Detection of microbleeds associated with sentinel headache using MRI quantitative susceptibility mapping: pilot study

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OBJECT Sentinel headaches (SHs) associated with cerebral aneurysms (CAs) could be due to microbleeds, which are considered a sign that an aneurysm is unstable. Despite the prognostic importance of these microbleeds, they remain difficult to detect using routine imaging studies. The objective of this pilot study is to detect microbleeds associated with SH using a magnetic resonance imaging (MRI) quantitative susceptibility mapping (QSM) sequence and then evaluate the morphological characteristics of unstable aneurysms with microbleeds.

METHODS Twenty CAs in 16 consecutive patients with an initial presentation of headache (HA) leading to a diagnosis of CA were analyzed. Headaches in 4 of the patients (two of whom had 2 aneurysms each) met the typical definition of SH, and the other 12 patients (two of whom also had 2 aneurysms each) all had migraine HA. All patients underwent imaging with the MRI-QSM sequence. Two independent MRI experts who were blinded to the patients’ clinical history performed 3D graphical analysis to evaluate for potential microbleeds associated with these CAs. Computational flow and morphometric analyses were also performed to estimate wall shear and morphological variables.

RESULTS In the 4 patients with SH, MRI-QSM results were positive for 4 aneurysms, and hence these aneurysms were considered positive for non-heme ferric iron (microbleeds). The other 16 aneurysms were negative. Among aneurysm shape indices, the undulation index was significantly higher in the QSM-positive group than in the QSM-negative group. In addition, the spatial averaged wall shear magnitude was lower in the aneurysm wall in direct contact with microbleeds.

CONCLUSIONS MRI-QSM allows for objective detection of microbleeds associated with SH and therefore identification of unstable CAs. CAs with slightly greater undulation indices are associated with positive MRI-QSM results and hence with microbleeds. Studies with larger populations are needed to confirm these preliminary findings.

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entinel headache (SH) is sudden, severe, and persistent pain that precedes spontaneous aneurysmal subarachnoid hemorrhage (aSAH) by days or weeks. Despite a 10%–43% reported incidence of SH in patients with aSAH, microhemorrhages associated with cerebral aneurysms remain difficult to detect clinically using routine imaging studies. There is an unmet medical need for an imaging modality capable of detecting microhemorrhages not detectable with other conventional imaging modalities. Such a modality would allow for screening of microbleeds associated with SH and potentially identify unstable aneurysms at risk of rupture long before a catastrophic aSAH. Moreover, as a result of our inability to reliably identify microbleeds associated with SH with conventional imaging modalities, morphological characteristics of unstable aneurysms associated with SH have been insufficiently characterized.

In 2012, the Cornell magnetic resonance imaging (MRI) research laboratory developed quantitative susceptibility mapping (QSM) to quantify tissue magnetic susceptibility. MRI-QSM can be used to quantitatively measure the non-heme iron content of brain structures. By addressing the limitations inherent in susceptibility-weighted imaging (SWI), MRI-QSM has allowed for more nuanced investigation. MRI-QSM is currently used to analyze cerebral non-heme ferric iron deposition in cavernous malformation, multiple sclerosis, Alzheimer’s, and a number of other neurodegenerative diseases.

We previously published a case report describing a 76-year-old man with SH who was found to have positive MRI-QSM results and underwent treatment. We therefore decided to perform a pilot study and include more patients in an effort to validate this finding. The objective of this pilot study was to detect microbleeds associated with SH using MRI-QSM and to clarify the morphological characteristics of unstable aneurysms with microbleeds.

Methods

Patient Population

This study was approved by the University of Iowa institutional review board. All participants signed informed consent for demographic data collection and image analysis. During the period from September 2017 to December 2017, 20 consecutive patients who presented to our outpatient neurosurgical clinic with an initial diagnosis of headache (HA) and cerebral aneurysm (CA) were enrolled in this study. Patients who presented with severe HA accompanied by focal neurological symptoms (e.g., third cranial nerve palsy), a history of loss of consciousness associated with onset of HA, positive lumbar puncture results, and/or noncontrast head CT positive for subarachnoid hemorrhage were excluded. All qualified study participants immediately underwent brain MRI-QSM and magnetic resonance angiography (MRA).

Definition of Sentinel Headache and Migraine

SH is characterized as a sudden-onset, severe, and persistent pain with features different from the usual HA. Patients with SH usually describe their severe HA as the “worst headache.” Because the HA is absent of any abnormal findings on brain CT or lumbar puncture, clinicians are often faced with the challenge of clinically diagnosing SH.

On the other hand, migraine is characterized as unilateral throbbing HA associated with nausea, vomiting, photophobia, osmophobia, cranial alldynia, or movement sensitivity. Migraine typically lasts for 4 to 72 hours. During the HA, patients often experience a constellation of cognitive, affective, and cranial autonomic symptoms.

Magnetic Resonance Imaging

Each participant underwent imaging with a 3-T clinical MRI system (MAGNETOM Skyra, Siemens) located at the University of Iowa Hospitals and Clinics. The protocol included T1-weighted imaging, T2-weighted imaging, fluid attenuation inversion recovery (FLAIR), time-of-flight (TOF)–MRA, SWI, and MRI-QSM. MRI-QSM images were obtained using the following protocol: response time (TR), 61 msec; echo time (TE), 7–56 msec; flip, 17; pixel bandwidth, 260 Hz/pixel; FOV, 110.08 × 110.08 mm; matrix size, 256 × 256 × 64; voxel size, 0.43 × 0.43 × 1.50; slice thickness, 1.5 mm; frequency, 416; phase, 320; number of averages, 1. MRI-QSM images were generated offline using the STI Suite provided by Duke University Brain Imaging and Analysis Center (http://people.duke.edu/~cl160/).

Aneurysm Modeling, Meshing, and Measurement

All imaging analysis was performed by MRI experts who were blinded to the subjects’ clinical presentations. TOF-MRA images output in the Digital Imaging and Communications in Medicine (DICOM) format were imported into Vascular Modeling Toolkit lab (VMTKLab) version 1.6.0. For vessel segmentation, the level set method with colliding front algorithm was applied. Subsequently, a computational unstructured grid was generated. The prism grids were fitted to the vessel wall with 3 layers having a total thickness of 0.3 mm. The total number of elements in the meshes ranged from 0.5 to 1.0 million. Finally, the aneurysms were measured using the automatic aneurysm morphology analysis module of the VMTKLab. Aneurysm absolute height, bottleneck size, maximum aneurysm neck diameter, average parent artery diameter, aspect ratio, bottleneck ratio, size ratio, aneurysm sac volume, ellipticity index, nonsphericity index, and undulation index were recorded.

3D Volume Measurement of the Microbleeds

MRI-QSM images output in the DICOM format were imported into Avizo 6.2 (Visualization Science Group). Assessment for microbleeds was performed by 2 independent MRI experts. Subsequently, segmentation for microbleeds was performed using pixel labeling methods with the optimal susceptibility threshold of 0.1 parts per million (ppm). During the segmentation for microbleeds, regions with high susceptibility were confirmed to have no underlying cerebral vasculature by overlaying TOF-MRA images onto MRI-QSM images. The volume of the regions associated with susceptibility of over 0.1 ppm on the aneurysm surface was calculated automatically.
Computational Fluid Dynamic Simulation

Computational fluid dynamic (CFD) simulations were performed using ANSYS Fluent version 17.2. Blood was modeled as an incompressible, Newtonian fluid with the following properties: density, $\rho = 1060 \text{ kg/m}^3$, and dynamic viscosity, $\mu = 0.0035 \text{ Pa/s}$. Vessel walls were assumed to be rigid, and the no-slip conditions were applied. The blood flow was simulated under steady-state conditions. Because patient-specific blood flow boundary conditions were not available, specific velocity profiles derived from a previous report were prescribed at each inlet.\(^{29}\) At all outflow boundaries, the pressure was fixed to 0 Pa. Based on the simulation results, spatially averaged, maximum, and minimum shear magnitude values were automatically calculated for the following: 1) the entire surface area of MRI-QSM–negative aneurysms, 2) the entire surface area of MRI-QSM–positive aneurysms, and 3) the MRI-QSM–positive portion of the aneurysm wall area in direct contact with microbleeds (for MRI-QSM–positive aneurysms).

Statistical Analysis

Statistical analysis and graphic display of data were performed using GraphPad software version 7.03. To confirm the statistical difference between 2 groups, we used the Student t-test, as well as the Mann-Whitney U-test, as a nonparametric alternative. To confirm the statistical difference between 3 groups, we used a one-way analysis of variance (ANOVA), as well as the Kruskal-Wallis test, as a nonparametric alternative. In all cases, a $p$ value of less than 0.05 was considered to indicate statistical significance.

Results

Twenty consecutive patients with an initial diagnosis of HA and CA were enrolled in the study. All of these patients underwent imaging with MRI-QSM sequence, but in 4 patients (with 1 aneurysm each), MRI-QSM map images were not obtained because of skull base bone artifact. The aneurysm locations in these 4 cases were anterior communicating artery (ACoA) (2 cases), internal carotid artery (ICA)–ophthalmic artery (1 case), and ICA–posterior communicating artery (PCoA) (1 case). Thus, data from 16 patients and 20 CAs were included in the analyses.

This group of 16 patients included 3 men and 13 women, and their mean age (± SD) was 70.6 ± 10.9 years. The 20 CAs were located on the middle cerebral artery (MCA) (7), ACoA (5), ICA (4), basilar artery (BA) (3), and distal anterior cerebral artery (ACA) (1).

The mean absolute height of the aneurysms was 5.09 ± 2.51 mm. The mean bottleneck size was 5.68 ± 2.31 mm. The mean aneurysm neck diameter was 4.96 ± 1.67 mm. The mean parent artery diameter was 2.46 ± 0.52 mm. The mean aspect ratio was 0.93 ± 0.32. The mean bottleneck factor was 1.13 ± 0.15. The mean size ratio was 2.16 ± 1.20. The mean ellipticity index was 0.29 ± 0.04. The mean undulation index was 0.04 ± 0.03.

Positive MRI-QSM for microbleeds was observed in 4 of 20 aneurysms (20.0%). Two patients, each with a single CA, had positive MRI-QSM and SH on their initial clinical presentation. Two other patients who presented with SH each had 2 CAs; in these cases, one CA was positive on MRI-QSM and the other CA was negative on MRI-QSM. All microbleeds were located on the interface of each aneurysm with the brain parenchyma (see Fig. 2C–F). On the other hand, the 12 controls with 14 CAs (two had 2 CAs, each of which was negative) had negative MRI-QSM results. The 4 patients with positive results on MRI-QSM had typical presentation of SH and had negative noncontrast head CT and lumbar puncture. The 12 controls had migraine HA as the initial presentation that led to diagnosis of their CAs.

During the diagnostic process for detecting microbleeds, there was a single disagreement between 2 readers. Thus, the interobserver agreement rate for detecting microbleeds was 95%. After discussion, the 2 readers finally judged this case as MRI-QSM negative. This patient has not had any symptoms associated with aSAH.

MRI-QSM Positive Versus Negative in Aneurysm Morphological Indices

There was no statistically significant difference between the MRI-QSM–positive group and the MRI-QSM–negative group with respect to patient age (mean 70.1 ± 3.0 years vs 72.5 ± 4.2 years, respectively; $p = 0.98$). The absolute height of aneurysms that were MRI-QSM positive tended to be greater on average than that of those that were MRI-QSM negative, but there was no significant difference between the 2 groups (mean 6.28 ± 1.26 mm vs 4.79 ± 0.64 mm, respectively; $p = 0.25$). Likewise, there was no significant difference between the 2 groups with respect to bottleneck size (mean 6.42 ± 0.85 mm vs 5.50 ± 0.63 mm, $p = 0.50$), aneurysm neck diameter (5.44 ± 0.70 mm vs 4.84 ± 0.45 mm, $p = 0.55$), parent artery diameter (2.26 ± 0.17 mm vs 2.51 ± 0.14 mm, $p = 0.41$), aspect ratio (1.12 ± 0.22 vs 0.88 ± 0.07, $p = 0.22$), bottleneck factor (1.18 ± 0.08 vs 1.11 ± 0.04, $p = 0.24$), size ratio (2.79 ± 0.53 vs 2.01 ± 0.31, $p = 0.18$), and aneurysm sac volume (154.3 ± 48.0 vs 128.2 ± 45.7, $p = 0.21$).

On the other hand, the undulation index was significantly higher for MRI-QSM–positive aneurysms than for MRI-QSM–negative aneurysms (mean 0.06 ± 0.01 vs 0.03 ± 0.01, respectively; $p = 0.02$). However, there was no significant difference between-groups difference in ellipticity index (0.27 ± 0.01 vs 0.30 ± 0.01, $p = 0.18$) or nonsphericity index (0.29 ± 0.01 vs 0.31 ± 0.01, $p = 0.43$).

Relation Between the Volume of Microbleeds and Aneurysm Morphological Indices

In the MRI-QSM–positive group, although the volume of microbleeds had a positive relation to the absolute height of the aneurysm ($R^2 = 0.73$), there was no statistical significance ($p = 0.15$). Likewise, there was no statistical significance in bottleneck size ($R^2 = 0.11$, $p = 0.66$), aneurysm neck diameter ($R^2 = 0.006$, $p = 0.92$), parent artery diameter ($R^2 = 0.59$, $p = 0.23$), aspect ratio ($R^2 = 0.59$, $p = 0.23$), bottleneck factor ($R^2 = 0.33$, $p = 0.42$), size ratio ($R^2 = 0.28$, $p = 0.47$), aneurysm sac volume ($R^2 = 0.54$, $p = 0.28$), and nonsphericity index ($R^2 = 0.54$, $p = 0.28$).
0.26), undulation index ($R^2 = 0.04$, $p = 0.79$), ellipticity index ($R^2 = 0.09$, $p = 0.70$), or nonsphericity index ($R^2 = 0.0002$, $p = 0.98$).

**Shear Magnitude**

Spatial averaged shear magnitudes in the entire surface of MRI-QSM–negative aneurysms (Fig. 1A), the entire surface of MRI-QSM–positive aneurysms (Fig. 1A), and the MRI-QSM–positive portion of the aneurysm wall (Fig. 1B) in direct contact with microbleeds (Fig. 1C) were $0.50 \pm 0.88$ Pa, $0.19 \pm 0.14$ Pa, and $0.08 \pm 0.03$ Pa, respectively. According to the Kruskal-Wallis test followed by Dunn’s multiple comparison test, the spatial averaged shear magnitude in the MRI-QSM–positive portion of the aneurysm wall area in direct contact with microbleeds was slightly lower than that in the overall surface of the MRI-QSM–negative aneurysms, and the difference was statistically significant ($p = 0.04$) (Fig. 1D). On the other hand, there was no significant difference between the 3 groups in maximum ($p = 0.09$) (Fig. 1E) or minimum ($p = 0.41$) shear magnitude (Fig. 1F).
Representative Cases

Case 1
This 75-year-old woman presented to our institution with a sudden onset of a severe, persistent headache. TOF-MRA revealed a BA aneurysm measuring 9.32 mm with a small daughter sac (A). MRI-QSM indicated high susceptibility at the interface of the aneurysm wall (white arrow, B). 3D images from MRI-QSM revealed that microbleeds were located on the daughter sac of BA aneurysm (white arrow, C). The volume of the microbleeds was calculated to be 32.94 mm³. D: Case 2, 3D image obtained in a 77-year-old woman with SH showing microbleeds at the interface of the left MCA aneurysm wall and brain parenchyma (white arrow). The volume of the microbleeds was calculated to be 0.3 mm³. E: Case 3, 3D image from MRI-QSM obtained in a 60-year-old woman with SH showing microbleeds at the interface of the BA top aneurysm wall and brain parenchyma (white arrow). The volume of the microbleeds was calculated to be 7.2 mm³. F: Case 4, MRI-QSM image obtained in a 78-year-old man with SH. MRI-QSM was positive in a left MCA aneurysm (white arrow), but negative in a left ICA top aneurysm (blue circle).

Case 2
This 77-year-old woman presented to our institution with SH. TOF-MRA showed a left MCA aneurysm measuring 7.3 mm with a small daughter sac (Fig. 2A). MRI-QSM was performed immediately and indicated high susceptibility at the interface of the aneurysm wall with the brain parenchyma (Fig. 2B). 3D images constructed from MRI-QSM revealed that microbleeds were located on the daughter sac of the BA aneurysm. The volume of the microbleeds was calculated to be 32.94 mm³ (Fig. 2C). Finally, the BA aneurysm was treated with coil embolization. The patient’s postoperative course was unremarkable, with no neurological deficits noted.

Case 3
This 60-year-old woman also presented to our institution with SH. TOF-MRA indicated a 7.1-mm BA top aneurysm with a broad neck. MRI-QSM scanning was performed immediately, and the resulting 3D images showed that microbleeds were located at the interface of the aneurysm wall and brain parenchyma (Fig. 2E). The volume of the microbleeds was calculated to be 7.2 mm³. Finally, the BA aneurysm was treated with stent-assisted coiling. Her postoperative course was unremarkable, with no neurological deficits noted.

Case 4
This 78-year-old man presented with SH. TOF-MRA indicated a left MCA aneurysm measuring 3.7 mm and a left ICA top aneurysm measuring 3.4 mm. MRI-QSM results were positive in the left MCA aneurysm but negative in the left ICA top aneurysm (Fig. 2F). The left MCA aneurysm was treated with coil embolization. The patient’s postoperative course was unremarkable with no evidence of rupture of the left ICA top aneurysm and no remarkable neurological deficits.
Discussion

Until now, there has been only speculation that SH associated with CA is due to either microbleeds that cannot be detected with noncontrast head CT and lumbar puncture or physical structural change in the CA (enlarging or developing a daughter sac) or both. No previously published report has objectively described imaging microbleeds associated with SH, which is clinically considered an ominous sign of impending aSAH. Correct identification of microbleeds associated with SH is critical, yet it remains difficult. Typically, patients with a clinical presentation suspicious for SH are evaluated with noncontrast head CT and CTA and/or MRA, followed by lumbar puncture if imaging studies reveal an aneurysm without evidence of SAH. Treatment is clearly indicated in patients with large aneurysms despite negative results on these studies (> 7 mm). The real utility of MRI-QSM may lie in identifying microbleeds in patients with small aneurysms (< 7 mm) without aSAH or elderly patients (> 70 years old) with aneurysms of borderline size (∼ 7 mm) without aSAH. In these individuals, the indications for treatment are less clear. Arming the neurosurgeon with information regarding the risk of rupture in these patients may help avoid imminent catastrophic aSAH. In this pilot study, microbleeds were detected with MRI-QSM in all patients with SH. Additionally, MRI-QSM can identify the culprit aneurysm in patients with multiple CAs.

The undulation index (UI) has been found to discriminate ruptured from unruptured aneurysm in many studies. It is defined as $UI = 1 - (V/V_{ch})$, where V is the volume of the planar-isolated aneurysm and $V_{ch}$ is the volume of the convex hull of the planar-isolated aneurysm. Our results indicate that the undulation was significantly greater in aneurysms with positive findings on MRI-QSM (i.e., with microbleeds) than in those with negative findings on MRI-QSM (mean UI 0.06 vs 0.03, p = 0.02). Some caution is warranted in interpreting this finding, however, because even a UI value of 0.06 suggests generally low levels of undulation in the aneurysm sac.

The relation between wall shear stress (WSS) and risk for aneurysm rupture remains controversial. Though Cebral et al. and Meng et al. suggested that high WSS could be the cause of the risk for aneurysm rupture, Boussel et al. and Jou et al. indicated that low WSS could be the cause of the risk for aneurysm rupture. In addition, Shojima et al. pointed out that the WSS was markedly reduced at the top of the aneurysm or within a bleb area. Furthermore, Kondo et al. and Dardik et al. reported that WSS below an adequate value might cause apoptosis in vascular endothelial cells and eventually lead to aneurysm rupture. Our results might lead to the same conclusion as these reports.

MRI-QSM has several limitations. About 1 hour of offline image processing is required for a case in which MRI-QSM is being used to identify possible microbleeds in association with SH. This manual image processing may ultimately be automated as a result of further research. Additionally, interobserver reliability for detecting microbleeds with MRI-QSM is a very important issue. Because susceptibility of the vessel is also high, regions with high susceptibility should be confirmed to have no underlying cerebral vascularule by overlaying TOF-MRA images or magnetic resonance venography onto MRI-QSM images. Furthermore, in close proximity to the skull base, where most aneurysms are located, MRI-QSM may be impacted by bony artifact. These limitations are subjects of future work.

Our current study is limited by the number of participants. Nevertheless, we were able to successfully identify microbleeds in all 4 patients who presented with SH and identify the culprit CA in the patients with multiple CAs. Correct identification of microbleed-associated SH may help guide therapeutic decision-making, allowing for treatment of at-risk aneurysms weeks before catastrophic aSAH.

Conclusions

MRI-QSM allows for objective detection of microbleeds associated with SH and therefore unstable CAs. MRI-QSM may serve as a valuable objective screening tool in the outpatient setting and emergency departments to differentiate SH from other HAs and thus prevent catastrophic aSAH. Future research that builds on this preliminary effort to optimize this imaging technique and test it in a larger cohort is of clinical importance.

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**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Hasan, Nakagawa, Magnotta, Awad, Carroll, Torner, Raghavan. Acquisition of data: Hasan, Nakagawa, Awe, Zanaty, Nagahama, Cushing, Hayakawa, Allan, Greenlee. Analysis and interpretation of data: Hasan, Nakagawa, Kudo, Nagahama, Cushing, Magnotta, Hayakawa, Greenlee, Awad, Carroll, Torner, Raghavan. Drafting the article: Hasan, Nakagawa, Awe, Zanaty, Nagahama, Allan, Greenlee, Awad, Carroll. Critically revising the article: Hasan, Nakagawa, Kudo, Awe, Zanaty, Nagahama, Magnotta, Hayakawa, Allan, Greenlee, Awad, Carroll, Torner, Raghavan. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hasan. Statistical analysis: Hasan, Nakagawa, Torner, Raghavan. Administrative/technical/material support: all authors. Study supervision: Hasan, Kudo, Carroll, Torner, Raghavan.

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