TITLE: Intraplaque hemorrhage on Magnetic Resonance Angiography: How often do signal abnormalities persist on follow-up imaging?

ABSTRACT

Background and Purpose: Intraplaque hemorrhage (IPH) in carotid atherosclerosis demonstrates increased signal on MRA images. Little remains known about how this signal changes on subsequent examinations.

Materials and Methods: A retrospective review was completed of patients that had IPH on a neck MRA between 1/1/2016 and 3/25/2021, defined as ≥200% signal intensity of the sternocleidomastoid muscle on MPRAGE images. Examinations were excluded if the patients had undergone carotid endarterectomy between examinations or had poor quality imaging. IPH volumes were calculated by manually outlining IPH components. Up to 2 subsequent MRAs, if available, were assessed for both the presence and volume of IPH.

Results: 102 patients were included, of which 90 (86.5%) were male. IPH was on the right in 48 patients (average volume = 174.0 mm^3), and on the left in 70 patients (average volume 186.9 mm^3). 22 had at least one follow-up (average 444.7 days between exams), and 6 had two follow-up MRAs (average 489.5 days between exams). On the first follow-up, 19 (86.4%) plaques had persistent hyperintense signal in the region of IPH. The second follow-up showed persistent signal in 5/6 plaques (88.3%). Most IPH volumes (17/22; 77.3%) decreased on the first follow-up (average change: -50.1 mm^3), whereas 4/6 (66.7%) increased between the first and second follow-up exams (average change: +22.7 mm^3).

Conclusions: IPH usually retains hyperintense signal on follow-up MRAs, possibly representing recurrent hemorrhage or degraded blood products. IPH volume changes are less predictable, and tend to decrease on the first follow-up, but increase on the second.

INTRODUCTION

Over the past decades, numerous high-risk markers have been identified in both histologic and imaging analyses of carotid artery atherosclerotic plaques.[1] These vulnerable plaque characteristics put patients at increased risk for both thromboembolic events and accelerated plaque growth, even in the setting of relatively mild luminal stenosis.[2] Intraplaque

hemorrhage (IPH) is the most well-established high-risk feature; it significantly increases the risk of ipsilateral neurologic ischemic events and acts as a potentiator of plaque growth.[3,4,5]

Advances in carotid plaque imaging have allowed for accurate non-invasive identification of IPH, with good correlation to histological specimens.[6] MRA is currently the gold standard for IPH detection, in which blood products appear as high-intensity signal on T1-weighted images.[7] Heavily T1-weighted sequences such as Magnetization Prepared-Rapid Gradient Echo (MPRAGE) are particularly adept at identifying the T1 shortening associated with intraplaque blood products.[8] Typically, IPH is detected by comparing the intraplaque signal intensity to the adjacent sternocleidomastoid muscle, allowing for highly accurate identification of plaque hemorrhage.[9]

Some prior studies have indicated that high signal intensity within the region of IPH can persist on follow-up imaging.[10] Yet, this subject remains mostly unexplored. The existing studies that have addressed this question have typically relied on now outdated MRA sequences.[11] This study therefore sought to determine how often hyperintense signal related to IPH persists on imaging in a cohort of patients with plaque hemorrhage seen on MRA.

MATERIALS AND METHODS

Study Population

This study proceeded following approval from the local Institutional Review Board. A retrospective review was completed of sequential patients that underwent MRA imaging of the cervical carotid vasculature between 1/1/2016 and 3/25/2021. Included patients had 1) MPRAGE images obtained as part of their study and 2) evidence of IPH in at least 1 carotid artery plaque based on the initial interpretation of the exam. Patients were excluded if no IPH was noted on re-analysis of the images. Individual MRA examinations were not included if the imaging was of poor quality (n=1), or if the patient had undergone a prior carotid endarterectomy (n=1).

MR Imaging Protocol

Neck MR imaging was typically performed on a 3T MRI scanner (GE 750, GE Healthcare, Milwaukee, WI) with a 16-channel head/neck/spine (HNS) coil. A 3D MPRAGE sequence was obtained with a/TE = 13.2 ms/3.2 ms, flip angle = 15°, slice thickness = 1 mm, number of

excitations = 2, TI = 304 ms, in plane spatial resolution = 0.63 mm × 0.63 mm, and acquisition time = 3 min 50 s. Both 1) 2D time of flight (TOF) and 2) gadolinium bolus carotid imaging acquired in the coronal plane were routinely performed. Most patients also underwent pre- and post-gad T1 fat-saturated CUBE imaging acquired in the coronal plane to assess for the presence of lipid-rich necrotic core (LRNC) and plaque enhancement; data regarding these findings is reported in a separate manuscript.

Image Analysis

All MRA examinations were reviewed by a single board-certified neuroradiologist. Each study was assessed for the presence or absence of IPH at the carotid bifurcation or ICA origin, defined as maximum intralesional signal intensity (SI) ≥200% of the adjacent sternocleidomastoid muscle.[12] The volume of each carotid artery IPH component was manually outlining the region of interest in the institution's PACS system (Visage, Visage Imaging Inc., San Diego, CA).

Up to two subsequent MRA examinations were evaluated for the presence of persistent hyperintense IPH-like signal. Note that this manuscript will refer to such findings as "persistent signal" rather than IPH, since it remains unproven what these abnormalities represent (see discussion for more details). If present, the volume of any persistent signal was similarly calculated using manual demarcation of the signal borders. If the initial IPH had been replaced by markedly hypointense ("jet black") signal, this was considered to represent calcifications.[1314]

Statistical Analysis

Means and standard deviations (STDs) were calculated for all continuous variables. Statistical calculations were performed using BlueSky Statistics software (Bluesky Statistics LLC, Chicago, IL, USA). Chi-square test was used to calculate differences between categorical variables. Any p-value below 0.05 was considered statistically significant.

RESULTS

Patient Cohort

Of 120 patients, 16 were excluded as no IPH was found during re-review of imaging, and 2 were excluded because imaging demonstrated large intra-luminal thrombi. 102 patients therefore made up the final patient cohort, with 204 total carotid arteries available for

analysis. Of these, 1 follow-up examination was excluded both because the imaging was of poor quality and because the patient had undergone a unilateral carotid endarterectomy between the initial and follow-up examinations. 88 (86.3%) were male. Average age was 73.5 (STD=9.0).

Imaging Findings

Of 204 carotid arteries, 118 (57.8%) had IPH: on the right in 48 patients and on the left in 70 patients; IPH was present significantly more often on the left side ($p<0.0001$). 86 (42.2%) carotid arteries had no IPH on initial imaging. Average volume of right-sided IPH was 174.0 mm^3 (STD=135.0), and average volume of left-sided IPH was 186.9 mm^3 (STD=198.0).

22 IPH positive plaques had at least one follow-up (average 444.7 days between exams), and 6 IPH positive plaques had two follow-up MRAs (average 489.5 days between the first and second follow-up exams). On the first follow-up, 19 (86.4%) plaques had persistent hyperintense signal in the region of IPH (**Fig. 1**). The second follow-up showed persistent signal in 5/6 plaques (88.3%). Most IPH volumes (17/22; 77.3%) decreased on the first follow-up (average change: -50.1 mm^3), whereas 4/6 (66.7%) increased between the first and second follow-up exams (average change: +22.7 mm^3). No patients demonstrated new IPH on a follow-up exam.

DISCUSSION

This study showed that hyperintense MPRAGE signal compatible with IPH usually persists on subsequent examinations. These signal abnormalities were observed on both the first and second follow-up MRAs, were which performed on average over 1 and over 2 years after the initial exam, respectively. Changes in IPH volume over time were less predictable, with most plaques showing decreased IPH volume on the first follow-up, but increased IPH volume on the second follow-up.

It is unclear what the observed persistent signal abnormalities represent. However, the most likely possibilities are recurrent intraplaque hemorrhage, stagnant proteinaceous remnants of lytic blood products, or some combination of both. Some authors have suggested that persistent signal at the site of plaque hemorrhage may be related to delayed degradation of blood products. Specifically, Takaya et al. proposed that the relative paucity of macrophages within a plaque's LRNC could help explain the slowing of the degradation process.[15]

Regardless, the results indicate that hyperintense MPRAGE signal should not serve as an indicator of acute/fresh hemorrhage. Instead, these signal abnormalities represent a marker of prior hemorrhage into the plaque, which occurred at an unknown time.

The results of the current study also indicate that IPH signal can resolve over time, though this only occurs in the small minority of cases. In most cases, the IPH signal seemed to fade into more of a LRNC appearance. In general, IPH is thought to be a atherogenic stimulus, leading to the formation of larger and more vulnerable plaques.[16] However, the current study indicates that hemorrhage does not always beget more hemorrhage. Instead, some plaques may undergo true resolution of the hemorrhagic components.

van der Bowhuijsen et al., in a comparison study that was smaller in length of follow-up (17 months), similarly found that the large majority (94%) of IPH remained present on follow-up exams.[17] The authors also found that IPH can both progress and regress – also like this study – with volumetric analysis demonstrating a slight trend toward decrease in size over time (-13.7 mm^3 per year). Other studies, too, have found that IPH signal commonly persists over time. Pletsch-Borba, using a cohort of 64 patients with IPH, found that 64.0% retained IPH on follow-up, though the authors made little mention regarding the appearance of IPH on imaging.[11] Yamada et al. noted nearly all (29/30) plaques with IPH persisted on follow-up, and that there was no significant change in volume over time (median interval of 279 days).[18]

Some authors have opined that the age of hemorrhage can be defined based on imaging characteristics on MRA, categorizing blood products as being fresh, recent, or old based on signal intensity patterns on time of flight (TOF), T1WI, and T2WI/PDW. However, there are several reservations regarding the use of this classification. MPRAGE was not used as part of this classification schema. Only moderate agreement was reported between such findings and histological analysis (Cohen κ listed as 0.4 and 0.7 for the reviewers of the Chu et al study).[19] Finally, Takaya et al. found that the vast majority of IPH (94%) had unchanged hemorrhage "age" based on MRI at 18 months.[15] Thus, the validity of using MRI to determine the chronicity of intraplaque blood products is somewhat dubious.

The major limitation of this study was the lack of histologic validation for these findings. Because carotid endarterectomy specimens were not available for review, it remains uncertain whether the persistent signal abnormalities observed in this study represented

blood products or something else. In addition, though the primary patient cohort was large, only 28 follow-up exams were available for review (22 with one follow-up; 6 with two). Finally, future studies will need to be performed to further analyze the clinical importance of these findings. Specifically, it will be useful to assess whether the threat posed by IPH remains constant over time, or changes based on the chronicity of persistent signal abnormalities.

FIGURES

Fig. 1: Persistent hyperintense signal in a hemorrhagic plaque. Both the initial (**A**) and 12-month follow-up (**B**) axial MPRAGE images of the left ICA origin show unchanged IPH (*straight arrows*). (* *denotes ICA lumen*).

Fig. 2: Persistent IPH-related signal in a partially hemorrhagic right ICA plaque. This mixed-intensity plaque (**A**) was composed of both IPH (*straight arrows*) and jet-black calcifications (*curved arrows*). Both components appeared unchanged on the 3-month follow up exam (**B**). (* *denotes ICA lumen*).

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