees, 27 slices 4.5 mm apart; voxel size 0.9 × 0.9 × 3 mm) imaging of the brain.
matched for clinical characteristics and percent narrowing of the artery measured by ultrasound (Table 1). All patients in the symptomatic cohort received a final diagnosis of TIA or stroke. After review by 2 independent physicians, 24 patients were given a final diagnosis of stroke and 17 were given a final diagnosis of TIA according to World Health Organization criteria (27). The median time from symptom onset to MRI in the symptomatic group was 2.1 days (range 0.17 to 7.0 days). All patients were treated with aspirin and statin therapy.

**Plaque analysis.** The distribution of lesion types between the culprit and control arteries is shown in Figure 1. Features consistent with intraplaque hemorrhage, fibrous cap rupture, or mural thrombus (AHA type VI plaque) (Fig. 2) were seen in 22 of 41 (54%) symptomatic patients but in only 8 of 40 (20%; p < 0.01) asymptomatic patients. Significantly, 12 of 22 (55%) AHA type VI plaques in the symptomatic group were in vessels with <70% stenosis of the lumen, as assessed by ultrasound.

**AHA type VI plaque analysis.** Surface rupture was seen at all degrees of stenosis, including 4 cases causing <70% stenosis and 2 cases causing <50% stenosis of the carotid artery, as assessed by ultrasound (Fig. 3). Surface rupture was more common in symptomatic carotid arteries compared with asymptomatic arteries (24% vs. 5%; p = 0.03). Three patients in the symptomatic cohort showed evidence of mural thrombus within the arterial lumen, a feature that was not seen in the asymptomatic cohort (7% vs. 0%; p = 0.24). Two of these cases were associated with stroke and with luminal obstruction of >70% on carotid ultrasound, and the third case was associated with TIA and an ultrasound stenosis of only 30%. Intraplaque hemorrhage (characterized by bright signal on T-1, T-2, and TOF) was seen in 13 of 22 cases of AHA type VI plaque in the acutely symptomatic group and in 7 of 8 cases of AHA type VI plaque in the asymptomatic cohort.

**Follow-up imaging.** All patients in the acute cohort were invited for follow-up MRI, of which 30 of 41 (73%) attended. The mean time to follow-up scan was 90 days (range 30 to 250 days; SD 48 days). The mean ± SD age of patients undergoing the follow-up MRI was 73.8 ± 9.9 years (range 48.0 to 90.6 years), and the mean Barthel index at first presentation was 83.8.

**Follow-up plaque analysis.** Of the 30 patients who were scanned at follow-up, 14 had shown evidence of acute plaque rupture (AHA type VI) in the culprit artery at their initial scan, 6 of whom were subsequently treated by endarterectomy. Of the remaining 8 AHA type VI plaques scanned, 6 still had AHA type VI plaque characteristics at follow-up, although 2 plaques showed evidence of healing and were reclassified as AHA type IV/V plaque (Fig. 4). No plaque reclassification was necessary in any other follow-up scans (i.e., all other plaques initially classified as AHA types III, IV/V, and VI were unchanged).

**MRI assessment of brain injury.** Of the 41 patients in the acute group, evidence of cerebral injury on DWI was seen in 32 of 41 patients; the median number of lesions per patient was 7, and the median total lesion volume was 10.62 ml (range 0 to 522 ml). Overall, no significant associations were noted between AHA plaque type and downstream cerebral injury (Table 2). However, the presence of fibrous cap rupture was associated with a higher total DWI burden at presentation, and a higher number of DWI lesions overall, compared with all other plaque features (p < 0.05 for both) (Table 2, Fig. 5). In addition, patients with surface rupture also had higher total cerebral FLAIR signal at follow-up (p < 0.05) (Table 2). No DWI lesions were noted in the control group, and no significant associations were found in the control group between plaque characteristics and FLAIR signal.

**DISCUSSION**

This study used MRI at 3-T to undertake combined carotid artery plaque and brain imaging in patients presenting acutely with minor stroke or TIA. In this group of high-risk patients, features of
complex (AHA type VI) plaque were found more frequently than in a matched cohort of patients with asymptomatic carotid artery disease. Specifically, fibrous cap rupture was more common in the symptomatic group and was associated with more extensive downstream brain injury (quantified by using DWI). Although current treatment algorithms incorporate measures of the degree of stenosis, the majority of cases of symptomatic AHA type VI plaque were associated with <70% luminal stenosis on ultrasound, the current cutoff for surgical endarterectomy. Compared with previous studies, the current investigation combines important new insights gained from 4 distinctive approaches: 1) patients were imaged in the first hours of presentation (i.e., close to the index event, corresponding to the period of highest risk of recurrence); 2) a “stable” control group matched for clinical indices and for degree of luminal stenosis was included; 3) follow-up scans were conducted to define changes over time; and 4) the pathological significance of the MR features of carotid plaque was investigated by quantification of downstream brain injury.

A majority of patients with acute neurological symptoms showed evidence of plaque instability in the ipsilateral carotid artery (AHA type VI plaque [54%]). A further large proportion of symptomatic patients had plaque that demonstrated “vulnerable” or “high-risk” features but no signs of acute rupture (AHA types IV/V [29%]). These findings are in keeping with earlier histological analyses of plaques removed at carotid endarterectomy. For example, Redgrave et al. (28) analyzed 526 carotid plaques from patients undergoing endarterectomy after acute neurological symptoms and found that 59% of patients had ruptured plaque, similar to the rate seen here. In patients undergoing carotid endarterectomy...
ectomy, with preoperative carotid MRI, Yuan et al. (15) described an increased incidence of MRI-defined fibrous cap rupture of 70%; patients in whom ruptured cap was identified were 23 times more likely to have suffered a TIA or stroke in the preceding 90 days.

Studies of patients undergoing carotid endarterectomy are inevitably biased toward severely stenosed arteries. Although it is well established that degree of carotid stenosis predicts risk when the stenosis is >70%, the relationship between stroke risk and lesser degrees of stenosis is weaker (29). Carotid ultrasound imaging does not provide detailed information on plaque morphology or composition, and it is possible that important pathology in mild to moderately stenotic plaque is overlooked. More refined characterization of the arterial wall may allow stratification of risk and suggest differential treatment pathways accordingly. In symptomatic patients in the present study, 55% of AHA type VI plaques were found in lesions of <70% stenosis. These findings are consistent with the recent report of Parmar et al. (22), who found that type VI plaque identified with acute MRI at 1.5-T was associated with ipsilateral TIA and ischemic stroke.

The present study for the first time uses MRI systematically to connect specific features of acutely symptomatic carotid plaque with burden of brain injury. The association of ruptured fibrous cap and downstream infarction suggests that stratification of patients on the basis of MRI plaque characteristics may be of benefit in future intervention trials, as has been suggested by previous histological (30) and ultrasound (31) studies. Long-term studies are underway that aim to understand the association between features of plaque vulnerability on MRI and the risk of future cardiovascular events, independent of the degree of luminal stenosis (18).

The natural history of acutely symptomatic carotid plaque was evaluated by using interval imaging. Changes over time have previously been inferred by comparing features such as cap rupture, macrophage content, lipid-rich core, and calcification in endarterectomy samples obtained from patients at various time intervals after an acute event (28). To the best of our knowledge, this has not been attempted previously by serial imaging. Strikingly, even with the high-resolution and signal-to-noise ratio offered by 3-T MRI, a large majority of vulnerable (AHA type IV/V) and unstable (AHA type VI) plaques did not show any evidence of change in the initial weeks after acute stroke or TIA. This finding is consistent with the persistence of increased risk of recurrence of same-territory stroke within the first month of acute first presentation and may suggest that a ruptured plaque remains as a nidus for...
thrombus formation in the early stages. The data are also consistent with a previous study in which only 4 of 28 patients with ruptured coronary artery plaques demonstrated healing after 1 year, as assessed by using intravascular ultrasound (32). Although plaque rupture is thought to be one method by which atherosclerotic plaque disease progresses (33), the current data suggest that such stepwise progression does not occur commonly in the short term. Further long-term follow-up will be needed to determine if some ruptured plaques go on to heal at a later stage.

Although ultrasound (34) and CT (35) studies have attempted to link carotid plaque characteristics with the extent of cerebral injury in patients with stroke, these studies have not been conducted during the acute phase of presentation. Furthermore, these modalities cannot provide the detailed plaque characterization afforded by 3-T MRI. The present study related the detailed plaque findings with quantitative measures of acute and chronic cerebral injury. No relationship could be established between the presence of conventionally defined AHA type VI plaque and the extent of ipsilateral cerebral injury, in either the acute or chronic phase. However, when acute infarcts were quantified by using DWI, the presence of ruptured fibrous cap was associated with both an increased number of DWI lesions and a greater total DWI load. Surface rupture was also associated with a higher overall volume of established infarcts quantified by FLAIR injury at follow-up.

**Study limitations.** Twenty-seven percent of patients in the acute group were unable to attend for follow-up scans. Of these patients, the mean age was higher (83 years; p < 0.05) and the mean Barthel score at presentation was lower (55; p < 0.01) than those who did return. Thus, those who were unable to return were more elderly and had experienced more severe disability after their stroke and were unable to undergo what was an elective follow-up study.

At the commencement of this real-world study, administration of gadolinium-based contrast agents was not permitted because the majority of patients presented with an estimated glomerular filtration rate <60 ml/min. A previous study by Cai et al. (36) found that use of gadolinium contrast can enhance the definition of intact fibrous cap, although that study deliberately excluded patients with fibrous cap rupture. We used the parameters described by Hatsukami et al. (10), which do not include the use of gadolinium contrast, to confirm fibrous cap rupture. Therefore, it is possible that detection of fibrous cap rupture may have been further improved by the use of gadolinium contrast, although its use is likely to be contraindicated in a significant number of elderly patients with established vascular disease.
CONCLUSIONS

Use of high-resolution MRI at 3-T to characterize carotid plaques of patients within 7 days of minor stroke or TIA was feasible and showed a higher proportion of complex AHA type VI plaques compared with asymptomatic control patients. Greater than 50% of complex plaques were found in arteries of <70% luminal stenosis. Plaque rupture was associated with increases in both DWI and FLAIR lesions in the brain. These findings may provide a basis for stratification of patients acutely according to lesion type and not merely by the extent of luminal narrowing.

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