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Research article

Dynamic change of carotid intraplaque hemorrhage volume in subjects with mild carotid stenosis☆

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ABSTRACT

Background and Purpose: Early detection of intraplaque hemorrhage (IPH) in the carotid artery is important as it is correlated with an increased risk of cerebral ischemic events. We examined changes in IPH with magnetic resonance imaging (MRI) over an extended follow-up period in patients with mild carotid stenosis.

Materials and Methods: From November 2013 to November 2015, we retrospectively reviewed cerebral MRI of 2036 patients, including magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequences obtained with a 3.0 T (T) MRI unit. An experienced neuroradiologist reviewed all studies and found 38 patients with carotid IPH and carotid stenosis that were categorized as mild (< 30%), according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Twenty-five patients agreed to join this study and signed informed consent for (MPRAGE) sequence imaging. We used semi-automated software to measure IPH volume on both the initial and follow up scans.

Results: The median follow-up time of patients with mild carotid stenosis and IPH was 33.3 months. IPH volume increased in 10 of 27 carotid arteries (37.0%), with a mean volume increase of 42.6 ± 44.0 mm^3. IPH volume decreased in 17 of 27 carotid arteries (63%), with a mean volume decrease of 17.2 ± 22.8 mm^3. Two patients without IPH at baseline showed IPH development on follow-up imaging. There were no significant differences in patient demographics between the two groups.

Conclusions: Carotid IPH volume in subjects with mild carotid stenosis can change over time and may not be correlated with any typical patient demographics.

1. Introduction

Intraplaque hemorrhage (IPH) of carotid atherosclerotic deposits has been established as a primary cause of carotid plaque instability [1–4] and plays a critical role in the progression of atherosclerotic disease [5,6]. Repeated bleeding into the plaque may cause progression of atherosclerosis by increasing lipid core and plaque volume and create new destabilizing factors [5–7]. Other studies have shown that carotid intraplaque hemorrhage, as identified by magnetic resonance imaging (MRI), is associated with greater risk for cerebrovascular events [8–11]. Saam et al.[12] observed that the presence of IPH was associated with a 6-fold higher risk for cerebrovascular events, and further found that the annualized cerebrovascular event rate in subjects with detectable IPH was 17.71%, compared with just 2.43% in patients without IPH. For these reasons, early detection of intraplaque hemorrhage of the carotid artery is very important.

Cross-sectional studies have shown the relationship between carotid plaque components and lipid lowering therapy [5,7,13–16]. In particular, changes in IPH are important determinants of plaque progression and a patient's subsequent clinical course. Several authors have found that IPH was related to an increase in both necrotic core size and plaque burden in advanced carotid stenosis [5,7,17]. However other studies have reported that IPH either remained stable or underwent dynamic changes during the follow-up period [18,19]. These papers either used various types of T1-sequence MRI techniques for detection of IPH or included subjects with variable carotid stenosis. Our study sought to determine changes in IPH volume over 2 or more years of follow-up in asymptomatic patients with incidental mild eccentric plaque.

2. Materials and methods

2.1. Study population

This study was approved by the Institutional Review Board of our institute, and informed consent was obtained from all individuals or

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their caregivers. Between November 2012 and November 2015, 2036 outpatients, whose standard cerebral MRI protocol included both carotid magnification-prepared rapid acquisition with gradient-echo (MPRAGE) sequence and carotid contrast-enhanced MR angiography (CE-MRA) data, were studied. Imaging was performed on a 3.0 T MRI machine (Achieva; Philips Healthcare, Best, The Netherlands). All patients were symptomatic and underwent outpatient cerebral MRI for evaluation of complaints such as headache, dizziness, giddiness, vertigo, or possible tumor. One hundred eighteen patients had IPH on MPRAGE MRI sequences. Of this group, 30 patients with mild eccentric plaque of less than 30% by NASCET criteria were selected for this study. We were able to obtain informed consent from 25 patients for follow-up examinations. Two patients, one of whom died, were lost to follow-up, and the studies of 3 patients were excluded because of poor image quality.

2.2. MR imaging protocol

Our MR protocol included standard cerebral MRI with carotid CE-MRA and carotid MPRAGE imaging. Routine CE-MRA was performed in the coronal plane using a T1-weighted spoiled gradient-echo sequence optimized for high spatial resolution and a short acquisition time. The following parameters were used: TR/TE, 3.4/1.2 ms; flip angle (FA), 21; slice thickness, 1.0 mm; gapless, matrix, 448 × 280; field of view (FOV), 273 × 350 mm; number of slices, 80; and acquisition time, 90 s (60 maximum-intensity-projection reformatted images). For carotid MPRAGE, segmental acquisition was performed with sequence repetition time, inversion preparation time (TI), and phase encoding order adjusted to optimally identify IPH as a hyperintense feature. Image parameters were as follows: TR/TE/TI, 8.7/5.3/304 ms; FA, 15; echo train length, 32; FOV, 140 × 140 mm; and matrix, 216 × 192. Images were obtained from 20 mm below the carotid bifurcation to 20 mm above the carotid bifurcation in slice thickness increments of 1.0 mm. TI time was chosen relative to phase-encoding acquisition to maximize the contrast between hemorrhage and inflowing blood. Chemical fat saturation was used.

2.3. Quantitative assessment of change in IPH

MR-positive IPH was defined as the presence of a hyperintense intraplaque lesion, with signal intensity greater than 200% of that of the adjacent muscle, for at least 2 consecutive sections on MPRAGE imaging. For quantitative analysis of IPH volume, we used semi-automated software (Rapidia; Infinite, Seoul, Korea). IPH segmentation was performed with a piecewise smooth regional level set method. A region of interest was then delineated by manually drawing around the outer boundary of the carotid artery. IPH volume was measured as the area of signal intensity greater than 200% of the intensity of the adjacent muscle (Fig. 1).

2.4. Risk factors of change in IPH

Cardiovascular risk factors were assessed before the baseline and follow-up MRI scans. We included the following parameters in the study: age, gender, hypertension, diabetes mellitus, hypercholesterolemia, body mass index, current or past smoking history, and prior history of cardiovascular disease or stroke. *Additionally, we reviewed the medication history of patients and included antihypertensive drug and statin use in the study (Rev#2-1).*

2.5. Statistical analysis

Our analysis showed that some patients had progression of IPH and some patients had IPH regression. We evaluated differences between these two groups using the Student *t*-test for continuous variables and the Fisher test for categorical variables. We applied linear regression to analyze factors which correlated with changes in IPH volume for all carotid arteries with IPH at baseline. Data on continuous variables were expressed as mean ± standard deviation (SD). All calculations were made with SPSS Version 23 for Windows. Statistical significance was defined as a P value of less than 0.05.

3. Results

Table 1 shows clinical characteristics of the 25 patients in the study population. The average age of the patients was 70.5 ± 7.2 years, and 85.2% were men. Follow-up time was 33.0 ± 6.7 months. For the group as a whole, baseline carotid stenosis was 8.2 ± 10.5%. Of the 25 patients, 2 had bilateral carotid IPH, resulting in 27 carotid artery studies being included in this report.

Of 27 carotid arteries studied, 17 (63.0%) showed decreased IPH volume and 10 (37.0%) showed increased IPH volume during the follow-up period (Fig. 2). Table 2 compares the changes in carotid plaques between arteries in which IPH progressed and arteries in which IPH regressed over the follow-up period. The maximal thickness of the carotid wall in the total study population was subtly increased (0.4 ± 0.5 mm). Similarly carotid artery stenosis was also slightly increased (5.2 ± 7.2%, NASCET criteria). Mean IPH volume change in those arteries with IPH progression was 42.6 ± 44.0 mm^3, and mean IPH volume change in those arteries with IPH regression was –17.2 ± 22.8 mm^3 (Fig. 3 and 4). The change in maximal carotid artery wall thickness was similar in both IPH progression and IPH regression groups (0.5 ± 0.5 mm and 0.3 ± 0.5 mm respectively, $P = 0.182$). Similarly, the change in percentage of carotid stenosis between IPH progression and IPH regression groups was similar during the follow-up period (5.3 ± 8.5% and 5.1 ± 6.0% respectively, $P = 0.940$).

Of 25 patients in our study group, 2 showed decreased volume of baseline IPH on the original side of the carotid, and new IPH on the contralateral side during the follow-up period. Comparing the 2 patients with bilateral IPH, one showed regression of both carotids and the other showed the regression of IPH in the right carotid and progression of IPH in the left carotid. Of 21 patients with unilateral IPH volume change, 12 showed decreased IPH volume and 9 showed increased IPH volume during the follow-up period. There was no significant association between cardiovascular risk factors and changes in carotid IPH volume (Table 3). *However, the p-value of the previous cardiovascular event and antihypertensive drug use were 0.063 and 0.067, respectively, which was close to the p-value cutoff 0.05.(Rev#2-1)*

4. Discussion

This study demonstrated that carotid IPH in patients with mild carotid stenosis can undergo a variety of changes, including both progression and regression, without any change in the degree of carotid stenosis. Cardiovascular risk factors assessed were not significantly associated with these IPH changes. *However, the p-value of the previous cardiovascular event and antihypertensive drug use were close to the p-value cutoff, and these results are considered to be somewhat meaningful.(Rev#2-2)*

Carotid IPH is mainly thought to result from leakage through imperfect endothelial junctions in plaque associated neo-vascularization, and insufficient support by smooth muscle cells [4,20]. Carotid IPH may contribute to several biologic processes involved in local inflammation, including deposition of free cholesterol and release of proteolytic enzymes, which may result in plaque growth and plaque destabilization [21,22]. Although de Rotte et al. [23] reported that IPH was not related to either old or recent cortical and subcortical infarctions in patients with 30 to 69% carotid artery stenosis, the presence of IPH in meta-analysis studies is associated with an approximately a 4.59–5.6 fold higher risk for cerebrovascular events, compared to the risk for patients without IPH [8,12].