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Carotid intraplaque hemorrhage in patients with greater than fifty percent carotid stenosis was associated an acute focal cerebral infarction

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Abstract

Objective: The purpose of this study was to assess associations between acute focal cerebral infarction of anterior circulation and carotid intraplaque hemorrhage (IPH) on magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) in patients with acute neurologic symptoms. *Methods:* From January 2013 to August 2017, 397 patients *(median age, 76 years; male, 78.6%)* with acute focal cerebral infarction on diffusion weighted imaging (DWI) were evaluated to determine the maximal wall thickness of the carotid artery, and to look for IPH on carotid MPRAGE sequences. Carotid plaques were defined as carotid artery wall thickness greater than 2 mm in at least two consecutive slices. IPH was defined as the presence in a carotid plaque of MPRAGE signal intensity greater than 200% of the intensity of adjacent muscle. *Results:* Of these patients with focal cerebral infarction, 165 patients of 195 carotid plaques were included this study. Sixty one (31/3%) carotid plaques of 50 (30.3%) patients were detected MPRAGE positive IPH. Maximal carotid wall thickness and degree of carotid stenosis were significantly higher in the MPRAGE positive group. MPRAGE positive IPH in patients with greater than 50% carotid stenosis was associated with an increased risk of an acute stroke event ($p < 0.001$), and a 2.64-fold increase in the relative risk of an acute focal stroke, compared to patients with MPRAGE negative scans.
Conclusions: Carotid MPRAGE positive IPH in patients with greater than 50% carotid stenosis was associated with acute focal cerebral infarction. MPRAGE positive patients showed higher maximal carotid wall thickness and a higher percentage of carotid stenosis.

Keywords: Carotid artery; Magnetic resonance imaging (MRI); Intraplaque hemorrhage; Stroke

INTRODUCTION

Major identified causes of acute ischemic stroke include carotid atherosclerotic disease, cardio-embolic sources, microvascular disease, aortic arch atheroma, and idiopathic factors.[1] Extracranial carotid artery stenosis is considered a causative factor in 20%-30% of all strokes.[2-4] Progression of carotid atherosclerosis is frequently attributed to factors affecting the plaque itself, such as intraplaque hemorrhage (IPH), lipid deposition and necrosis, ulceration, thin fibrous caps, and plaque disruption.[1,5-7] These factors correspond to American Heart Association Type IV carotid plaque classification. In addition, IPH is associated with a number of factors, including a lipid-rich necrotic core (LRNC), rapid plaque growth, instability, rupture, and subsequent embolization; and carotid stenosis.[5,8]

High-resolution MRI, which demonstrates excellent tissue contrast and spatial resolution, has superior ability to delineate composition and structure of the carotid plaque, including the presence of a fibrous cap, LRNC, the presence of calcium deposition, and intraplaque hemorrhage.[5,6,9-11] Historically, T1-weighted sequences and time-of-flight (TOF) MRI were used to detect IPH as high intensity signals within the carotid wall.[12,13] However, hyperintense areas on T1-weighted MRI sequences or TOF MRI can be seen with other plaque alterations, such as lipid deposition or plaque necrosis.[13-15] Alternative techniques proposed for more accurate detection of IPH include heavily T1-weighted techniques such as the magnification-prepared rapid acquisition with gradient-echo (MPRAGE) sequence.

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Ota *et al*.[16] reported that MPRAGE sequences demonstrated higher diagnostic capability in detecting IPH compared with conventional T1-weighted sequences or TOF MRI imaging.

Many papers have reported that carotid plaque with a thinned or ruptured fibrous cap, IPH, large LRNC, and large maximum wall thickness by MRI were associated with the occurrence of subsequent cerebrovascular events.[17-19] A recent meta-analysis found that IPH is associated with an approximately 6-fold higher risk for cerebrovascular event.[19] McNally *et al*.[20] performed standard MRI/MRA protocols and included carotid MPRAGE sequences in patients with suspected acute stroke. These authors reported that a carotid MPRAGE positive signal was associated with an increased risk of subsequent ipsilateral cerebral ischemic events, as detected by brain diffusion tensor imaging. However, they included patients without carotid plaque and with lobar infarction in their study. Consequently, we postulated that acute stroke related to carotid artery plaque may occur through two mechanisms: (1) focal infarction related to carotid plaque rupture and migration of plaque components; and (2) migration of a massive thrombus related to severe stenosis of the proximal carotid artery, leading to a lobar infarction. As a result, our study only included subjects with acute focal infarction, to investigate whether MR positive IPH contributes to acute focal cerebral infarction through mechanism. Our study sought to assess correlations between acute focal cerebral infarction and IPH on MPRAGE MRI sequences, in patients with acute ischemic strokes confined to the ipsilateral carotid distribution.

METHODS

Patients

This study was conducted with Institutional Review Board approval. Informed consent was waived by our Institutional Review Board. From January 2013 to August 2017, 3,780 consecutive patients with suspected acute stroke were imaged according to our MR stroke protocol, which included diffusion weighted MR imaging (DWI) and carotid MPRAGE sequences. Of these patients, 794 carotid arteries of 397 patients were eligible for data analysis (Figure 1).

Stroke MR and MPRAGE sequences

All patients with acute neurological symptoms were immediately examined with baseline cranial CT scans in the emergency department to rule out intracranial or subarachnoid hemorrhage. MR examinations were then obtained using an Achieva 3.0-T Scanner (Philips Medical Systems, Best, Netherlands) with a 16-channel head coil. According to our stroke protocol, MR imaging was performed immediately following CT

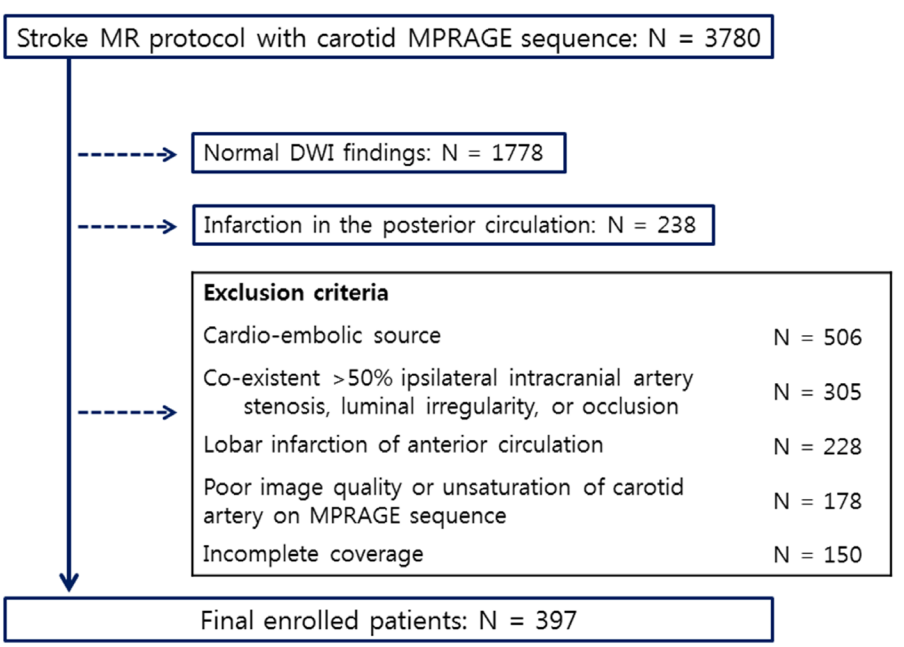

Figure 1. Flow diagram of the current study

scanning to evaluate the carotid arteries, using the following techniques: (1) cerebral DWI, (2) three-dimensional TOF (3D-TOF) MRA of the intracranial arteries, (3) susceptibility-weighted imaging (SWI), (4) perfusion-weighted imaging (PWI), (5) contrast-enhanced MRA, and (6) an additional MPRAGE sequence. The total scan time was approximately 20-30 minutes per patient.

DWI was performed using a spin-echo type echo planar imaging (EPI) sequence with b values of 0, 500, and 1,000 sec/mm^2 along all 3 orthogonal axes. Other parameters were as follows: TR/TE=3000/80ms, FA=90°, sensitivity encoding=3, FOV=220×220 mm, matrix=128×128, section thickness/gap=5 mm/30%, and scanning time=35–38 seconds. Axial dynamic gradient-echo echo-planar PWI was performed after tracking a bolus of 0.03 mmol/kg gadofosveset trisodium (Vasovist, Schering, Berlin, Germany). Acquisition parameters were as follows: TR/TE=1850/35 ms, FA=40°, FOV=230×230 mm, matrix=132×132, and section thickness/gap=5 mm/30%. After image reconstruction and processing, PWI data were transferred to a workstation (ADW 4.2; GE Healthcare, Milwaukee, WI, USA). For MRA, 3D multi-slab TOF-MRA from the petrous portion of the ICA was generated with the following parameters: TR/TE=23/3.45 ms, FA=20°, FOV=200×200 mm, matrix=488×249, sensitivity encoding factor=2.5, slice thickness=1.2 mm, echo train length (ETL)=1, and number of average=1. Contrast enhanced MRA of the entire cranium, starting at the aortic arch, was performed using coronal planes with a 3D spoiled gradient echo sequence optimized for high spatial resolution. The following imaging parameters were used in these studies: TR/TE=4.9/1.7 ms, FA=27°, slice thickness=1.0 mm, matrix size=384×384, and voxel size =1×1×0.7 mm.

Image parameters were as follows for the 3D MPRAGE sequence, :TR/TE/TI=8.7/5.3/304ms, FA=15°, ETL=32, FOV=140×140mm, and matrix=216×192. Images were obtained from 20 mm below the carotid bifurcation to 20 mm above the carotid bifurcation, with slice thickness increments of 1.0 mm. TI time was chosen relative to the phase encoding acquisition to maximize contrast between hemorrhage and inflowing blood. Chemical fat saturation was used.

Image analysis

Two experienced neuroradiologists determined MPRAGE status in an objective manner independent of brain MR results. Consensus interpretation was used for the final analysis when separate interpretations differed. Only MPRAGE images of the carotid bifurcation and the proximal internal carotid artery were used for quantitative evaluation of image parameters.

Carotid plaques were defined as carotid artery wall thickness greater than 2 mm in at least two consecutive slices on MPRAGE imaging. Interpretation of MPRAGE images for detection of carotid plaque and maximal wall thickness was done using plaque analysis software (MRI-PlaqueView, VP Diagnostics, Seattle, WA). Data was then analyzed by researchers who were trained in the evaluation of carotid plaque MRI and blinded to study goals. For MPRAGE positive IPH analysis, signal intensities were measured in a 6- to 8-mm^2 circular region of interest over the carotid plaque. IPH was defined as being present in a carotid plaque when the signal intensity on MPRAGE imaging was greater than 200% of the intensity of adjacent muscle in at least two consecutive slices. This method has been previously validated with histologic confirmation using a 3.0 T MRI machine.[16] Maximal wall thickness was defined as the carotid plaque thickness at the point of the most severe stenosis on MPRAGE images. Carotid plaque stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria based on contrast-enhanced carotid MR angiography and divided into groups having either 1%-49% stenosis (<50%), or 50%-99% stenosis (≥50%).

A DWI positive signal was defined as a hyperintense signal on the DWI image with an associated decrease in signal on the apparent diffusion coefficient map corresponding to an acute ischemic event at the time of the scan. We classified acute ischemic events based on arterial distribution patterns: ipsilateral ICA region, ipsilateral basal ganglion region, and posterior circulation. Only DWI positive events in the ipsilateral ICA territory were deemed to be DWI positive. Two neuroradiologists, blinded to the carotid MPRAGE results, interpreted all DWI images. Final interpretations were reached by consensus when initial readings diverged.

Statistical analysis

Continuous values were expressed as medians and/or ranges while categorical data were expressed as counts and percentages. Continuous and categorical variables were compared between groups using the Mann-Whitney test

Table 1: Patient demographics

	Patients (n = 397 patients)	Carotid plaque		
		(+) (n = 165)	(–) (n = 232)	*p*
Patient demographics				
Median age, y	72	75	71	
Age range, y	55 – 88	58 – 87	55 – 88	
Sex (male)	312 (78.6%)	133 (80.6%)	179(77.1%)	0.479
Carotid risk factor				
Diabetes	119 (30.0%)	47 (28.5%)	72 (31.0%)	0.675
Hypertension	238 (59.9%)	93 (56.4%)	145(62.5%)	0.269
Current smoking	138 (34.8%)	63 (38.2%)	75 (32.3%)	0.272
Hyperlipidemia	112 (28.2%)	53 (32.1%)	59 (25.4%)	0.183
Previous heart disease	87 (21.9%)	38 (23.0%)	49 (21.1%)	0.748
Previous stroke history	76 (19.1%)	36 (21.8%)	40 (17.2%)	0.310

and Fisher's exact test. Likelihood ratios from a 2×2 table were used to estimate the relative risk of a cerebrovascular ischemic event in patients with MR-positive IPH lesions, using a 95% confidence interval (CI). All calculations were made with SPSS Version 23 for Windows. Statistical significance was defined as a P value of less than 0.05.

RESULTS

A total of 397 patients (median age, 72 years; range, 45 – 88 years) with acute focal cerebral infarctions in the anterior circulation qualified for study inclusion. Of 794 carotid arteries in these patients, 195 arteries of 165 patients had atherosclerotic plaque on MPRAGE sequence. Demographic data between carotid plaque group and normal carotid artery group are shown in Table 1. The demographic data between two groups was similar.

Of 397 patients with DWI positive focal cerebrovascular events, 189 had a right sided territorial focal infarction, 208 had a left territorial focal infarction. None had bilateral focal infarctions. Of 165 patients with carotid atherosclerotic plaque, 58 had plaque on the right side, 73 had plaque on the left side, and 32 had plaque on both sides. Of these patients, 50 (30.3%) had an MPRAGE-positive IPH in the carotid atherosclerotic plaque. Twenty one patients had a right sided MPRAGE-positive carotid IPH, 18 patients had a left sided MPRAGE-positive carotid IPH, and 11 patients had MPRAGE-positive carotid IPH bilaterally. 61 carotid plaques (31.3%) were detected MPRAGE positive IPH.

Data on the carotid plaque findings for MPRAGE-positive and MPRAGE-negative patients are shown in Table 2. Maximal carotid wall thickness and the degree of carotid stenosis were significantly higher in the MPRAGE-positive group.

Data regarding the relationship between MPRAGE-positive IPH and territorial focal infarctions in patients with carotid atherosclerotic plaque are shown in Table 3. MPRAGE-positive

Table 2: Carotid plaque findings for MPRAGE-positive and MPRAGE-negative patients

	165 patients with 195 carotid plaques		
	MPRAGE (+)	MPRAGE (-)	*p*
Patients	50	115	
Carotid arteries	61	134	
Maximal wall thickness	4.75± 1.38	4.01 ± 0.89	<0.0001
Stenosis (NASCET criteria)	45.6 ± 33.8	30.5 ± 27.1	0.001

Note – MPRAGE = Magnetization-Prepared Rapid Acquisition with Gradient-Echo. NASCET = North American Symptomatic Carotid Endarterectomy Trial

Table 3: Data of MPRAGE-positive carotid IPH in patients with carotid atherosclerotic plaques

	Total (n = 195)		< 50% carotid stenosis (n = 129)		≥50% carotid stenosis (n = 66)	
	MPRAGE (+)	MPRAGE (-)	MPRAGE (+)	MPRAGE (-)	MPRAGE (+)	MPRAGE (-)
Carotid arteries	61	134	29	100	32	34
Matched DWI (+)	35	69	13	61	22	8
Mismatched DWI (+)	26	65	16	39	10	26
Prevalence of MPRAGE (+),%	31.3		22.5		48.5	
Sensitivity, % (95% CI)	57.4 (44.1 – 70.0)		44.8 (26/5 – 64.3)		68.8 (50.0 – 83.9)	
Specificity,% (95% CI)	48.5 (39.8 – 57.3)		39.0 (29.4 – 49.3)		76.5 (58.8 – 89.3)	
Accuracy,% (95% CI)	51.3 (44.0 – 58.5)		40.3 (31.8 – 49.3)		72.7 (60.4 – 83.0)	
Relative risk (95% CI)	1.178 (0.772 – 1.797)		0.504 (0.317 – 1.149)		2.640 (1.494 – 4.665)	
p value	0.536		0.139		<0.0001	

Note – MPRAGE = Magnetization-Prepared Rapid Acquisition with Gradient-Echo. CI = confidence interval

IPH in patients with high-grade carotid stenosis was associated with an increased risk of a DWI-positive acute focal stroke event ($p < 0.001$) (Figure 2). In patients with high grade carotid stenosis, the relative risk of an acute focal stroke event was 2.64-fold higher in patients with MPRAGE-positive IPH than in patients with MPRAGE-negative carotid studies.

DISCUSSION

Our study showed that maximal carotid wall thickness and degree of carotid stenosis were significantly higher in the MPRAGE-positive IPH group. MPRAGE-positive IPH in patients with high-grade carotid stenosis was associated with an increased risk of a DWI-positive acute focal stroke event. MPRAGE-positive carotid IPH is not associated with acute focal infarction

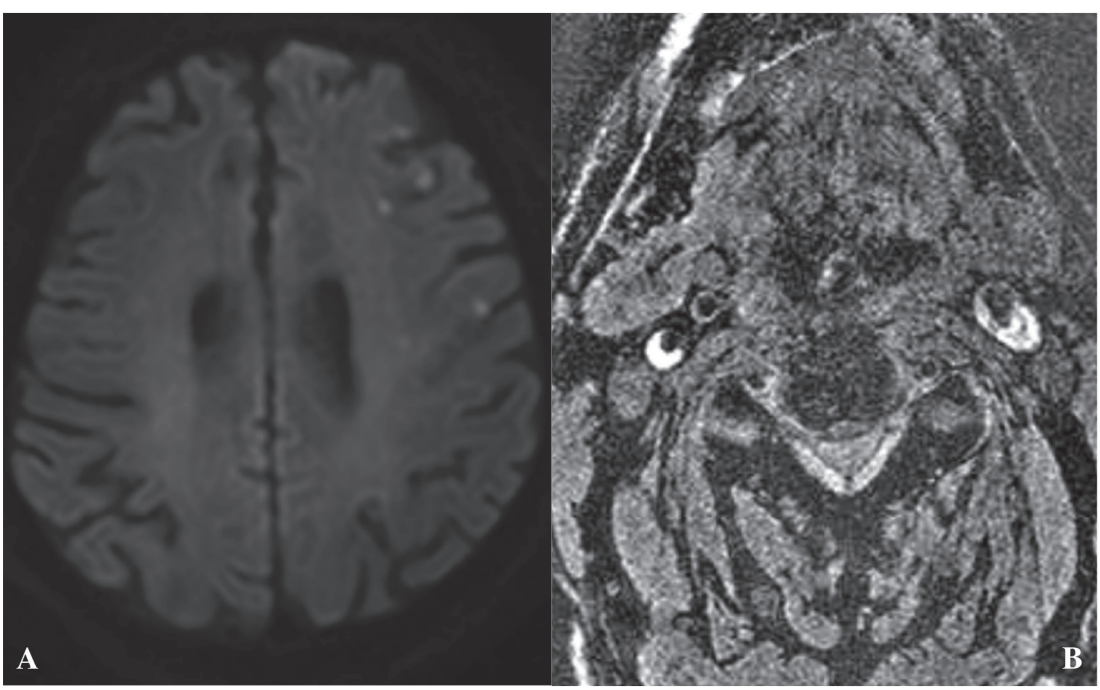

Figure 2. A 64-year-old man with an acute multifocal embolic infarction in the left frontal cortex. (A) Diffusion-weighted image (DWI) shows multifocal diffusion restriction in the left frontal cortex. (B) Magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) images shows a bilateral high signal intensity in the proximal carotid artery. Note the MPRAGE-positive carotid artery coupled with left territorial stroke events on DWI.

in patients with less than 50% carotid stenosis.

Recent prospective studies have found a relationship between the presence of IPH at baseline and the development of ischemic stroke in both previously asymptomatic and previously symptomatic patients.[17-19] IPH is associated with plaque progression and consequently induces luminal narrowing. Thus IPH may serve as a measure of risk for the development of future ischemic stroke.[5,6] Recently, McNally *et al*.[20] performed standard cerebral MRI and MRA examinations and included carotid MPRAGE sequences for evaluation of carotid IPH in patients with suspected acute stroke. Carotid MPRAGE-positive signal was associated with an increased risk of cerebral ischemic events in the related cerebral circulation, as detected by brain diffusion tensor imaging, in patients with either mild or high-grade stenosis. Prior to this article, another study had reported that the relative risk of association of carotid IPH and regional acute cerebral infarction, in patients with acute neurological symptoms, was increased in high-grade stenosis.[21] However, neither of these papers determined the distribution of infarction, such as whether it was lobar or focal. Also, McNally *et al*.[20] included patients without carotid plaque for statistical analysis. Therefore, we performed our study according to the following premises: (1) The stroke pattern related to carotid IPH might be a focal infarction because of the migration of plaque lipid content secondary to plaque rupture and plaque progression. (2) Of those patients with carotid plaque, IPH might constitute a higher risk factor for acute focal infarction.

Previously a T1-weighted MRI sequence was commonly used to detect IPH for clinical examinations. Degradation of hemoglobin into methemoglobin in the intraplaque hemorrhage results in T1 shortening and causes high signal intensity on T1-weighted images. When employing T1-weighted sequences, a black-blood fast spin-echo sequence with short repetition time and a bright-blood spoiled gradient-echo sequence are commonly used for clinical examinations.[16] The MPRAGE sequence is an alternative technique for IPH detection. This sequence was recently optimized for IPH detection at 3.0 Tesla magnetic field strength, with field-dependent changes in T1 in the vessel wall and blood taken into account.[22] MPRAGE imaging facilitates suppression of signals from background tissues by means of a nonselective inversion pulse and spectrally selective water excitation or fat suppression.[22,23] The uniformly hypointense signal of background tissue and the suppressed blood signal facilitate image interpretation and result in better diagnostic performance of MPRAGE sequences. Our study used the MPRAGE MRI sequence due to its higher sensitivity and specificity in detecting hemorrhage compared with conventional techniques.

Two recent studies reported changes in carotid IPH in non-hospitalized patients using serial MR imaging.[24,25] Pletsch-Borba *et al*.[24] studied changes in several carotid plaque parameters, such as IPH, carotid artery calcification, and plaque necrotic core size, over a 4 year follow-up study period using serial MR imaging. All plaque components significantly changed over time. New development of IPH during the follow-up period occurred in 64 of 346 patients (18.5%), and IPH regression was seen in 18 of 50 patients (36%). The factors most strongly associated with the incidence of IPH were use of antihypertensive drugs and severe hypertension. Another study measured serial changes in IPH in non-hospitalized patients with mild carotid stenosis (NASCET criteria < 30%).[25] Visual progression of IPH volume was present in 14 of 53 carotid MRI studies (26%), and visual regression was present in 16 of 53 studies (30%).

A higher degree of carotid stenosis is a well-known risk factor for ischemic stroke. Randomized controlled trials have demonstrated the benefit of carotid endarterectomy in patients with symptomatic severe carotid stenosis.[26] Sixty six of 195 carotid plaques studied (33.8%) had high grade stenosis by NASCET criteria (≥50%) as shown in Table 3. There was significantly higher maximal carotid wall thickness and percentage of carotid artery stenosis, in the MPRAGE-positive IPH group compared to the MPRAGE-negative IPH group. However, the percentage of stenosis itself did not have a high predictive value. Altaf *et al*.[26] showed that the highest cerebrovascular event rate and shortest time to a subsequent event were observed in patients with IPH and severe stenosis. Samm *et al*.[19] reported that symptomatic patients with greater than or equal to 50% carotid stenosis and IPH have a particularly high risk of recurrent cerebrovascular events. The current study results are compatible with those of previous studies.[19,27] In our report, MPRAGE-positive IPH in patients with high-grade carotid stenosis was associated with increased risk of a DWI-positive acute focal stroke event. The relative risk of an acute focal stroke event in a patient with an MPRAGE-positive carotid was 2.64-times higher than that of a patient with an MPRAGE-negative carotid. For patients with less than 50% carotid stenosis, there was no statistically significant difference

between the MPRAGE-positive IPH group and MPRAGE-negative IPH group regarding the risk of acute stroke on DWI. These results are in contrast with those of a previously published study by McNally *et al*.[20], who reported that the risk of concurrent ischemic events was increased for all stenosis categories in their emergency stroke evaluations. Thus further research is required to evaluate the potential benefit of IPH detection by MRI in mild to moderate carotid stenosis.

Our study had some limitations. First, the MPRAGE sequences used in this study required approximately 4 minutes to perform. Scan time in acute stroke MR examination has important implications for treatment timing and prognosis. The scan time for MPRAGE imaging is longer than what is required for other imaging methods, such as DWI, susceptibility weighted imaging (SWI), perfusion weighted imaging (PWI), or TOF-MRA. Second, MR data was analyzed at a single point in time. Serial changes in IPH were not evaluated with repeat MR examinations. Previously, Yamada *et al*.[17] reported that carotid plaque signal hyperintensity on T1-weighted images persisted in arteries over a period of months. Third, only focal cerebral infarction was included while lobar infarction on DWI was excluded. We reasoned that lobar infarction related to carotid plaque might occur as the result of the migration of intraluminal thrombus in patients with severe stenosis of the carotid artery. Therefore, this study only included subjects with acute focal cerebral infarction, in order to investigate whether MPRAGE-positive IPH contributes to that occurrence. Fourth, our report focused on IPH in the carotid plaque. Common causes of acute ischemic stroke not related to carotid artery pathology include atheroma of major arteries, cardio-embolic sources, microvascular disease, and idiopathic factors. Also, the incidence of acute ischemic stroke in the setting of unstable carotid plaques, such as those with IPH, fibrous cap ruptures, or ulcers, is relatively low compared to other causes. Lastly, hemorrhage age and location within the plaque were not investigated. A previous study demonstrated significant differences in the composition and morphology of symptomatic and asymptomatic plaques.[28] While this information would potentially improve risk stratification, it was not specifically analyzed in this study.

In conclusion, patients with MPRAGE-positive IPH in their carotid plaques and greater than 50% carotid stenosis were shown to have a significantly increased risk of acute focal ischemic cerebral infarctions. The use of MPRAGE sequences in stroke MR examinations may lead to more accurate treatment determinations in patients presenting with symptoms of acute stroke.

DISCLOSURE

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Conflict of interest: None

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