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# Arterial Spin-Labeling MR Imaging in the Detection of Intracranial Arteriovenous Malformations in Patients with Hereditary Hemorrhagic Telangiectasia

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease that causes vascular malformations in a variety of organs and tissues, including brain AVMs. Because brain AVMs have the potential to cause disabling or fatal intracranial hemorrhage, detection of these lesions before rupture is the goal of screening MR imaging/MRA examinations in patients with HHT. Prior studies have demonstrated superior sensitivity for HHT-related brain AVMs by using postcontrast MR imaging sequences as compared with MRA alone. We now present data regarding the incremental benefit of including arterial spin-labeling (ASL) perfusion sequences as part of MR imaging/MRA screening in patients with this condition.

**MATERIALS AND METHODS:** We retrospectively analyzed 831 patients at the UCSF Hereditary Hemorrhagic Telangiectasia Center of Excellence. Of these, 42 patients had complete MR imaging/MRA, ASL perfusion scans, and criterion-standard DSA data. Two neuroradiologists reviewed imaging studies and a third provided adjudication when needed.

**RESULTS:** Eight patients had no brain AVMs detected on DSA. The remaining 34 patients had 57 brain AVMs on DSA. Of the 57 identified AVMs, 51 (89.5%) were detected on ASL and 43 (75.4%) were detected on conventional MR imaging/MRA sequences ($P = .049$), with 8 lesions detected on ASL perfusion but not on conventional MR imaging.

**CONCLUSIONS:** ASL provides increased sensitivity for brain AVMs in patients with HHT. Inclusion of ASL should be considered as part of comprehensive MR imaging/MRA screening protocols for institutions taking care of patients with HHT.

**ABBREVIATIONS:** *ACVRL1* = activin A receptor type II-like 1 gene; ASL = arterial spin-labeling; *ENG* = endoglin gene; HHT = hereditary hemorrhagic telangiectasia; PCASL = pseudocontinuous arterial spin-labeling

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is an autosomal-dominant disease with a prevalence of 1/5000 and results in the formation of dysplastic vessels.[1] These vascular malformations can form on mucocutaneous surfaces or within internal organs.[2] Diagnosis of HHT is established through either the clinical Curacao criteria or genetic testing.[3] The Curacao criteria, developed in 2000 at the HHT Scientific Advisory Board Meeting to standardize clinical diagnoses of HHT, include: recurrent epistaxis, multiple cutaneous or mucocutaneous telangiectasias in characteristic locations, visceral AVMs, and a family history of HHT. HHT is suspected when at least 2 criteria are met, though diagnosis requires 3.[4] Diagnosis can also be made if an individual tests positive for a known causative mutation including those in the endoglin (*ENG*), activin A receptor type II-like 1 (*ACVRL1*), *GDF2*, and *SMAD4* genes.[3]

While epistaxis is the most frequently presenting symptom of HHT, complications secondary to pulmonary and cerebral vascular malformations can result in severe morbidity and mortality.[5] Studies have shown that approximately 23% of individuals with HHT develop cerebral vascular malformations, some of which, including capillary telangiectasias, can be very small and missed on MR imaging.[3,6] AVMs are the most common cerebral lesions and have a risk of rupture of 0.4%–1.3% per year per patient.[7-10] The current criterion standard for diagnosing AVMs is via catheter DSA, an invasive test.[11] Current guidelines recommend screening all adult patients with suspected or definite HHT for cerebral

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vascular malformations by using MR imaging with and without contrast administration with at least 1 sequence sensitive to the presence of blood products.[3,12,13] For children, recommendations are for brain AVM screening as soon as possible after birth by using MR imaging.[3,13] Our prior study showed that the sensitivity and specificity of MR imaging as a whole in detecting brain AVMs in patients with HHT were 80.0% and 94.4%, respectively, with 3D-T1 and 2D-T1 postgadolinium sequences being the most sensitive, by using DSA as the criterion standard.[14] Other sequences evaluated in the study were T2, SWI, and MRA.

Arterial spin-labeling (ASL) MR perfusion imaging was conceived nearly 30 years ago and relies on magnetically labeled arterial blood water protons as an endogenous tracer to measure tissue perfusion.[15-17] This noninvasive noncontrast MR imaging technique is particularly useful because it does not require radioactive tracers or exogenous contrast agents, allowing it to be performed on a broad range of patient populations that may otherwise not tolerate contrast-enhanced studies.[18] Further expanding the clinical utility of ASL, slight alterations can be made to the standard pseudocontinuous arterial spin-labeling (PCASL) sequence protocol to optimize its sensitivity for different pathologies, such as acute ischemic strokes, tumors, AVMs, and others.[19] One study found ASL to have a sensitivity of 95% for detecting intracranial arteriovenous shunting.[20] This sensitivity arises from the high concentration of labeled protons flowing through shunts as the protons bypass the microvascular/tissue network and are directly delivered to the draining veins in AVMs. However, there are limited data demonstrating the utility of ASL as a screening tool in the detection of intracranial AVMs in patients with HHT. Because detection of AVMs is essential in the prevention of intracranial hemorrhage in persons with HHT, improvements in screening with noninvasive imaging techniques may benefit to patients with HHT. This study aims to evaluate the added value of ASL perfusion in the HHT population by comparing the sensitivity of MR imaging with ASL to that of conventional MR imaging without ASL.

## MATERIALS AND METHODS

### Subject Inclusion Criteria

All patients referred to the University of California, San Francisco HHT Center of Excellence by November 2022 underwent screening for potential inclusion in this retrospective study ($n = 831$). Approval for this study was obtained from the University of California, San Francisco Institutional Review Board. Patients were further narrowed down to include those who subsequently underwent brain imaging or had history that raised suspicion of possible brain AVMs ($n = 154$). Patient charts were reviewed, and pertinent data recorded included sex, age, Curacao criteria, genetic testing, and dates of cerebral imaging (including MR imaging and DSA). Mean ± standard deviation and median age for the cohort were calculated. Inclusion criteria for the study included suspected or definite diagnosis of HHT via Curacao criteria or genetic testing and at least 1 brain MR imaging with ASL perfusion and 1 cerebral DSA within the same stage of the patient's initial evaluation or ongoing treatment/management. Any patient whose MR imaging/ASL examinations were obtained in a separate treatment/management stage as the DSA examination were excluded to minimize the influence of treatments (such as interval gamma knife or surgical resection) on the sensitivity or specificity of MR imaging/ASL. This is a similar cohort as our prior study,[14] updated with patients enrolled since that time.

### Image Analysis

A fellowship-trained neurointerventional radiologist (S.W.H.) reviewed the cerebral DSA images for all 42 patients and recorded the total number and specific locations of intracranial AVMs, which served as the reference standard for this study. The first MR with ASL imaging that occurred immediately before the DSA was retrospectively reviewed by 2 fellowship-trained neuroradiologists (W.H. and Y.L.). For patients with multiple ASL imaging, the one that was closest in time to the patient's first DSA was selected. A third fellowship-trained neuroradiologist (S.W.H.) adjudicated any discrepancies between the 2 readings. The neuroradiologists first reviewed the MR imaging as a whole and recorded the total number of cerebral AVMs detected on conventional sequences only, as well as which individual sequences the AVMs were visible on (SWI, T2-weighted, MRA, 2D-T1-weighted postgadolinium, and 3D-T1-weighted postgadolinium). The readers then reviewed the ASL perfusion images available for each of these MR imaging examinations in the context of the MR imaging as a whole and recorded their results for detection of cerebral AVM in a binary fashion.

A number of these MR images were performed at different institutions and on different scanners with varying field strengths and other parameters. As a result, there was no standardized set of sequences and parameters for the MR images and ASL perfusion studies. All ASL sequences were performed with PCASL. The standard postlabeling delay time for adults and pediatric patients were 2025 ms and 1500 ms, respectively. No additional postprocessing or adjustment was performed on ASL images acquired at outside institutions. Using DSA as the reference standard, true- and false-positives for ASL perfusion and conventional MR imaging were calculated for each lesion. From there, sensitivity for ASL and conventional MR imaging were calculated and compared. Cohen $\kappa$ for interreader reliability between the 2 readers for both ASL perfusion and conventional MR imaging sequences was also calculated. Statistical analyses were performed by using Excel (Microsoft). The McNemar test was used to compare MR imaging and ASL for only the DSA-positive AVMs to determine whether there was a statistically significant difference ($P < .05$) between conventional MR imaging alone and MR imaging plus ASL.

## RESULTS

Of the 343 patients reviewed, 38 patients met all inclusion criteria. An additional 4 patients had a Curacao score of 1 and either had no genetic testing available or tested negative for known HHT-causing mutations. However, clinical suspicion for HHT remained high for these 4 patients because some manifestations of HHT, such as epistaxis and oral/dermal telangiectasias, may not occur until later in life, rendering Curacao criteria less accurate in young patients.[21-23] Therefore, these 4 patients were included in the study, resulting in 42 patients total.

The study consisted of 42 patients ranging in age from 1.5 months to 71 years. The mean age at the time of MR imaging with ASL was 17 ± 18 years and 60% of the patients were female (Table 1). The median time between ASL and DSA was 151 days with an interquartile range of 617. Most patients had a Curacao score of 2 (43%). Thirty-six patients (85%) underwent genetic testing and 50% of them tested positive for mutations in the *ENG* gene. Five patients had no genetic testing data available. Three of these 5 patients had a Curacao score of 2, while the other 2 patients had a Curacao score of 1. These 2 patients were still included because their ages were only 1.5 and 2.5 months at the time of ASL imaging and they were determined to have a high likelihood of HHT despite their Curacao score.

A total of 8 patients had no brain AVMs detected on DSA. The remaining 34 patients had a total of 57 intracranial AVMs that were positive on DSA. These 57 AVMs were located in a variety of locations, with the frontal lobe being the most common (Online Supplemental Data). Of the 57 identified lesions, 51 (89.5%) were positive on ASL and 43 (75.4%) were positive on conventional MR imaging ($P = .0455$, McNemar), with 8 lesions detected on ASL perfusion but not on conventional MR imaging.

**Table 1: Demographics of patients included in the study**

| Demographics | |
|---|---|
| Total No. of patients | $n = 42$ |
| Female sex | 25/42 (60%) |
| Age (yr) at time of ASL imaging (mean ± SD) | 17 ± 18 |
| Age (yr) at time of ASL imaging (median) | 25 |
| Proportion of patients with 1 or more brain AVMs | 34/42 (81%) |
| Time between ASL and DSA image in days (median, IQR) | 151, 617 |
| Curacao score | |
| 1 | 4/42 (10%) |
| 2 | 18/42 (43%) |
| 3 | 13/42 (31%) |
| 4 | 7/42 (17%) |
| Genetic testing | |
| HHT-causing mutation | |
| *ENG* | 21/37 (57%) |
| *ACVRL1* | 2/37 (5%) |
| Family member positive | 1/42 (3%) |
| Negative genetic testing | 13/37 (35%) |
| No genetic testing available | 5/42 (12%) |

**Note:**—IQR indicates interquartile range; SD, standard deviation.

An example of these lesions can be seen in Fig 1, which demonstrates small subcentimeter nidus "microAVMs," which are otherwise occult on conventional MR imaging sequences and are a common cerebrovascular manifestation of patients with HHT (see Online Supplemental Data for more examples). There were 3 lesions identified on ASL and 1 lesion on MR imaging that were negative on DSA. One such example is seen in Fig 2, in which postoperative changes such as pericavitary hyperemia and truncation of the arterial feeders were likely reflected on ASL perfusion imaging as arterial transit artifact. Table 2 summarizes the total lesions detected on ASL and conventional MR imaging, with Cohen $\kappa$ interreader reliability coefficient displayed for both ASL perfusion as well as conventional MR imaging. Of all the conventional sequences, 3D-T1 postgadolinium had the highest sensitivity, with 41/56 (73%). Not every patient had each MR imaging sequence available, thus the total number of lesions for each sequence differed. The Online Supplemental Data present the sensitivity, specificity, positive predictive value, and negative predictive value of ASL perfusion, conventional MR imaging, and each individual sequence.

## DISCUSSION

Whereas previous studies have investigated the utility of conventional MR imaging/MRA sequences as a screening tool for intracranial AVMs in patients with HHT,[14] additional evidence has emerged over the past few years suggesting that ASL may be more sensitive than conventional MR imaging/MRA in the detection of AVMs and other intracranial arteriovenous shunting lesions.[19,24,25] Our study demonstrates that ASL perfusion, when interpreted in conjunction with conventional MR imaging/MRA, provides additional value in the detection of brain AVMs in patients with HHT compared with conventional MR imaging/MRA sequences alone, by using DSA as the criterion standard. Of the 57 DSA-confirmed AVMs in this patient population, the sensitivity of ASL perfusion (89.5%) in detecting these lesions was significantly higher than that of other conventional MR imaging/MRA sequences (28.1%–75.4%), with 8 of 57 DSA-confirmed AVMs detected on ASL but not on conventional MR imaging/MRA sequences. These values are also concordant with previously reported values in the literature regarding each technique.[19,24,25] Overall, our study provides support for the use

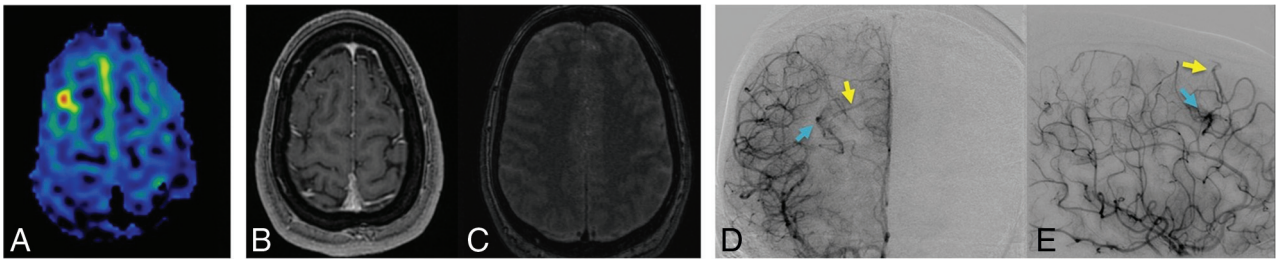


**FIG 1.** Adult patient with genetically confirmed HHT and mild epistaxis, presenting for a screening brain MR imaging and MRA. *A*, Postprocessed ASL image with a focus of increased signal along the right superior frontal gyrus. *B and C*, Postgadolinium 3D BRAVO (3D brain volume) and noncontrast time-of-flight MRA, respectively, with no corresponding vascular abnormality demonstrated on these conventional MR imaging sequences. Frontal (*D*) and lateral (*E*) DSA images acquired from a selective right ICA injection in the late arterial phase demonstrating an ill-defined compact 12-mm AVM nidus (*blue arrows*) associated with early filling of a superficial cortical vein (*yellow arrows*) along the right superior frontal gyrus draining into the superior sagittal sinus.

of ASL in addition to conventional MR imaging as a screening tool for brain AVMs in the HHT population, with strong interreader reliability and statistically significant increase in sensitivity for this cohort of patients.

Although this incremental value of ASL over conventional MR imaging/MRA in the detection of brain AVMs is well supported by our study, we must caution that these findings are only valid under the premise of ASL being a component sequence as part of a comprehensive MR imaging/MRA evaluation for patients with HHT. As previously mentioned, the blinded readers and adjudicator individually reviewed the ASL images of each study in the context of the MR imaging as a whole, which more accurately reflects how these studies are interpreted in clinical practice. As such, our data also support the essential role that conventional MR imaging continues to play in the detection of brain AVMs in the HHT population, with a sensitivity of 74.5%, similar to a previous study.[14]

The limitations of our study must also be noted, foremost of which is the heterogeneity of the MR imaging that was reviewed. Because the studies for this cohort of patients were performed at multiple different institutions, unavoidable variations existed in selection of protocol, magnetic field strength, the types of sequences obtained, the field of view for each sequence, and whether gadolinium-based contrast was given. For instance, the limited time-of-flight MRA field of view on many studies as well as the lack of postcontrast sequences in a few studies may account for some of the relatively decreased sensitivity of conventional MR imaging. Although all studies used the PCASL technique, readout methods varied between scanners and institutions. In ASL, images are acquired downstream from the initial blood labeling following a specified postlabeling delay, yielding a field of view that generally includes the entirety of the brain.[26] Such whole-brain coverage is particularly important for this patient population, because AVMs can be present at any location in the brain, not just near the circle of Willis.

Another limitation of our study is the nonrandomized, retrospective nature of our study, in which a significantly higher proportion of patients in this cohort had one or multiple AVMs (34/42, or 81%) than what has traditionally been reported in the literature (up to 23%). This may be due to the nature of our HHT practice to perform DSA only on patients with suspicious clinical or screening MR imaging/MRA findings. It is unlikely that a de novo brain AVM formed between the time of MR imaging and DSA; there are only a few case reports of this phenomenon in the HHT population, predominantly in children.[27]

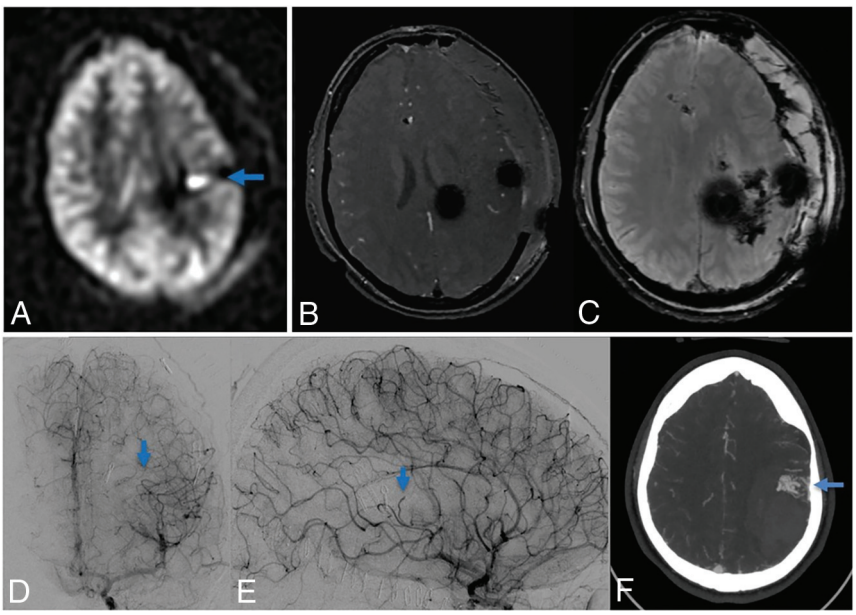


**FIG 2.** Teenage patient presenting with acute onset right hemiparesis and aphasia, found to have a large left frontoparietal hematoma with an associated vascular malformation suspicious for a ruptured AVM on noninvasive imaging. The patient was emergently taken to the operating room for decompressive hemicraniectomy and AVM resection. No preoperative angiogram was performed. Patient currently meets 1 of 4 Curacao criteria for HHT with genetic testing pending. However, given young age at presentation, clinical suspicion remained high for underlying HHT, because certain clinical manifestations such as epistaxis and oral/dermal telangiectasias, may not occur until later in life. *A*, ASL acquired on postoperative day 1 demonstrating a focus of increased signal along the left posterosuperior insula (*blue arrow*). Noncontrast time-of-flight MRA (*B*) and SWI (*C*) with expected postoperative changes in the operative bed, with no abnormality on MRA to suggest residual shunting. Frontal (*D*) and lateral (*E*) DSA images demonstrating abrupt cutoff/truncation of a posterior insular left M3 MCA branch (likely feeding artery) associated with a surgical clip, compatible with expected postoperative change. This finding corresponds to the focus of increased ASL signal and likely reflects arterial transit artifact as a result of postsurgical change rather than residual arteriovenous shunting. No residual AVM nidus or shunting was demonstrated. *F*, Preoperative CT angiogram demonstrating the left frontal AVM nidus in relation to the large acute left frontoparietal hematoma.

**Table 2: Number and percentage of AVMs detected on ASL and conventional MR imaging, with κ coefficient for interreader reliability**

| Sequence | Total Number of AVMs Detected | % of AVMs Detected ($n$ = 57) | Interreader Agreement (Cohen κ Coefficient)[a] |
|---|---|---|---|
| MR imaging with ASL | 51 | 89.5% | 0.801 |
| Conventional MR imaging without ASL | 43 | 75.4% | 0.704 |
| | | $P$ value .046 | |

[a] Strength of agreement based on Cohen $\kappa$ coefficient score: none to slight $\kappa < 0.20$, fair $\kappa = 0.21$–$0.40$, moderate $\kappa = 0.41$–$0.60$, substantial $\kappa = 0.61$–$0.80$, near perfect $\kappa = 0.81$–$0.99$. $P$-value derived from McNemar's test.

Furthermore, this relatively low number of "control" patients with HHT but negative DSA findings in our cohort limits our evaluation of the true specificities and negative predictive values of both ASL and conventional MR imaging, potentially accounting for the wider range of specificities and lower negative predictive values when compared with our prior study.[14]

Finally, because ASL remains a relatively novel sequence compared with conventional MR imaging/MRA sequences, standardization of technical parameters related to the acquisition and postprocessing of ASL may not be as widespread across different institutions and imaging centers as with conventional sequences. Our institution's HHT brain AVM screening protocol is included for readers' reference (Online Supplemental Data). Although the 2015 consensus paper provided general guidelines for clinical applications of ASL MR imaging,[28] there remained a relative lack of guidance on disease-specific parameters until the updated guidelines published by the ISMRM Perfusion Study Group more recently.[19] As elucidated in the literature, variability in technical parameters of ASL imaging such as the location of the labeling plane, presence of susceptibility artifact in the labeling plane or imaging plane, the postlabel delay time, and whether postprocessing software was used, all may affect quality and interpretation of the ASL images.[19] The fact that interreader agreement remained relatively high in our study further highlights the potential utility of ASL with more standardized protocols across institutions as well as possible quantitative data from ASL acquisition to reduce "operator" dependence. Future studies evaluating a prospective cohort of patients with HHT scanned with the same standardized MR imaging protocols and newer ASL imaging techniques such as multidelay ASL may help to confirm the true sensitivity of each of these sequences in this population.

## CONCLUSIONS

This study supports the use of ASL perfusion in conjunction with conventional MR imaging/MRA sequences as a more sensitive screening tool for cerebral AVMs in patients with HHT, when compared with conventional MR imaging sequences alone. The continued refinement of advanced MR imaging techniques such as ASL may see their sensitivity at detecting AVMs begin to approach that of the reference standard DSA, allowing for more accurate and widespread noninvasive diagnosis and risk stratification for patients with HHT.


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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.


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