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Comparison of MRI, MRA, and DSA for Detection of Cerebral Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia

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ABSTRACT

BACKGROUND AND PURPOSE: Patients with hereditary hemorrhagic telangiectasia (HHT) have a high prevalence of brain vascular malformations, putting them at risk for brain hemorrhage and other complications. Our aim was to evaluate the relative utility of MR imaging and MRA compared with DSA in detecting cerebral AVMs in the HHT population.

MATERIALS AND METHODS: Of 343 consecutive patients evaluated at the University of California, San Francisco HTT Center of Excellence, 63 met the study inclusion criteria: definite or probable hereditary hemorrhagic telangiectasia defined by meeting at least 2 Curacao criteria or positive genetic testing, as well as having at least 1 brain MR imaging and 1 DSA. MRIs were retrospectively reviewed, and the number of AVMs identified was compared with the number of AVMs identified on DSA.

RESULTS: Of 63 patients, 45 (71%) had AVMs on DSA with a total of 92 AVMs identified. Of those, 24 (26%) were seen only on DSA; 68 (74%), on both DSA and MR imaging; and 5 additional lesions were seen only on MR imaging. Of the 92 lesions confirmed on DSA, 49 (53.3%) were seen on the 3D-T1 postgadolinium sequence, 52 (56.5%) were seen on the 2D-T1 postgadolinium sequence, 35 (38.0%) were seen on the SWI sequence, 24 (26.1%) were seen on T2 sequence, and 25 (27.2%) were seen on MRA. The sensitivity and specificity of MR imaging as a whole in detecting AVMs then confirmed on DSA were 80.0% and 94.4%, respectively, and the positive and negative predictive values were 97.3% and 65.4%, respectively.

CONCLUSIONS: This study reinforces the use of MR imaging as a primary screening tool for cerebral AVMs in patients with hereditary hemorrhagic telangiectasia and suggests that 3D-T1 postgadolinium and 2D-T1 postgadolinium performed at 3T are the highest yield sequences.

ABBREVIATION: HHT = hereditary hemorrhagic telangiectasia

H ereditary hemorrhagic telangiectasia (HHT) is a rare, autosomal dominant disease characterized by the formation of mucocutaneous, lung, brain, and visceral organ vascular malformations.[1] Diagnosis of probable or definite HHT is defined by meeting ≥2 of the Curacao criteria or testing positive for known disease-causing mutations, including those in the *endoglin* (*ENG*), *activin A receptor like type 1* (*ACVRL1*), and *SMAD family member 4* (*SMAD4*) genes.[1,2] Up to 23% of patients with HHT develop cerebral vascular malformations, including brain arteriovenous malformations, cavernous malformations, developmental venous anomalies, capillary telangiectasias, vein of Galen malformations, arteriovenous fistulas, capillary vascular malformations, and transitional or mixed malformations.[3-6] Most of these lesions are cerebral AVMs, which have the risk of potential rupture.[4] Studies have reported the risk of rupture in patients with HHT from 0.4% to 1.3% per year per patient or 0.3%–0.7% per year per lesion.[7,8] Given this risk, current guidelines recommend screening with cerebral MR imaging for all adults with possible or definite HHT and all children with possible or definite HHT within the first 6 months of life.[1,9] These same guidelines suggest using sequences with and without contrast as well as blood-sensitive sequences but provide no further specific recommendations as to which sequences are of the greatest utility.[1,9]

While studies have proposed that specific MR images may be beneficial in evaluating the presence of AVMs in non-HHT populations, there are limited data demonstrating the specific utility of these sequences in screening for AVMs in patients with HHT.[10-12] Because the HHT population is undergoing screening to detect AVMs before they become clinically apparent, the AVMs this screening test seeks to find may often be smaller or have different characteristics compared with those seen on diagnostic examinations of symptomatic patients with AVMs in the general population.[1,4] We, therefore, sought to evaluate the relative utility of diagnostic screening MR imaging and MRA as well as the utility of specific MR imaging sequences compared with the criterion standard of DSA in detecting cerebral AVMs within the HHT population.

Table 1: Demographics of patients included in the study

Demographics	
Total No. of patients	$n = 63$
Female sex	41/63 (65%)
Age at time of MR imaging (mean) (yr)	36 ± 20
Curacao score	
1	1/63 (2%)[a]
2	18/63 (29%)
3	20/63 (32%)
4	24/63 (38%)
HHT-causing mutation	
ENG	23/63 (37%)
ACVRL1	5/63 (8%)
Variant of unknown significance	2/63 (3%)
Family member positive	6/63 (10%)
Negative genetic testing	9/63 (14%)
No genetic testing available	18/63 (29%)
Neurologic symptoms	
Present	50/63 (79%)
Absent	13/63 (21%)

[a] Genetically confirmed HHT.

FIG 1. Multiple brain AVMs in HHT: positive on MR imaging, MRA, and DSA. A 5-year-old boy with a frontopolar cerebral AVM (*white arrow*) demonstrated on SWI MR imaging (*A*), 3D postgadolinium T1 (*B*), time-resolved dynamic contrast-enhanced MRA (*C*), and DSA (*D*). A smaller AVM (*white arrowhead*) is suggested by hypointensity on SWI (*A*), enhancement on 3D postgadolinium T1 (*B*), and enhancement and subtle arteriovenous shunting on DSA (*D*). The smaller AVM is not seen on MRA (*C*).
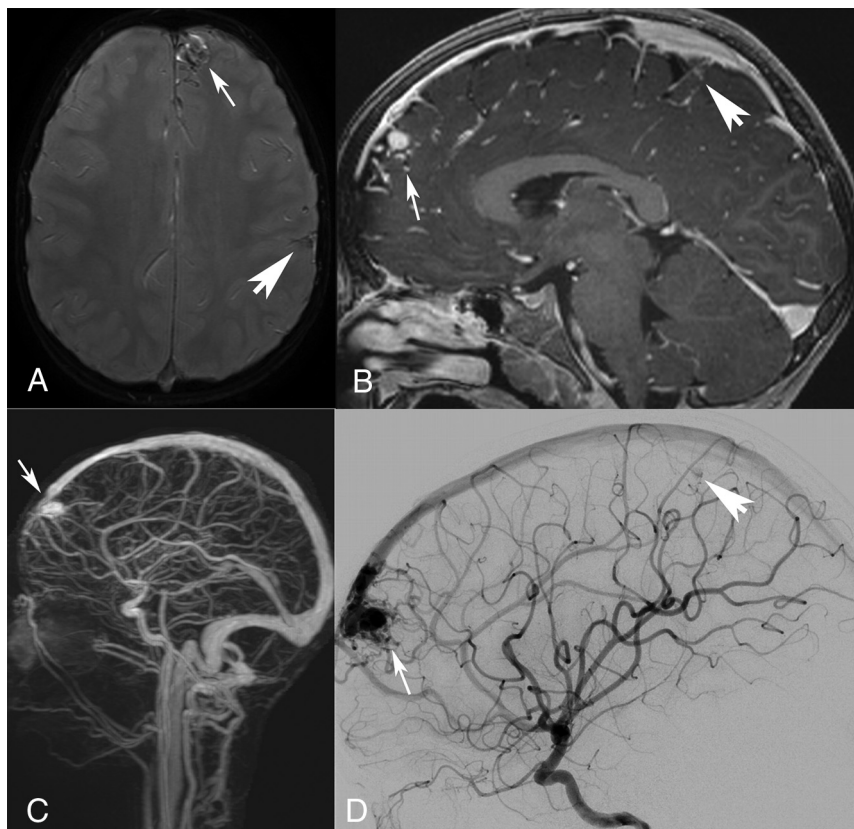
MATERIALS AND METHODS

This retrospective study was approved by the institutional review board and performed in compliance with Health Insurance Portability and Accountability Act. All patients evaluated at the University of California, San Francisco HHT Center of Excellence as of January 2017 were screened for inclusion in this study ($n = 343$). The medical charts of these patients were retrospectively reviewed, and demographic data including age, sex, Curacao criteria, genetic testing results, and the presence of patient-reported neurologic symptoms were collected, along with information on cerebral imaging to evaluate inclusion in this study.
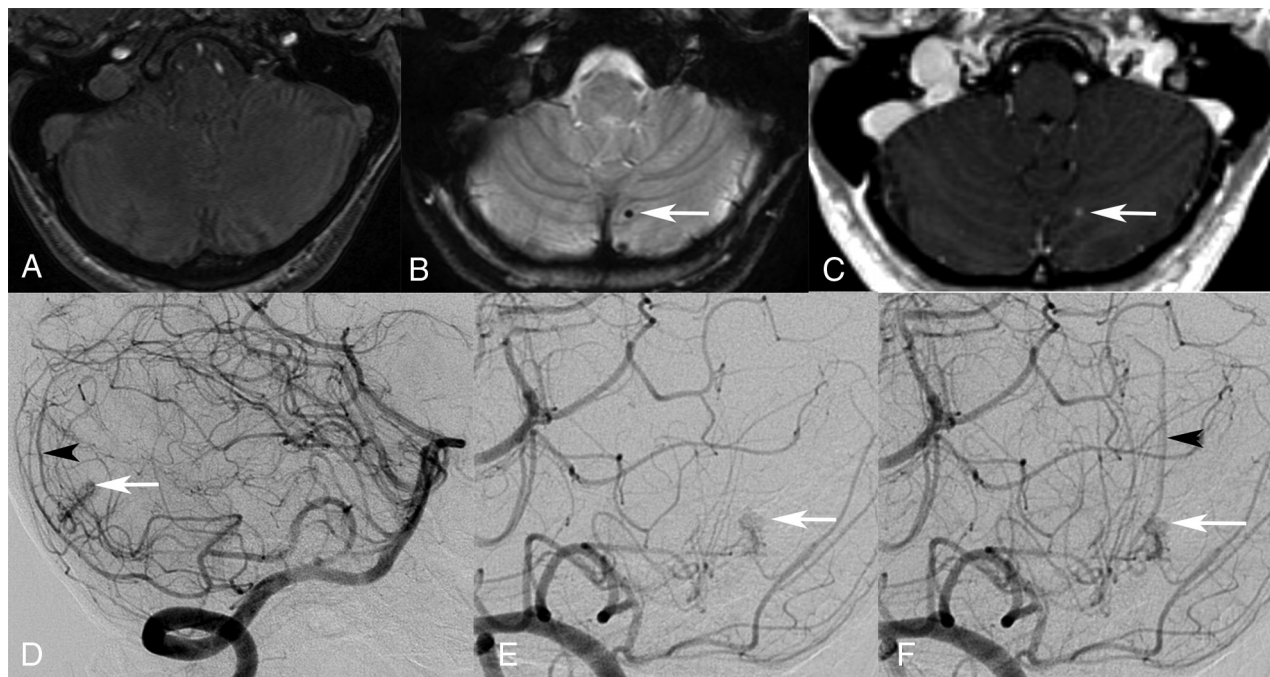
Inclusion criteria for the study were probable or definite HHT as defined by meeting at least 2 Curacao criteria or positive genetic testing as well as having at least 1 brain MR imaging and 1 cerebral DSA with images available for viewing on our PACS. Of the 343 patients reviewed, 246 met the study definition of probable or definite HHT, and of those, 63 patients had both sets of imaging available for our review and therefore met the full inclusion criteria.

All available MR imaging and MRA images for these 63 patients were retrospectively reviewed by a fellowship-trained neuroradiologist (M.D.A.), a subset of the studies (38 total) was reviewed by a second fellowship-trained neuroradiologist (M.C.M.), and any discrepancies between the 2 readers were adjudicated by a third fellowship-trained neuroradiologist (S.W.H.). All readers were blinded to the official reports. These readers evaluated each MR imaging study as a whole and recorded the total number of AVMs identified for each patient as well as on which sequences the AVMs were visible (3D-T1-weighted postgadolinium, 2D-T1-weighted postgadolinium, MRA, T2-weighted, SWI). Because these MRIs were performed at many different institutions (with patients later being referred to University of California, San Francisco) and on different types and field strengths (0.7T, 1.16T, 1.5T, and 3T) of MR imaging machines, there was no standardized set of sequences for the evaluated MRIs and MRAs. The cerebral DSA

FIG 2. Small cerebellar AVM in HHT: positive on MR imaging, negative on MRA, and positive on DSA. A 49-year-old woman with a cerebellar hemispheric AVM (*white arrow*) not apparent on TOF-MRA (*A*) but apparent with microhemorrhage on SWI (*B*), on 3D postgadolinium T1 (*C*), and on DSA (*D–F*). DSA (*D* and *F*) additionally distinguishes the AVM nidus (*white arrow*) from the AVM draining vein (*black arrowhead*).

images for all 63 cases were reviewed by a fellowship-trained neurointerventional radiologist (S.W.H.) who determined and recorded the total numbers of cerebral AVMs visible on DSA.

Once the totals were compiled, true- and false-positive rates of cerebral AVM detection were determined for each identified lesion, with DSA being used as the criterion standard. These data were then used to determine which MR imaging sequences had the highest rates of true-positive cerebral AVM detection. In addition, the sensitivity, specificity, and positive and negative predictive values of MR imaging as a whole (including all available sequences with and without gadolinium and including MRA if available) and each sequence individually were calculated. For these calculations, a true-positive screening MR imaging or sequence was considered to be one that showed any possible AVM even if the exact number of AVMs did not match the number seen on cerebral DSA.

RESULTS

Of the 63 patients evaluated, 65% were women, and the average age at the time of the evaluated MR imaging was 36 ± 20 years, with a range of 1–77 years (Table 1). The Curacao scores ranged from 1 to 4 because some included patients meeting only a single criterion had positive genetic testing. A total of 39 of the 63 patients underwent genetic testing for known HHT-causing gene mutations, the results of which are listed in Table 1. A total of 24 patients had not undergone genetic testing at the time of the study, 6 (9%) of whom had family members who tested positive for known disease-causing mutations. Self-reported neurologic symptoms ranging from headaches, dizziness, and paresthesias to syncope, seizures, transient ischemic attacks, and strokes were seen in 79% of patients. Two patients had clinically evident AVM rupture on presentation, both of whom were younger than 12 years of age.

Of the 63 patients whose imaging was evaluated, a total of 45 (71%) were found to have at least 1 cerebral AVM on criterion standard DSA imaging. A total of 92 individual cerebral AVM lesions were identified in these patients' cerebral DSAs. Of the identified lesions, 24 (26%) were seen only on cerebral DSA, 68 (74%) were seen on MR imaging and cerebral DSA, and 5 additional lesions were identified only on MR imaging. Examples of these lesions can be seen in Figs 1–4. Table 2 describes the percentage of total lesions seen on MR imaging as a whole as well as each evaluated sequence compared with the total number of lesions seen on MR imaging ($n = 73$) and DSA ($n = 92$). The lesions seen on MR imaging ranged from 2 to 55 mm. The sensitivity and specificity of MR imaging (including all available sequences with and without gadolinium) as a screening technique used to detect at least 1 cerebral AVM, which was then confirmed on criterion standard cerebral DSA, were 80.0% and 94.4%, respectively, and the positive and negative predictive values were 97.3% and 65.4%, respectively (Table 3).

Of the 63 MRIs evaluated, 54 (86%) included postgadolinium imaging, while the other 9 (14%) were noncontrast only. Table 4 describes additional characteristics of the MRIs performed, including the field strength and frequency of each type of sequence as well as the spatial resolution ranges for each sequence type. Of the 3 studies not performed on a 1.5T or 3T magnet, 1 was performed on a 0.7T magnet, 1 was listed as a 1.16T magnet, and 1 had the magnet strength information missing from the DICOM data. The sensitivity, specificity, and positive and negative predictive values of each of the sequences evaluated as well as MR imaging as a whole and MR imaging based on magnet strength are shown in Table 3.
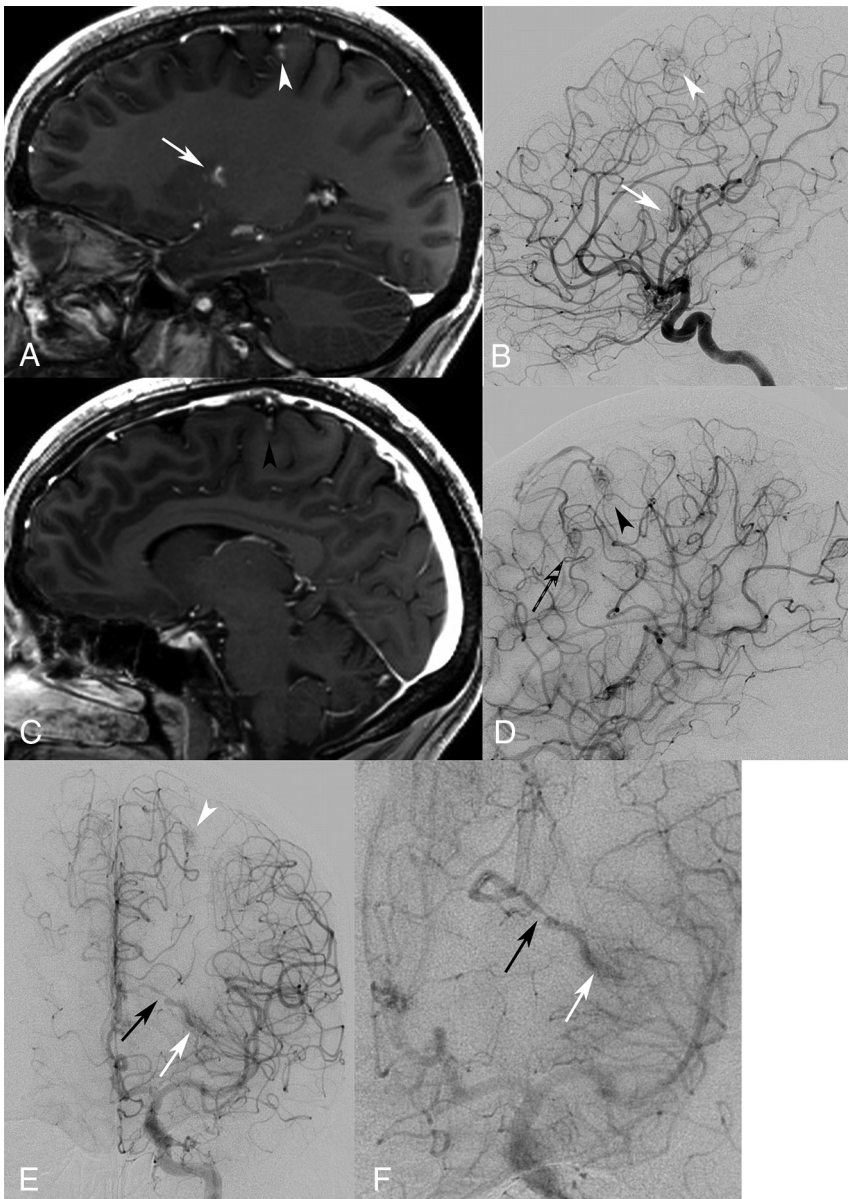
FIG 3. Multiple brain AVMs in HHT: positive on MR imaging, MRA, and DSA. A 23-year-old woman with 2 brain AVMs identified on MRA, 7 brain AVMs identified on MR imaging, and 11 identified on DSA. Selected images demonstrate a left basal ganglia AVM (*white arrow*) on 3D-postgadolinium T1 (*A*), left ICA lateral DSA (*B*), left ICA anterior-posterior arterial phase DSA (*E*), and magnified left ICA anterior-posterior capillary phase DSA (*F*). Note that the angioarchitecture of the basal ganglia AVM is best seen on DSA (*E* and *F*), including a high-grade stenosis of the deep draining vein of the AVM (*black arrow*). Although 3D-postgadolinium T1 image of the right hemisphere (*C*) demonstrates 1 cortical AVM (*black arrowhead*), right ICA lateral DSA (*D*) demonstrates 2 cortical AVMs; the more anterior of these lesions (*hashed arrow*) was only apparent on DSA.

The sensitivity, specificity, and positive and negative predictive values of each type of MRA can also be found in Table 3. Of note, the 2 postgadolinium-only MRA studies both yielded false-negative results, though the statistical significance of this finding is unclear, given the paucity of this type of case. In none of the 50 cases in which MRA was performed were there AVMs that were seen only on the MRA sequence and not on at least 1 additional sequence.

DISCUSSION

While current guidelines suggest that MR imaging be used as a screening tool for cerebral AVMs in patients with HHT, there are limited data on the accuracy of MR imaging in screening this particular patient population. Our study demonstrates that compared with the criterion standard DSA, MR imaging is relatively sensitive and specific when used to find cerebral AVMs in this population, with a sensitivity of 80.0%, specificity of 94.4%, and a negative predictive value of 65.4%. These data reflect the overall sensitivity and specificity of MR imaging as a screening technique, including all MR imaging sequences evaluated with and without gadolinium. This finding is similar to the reported 80%–95% sensitivity of MR imaging in detecting medium-to-large cerebral AVMs in the non-HHT population reported in the literature.[11-13] Our data, on the other hand, suggest that MRA alone (either TOF, postgadolinium, or a combination) as a screening technique is less optimal in the HHT population, with a sensitivity and specificity of 50.0% and 92.9%, respectively, and a negative predictive value of 41.9%. This finding is further supported by the fact that there were no cases in which a lesion was detected onl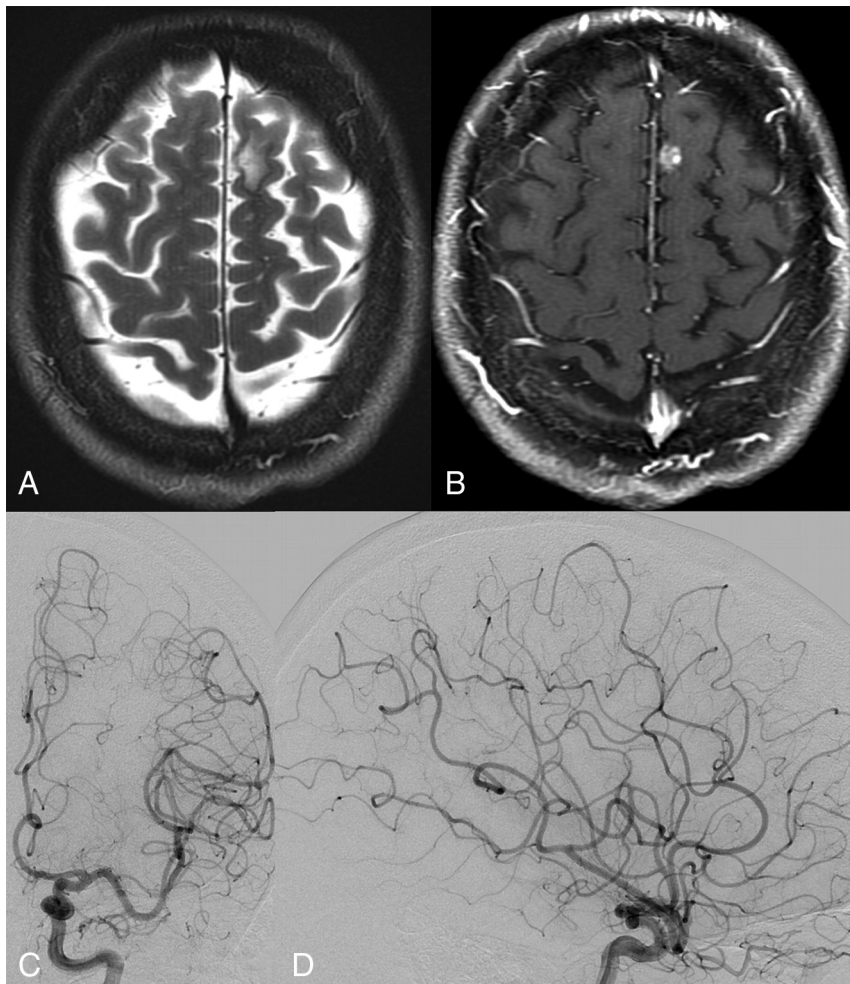y on an MRA sequence and not on other sequences as well, suggesting that the addition of MRA to the overall MR imaging did not affect the sensitivity and specificity of MR imaging as a whole. This study supports MR imaging performing well as a screening tool for brain AVMs in the HHT population seen at our Center of Excellence, while MRA should not be used as a sole screening tool for cerebral AVMs in this population.

Our data also suggest that of the MR imaging sequences analyzed, postcontrast imaging sequences were the most useful in detecting cerebral AVMs with 3D-T1 postgadolinium and 2D-T1

Of the patients evaluated, 50 had MRAs performed as part of their overall MR imaging examinations. Of these 50 MRAs, 26 (52%) were performed on a 1.5T magnet, 23 (46%) were performed on a 3T magnet, and 1 was reported as being performed on a 1.16T magnet. The sensitivity and specificity of MRA alone as a screening technique used to detect at least 1 cerebral AVM, which was then confirmed on criterion standard cerebral DSA, were 50.0% and 92.9%, respectively, and the positive and negative predictive values were 94.7% and 41.9%, respectively (Table 3).

FIG 4. Cerebral vascular lesion in HHT: positive on MR imaging and negative on MRA and DSA. A 72-year-old man previously treated with gamma knife radiosurgery for a left frontal AVM. T2 MR imaging (*A*) demonstrates gliosis in the superior frontal gyrus but no apparent AVM vessels, post-gadolinium 2D-T1 MR imaging (*B*) demonstrates an enhancing lesion in the superior frontal gyrus, and left ICA anterior-posterior (*C*) and lateral (*D*) DSA demonstrate no AVM.

Table 2: Number of AVMs seen on each evaluated MR image compared with the total number seen on each technique

Sequence	Total No. of AVMs Seen on Given Sequence	Percentage of all AVMs Seen on MR Imaging (*n* = 73)	Percentage of all AVMs Seen on DSA (*n* = 92)
Total AVMs seen on MR imaging	73	100.0%	79.3%
3D-T1 Postgad	49	67.1%	53.3%
2D-T1 Postgad	52	71.2%	56.5%
SWI	35	47.9%	38.0%
T2	24	32.9%	26.1%
MRA	25	34.2%	27.2%

Note:—Postgad indicates postgadolinium.

TOF-MRA alone showed poor sensitivity and negative predictive values, suggesting that these sequences would be poor screening tests, the studies that included both TOF and postcontrast MRA showed improved sensitivity and negative predictive values (70.0% and 75.0%, respectively, for the combination of TOF and postgadolinium MRA compared with 47.8% and 25.0%, respectively, for TOF-MRA alone), suggesting that the addition of postgadolinium MRA may improve the utility of this sequence.

In addition, our study suggests that 3T MR imaging is superior to 1.5T MR imaging, with a sensitivity of 85.7% and specificity of 100.0% compared with 72.7% and 92.9% in 3T versus 1.5T, respectively. While the MRIs performed on other field strengths also appeared to have high sensitivity and specificity, there were too few of these cases to draw firm conclusions.

Our study obviously has several limitations, the most important of which is the heterogeneity of the MR imaging studies that were evaluated. Because these studies came from many different sites, there was variation in the MR imaging magnet strength and the exact sequences performed; thus, we chose to stratify the sequences in the most general way possible rather than by individual manufacturer's sequence type. This heterogeneity of scanners and sequences may, therefore, lead our data to somewhat underestimate the true detection capability of these sequences. Additional studies evaluating a prospective cohort of patients with HHT all scanned on the same scanners with the same standardized protocol of imaging sequences may help to confirm the true sensitivity of each of these sequences in this population.

Whereas MR imaging is a noninvasive test used to screen patients with HHT for brain AVMs, DSA is an invasive test used to confirm findings on MR imaging and go beyond those findings to risk-stratify patients. Predicting the likelihood of future brain AVM rupture is the focus of many academic studies and is of paramount importance to individual patients and their physicians as they decide whether to treat any particular brain AVM. Susceptibility-weighted MR imaging sequences have demonstrated utility in detecting microhemorrhage within sporadic brain AVMs; this

postgadolinium sequences showing up to 56.5% of lesions later confirmed on cerebral DSA and 71.2% of those seen on MR imaging. These postgadolinium MR imaging sequences also showed good sensitivity and negative predictive values (86.2% and 69.2%, respectively, for 3D-T1 postgadolinium and 75.0% and 60.9% respectively, for 2D-T1 postgadolinium), which are desirable in a good screening test. While MRA on its own and more specifically

Table 3: Sensitivity, specificity, and positive and negative predictive values of MR imaging as a whole, individual MR imaging sequences, and MR imaging as a whole at different given magnet strengths for the presence of cerebral AVM[a]

	No. of Positive Studies	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Sequence					
MR imaging as a whole[b]	37	80.0%	94.4%	97.3%	65.4%
3D-T1 postgadolinium	25	86.2%	100.0%	100.0%	69.2%
2D-T1 postgadolinium	27	75.0%	100.0%	100.0%	60.9%
T2	20	54.1%	94.4%	95.2%	50.0%
SWI	23	51.2%	93.8%	95.7%	41.7%
MRA (any)[c]	19	50.0%	92.9%	94.7%	41.9%
TOF-MRA only	11	47.8%	100.0%	100%	25.0%
Postgadolinium MRA only	2	0.0%	NA	NA	0.0%
TOF and postgadolinium MRA	8	70.0%	90.0%	87.5%	75.0%
Magnet strength					
1.5T	17	72.7%	92.9%	94.1%	68.4%
3T	18	85.7%	100.0%	100.0%	50.0%
Other	2	100.0%	100.0%	100.0%	100.0%

Note:—NA indicates not applicable.

[a] A sequence (or MR imaging as a whole) was considered positive if it showed any number of AVMs even if the number did not ultimately match that seen on DSA.

[b] MR imaging as a whole included all available sequences with and without gadolinium evaluated for all patients.

[c] MRA (any) calculations included TOF and postgadolinium MRA either alone or in combination, depending on what was available for a given study.

Table 4: Characteristics of evaluated MRIs

Strength/Sequence	No. of Cases with Given Strength or Sequence (% of 63 Total Cases)	Range of Spatial Resolution
Magnet strength		
1.5T	36 (57.1%)	
3T	24 (38.1%)	
Other magnet strength	3 (4.8%)	
Sequence		
3D-T1 Postgadolinium	38 (60.3%)	0.4–5 mm
2D-T1 Postgadolinium	50 (79.4%)	1–5 mm
SWI	59 (93.7%)	1.6–6 mm
T2	53 (84.1%)	1–7.5 mm
MRA (any)	50 (79.4%)	0.5–2.6 mm
TOF-MRA only	28 (44.4%)	0.5–2.6 mm
Postgadolinium MRA only	2 (3.2%)	1–1.2 mm
TOF and postgadolinium MRA	20 (31.7%)	1–1.4 mm

finding is a predictor of future AVM rupture.[14] DSA can demonstrate detailed angioarchitectural features of AVMs that connote a higher risk of future rupture that are often not discernable on MR imaging, including feeding artery aneurysms, nidal aneurysms, and venous outflow stenosis.[15,16]

Our practice has been to perform DSA on patients with HHT who have either a brain hemorrhage or a potential brain AVM identified on screening MR imaging. Thus, another fundamental limitation of our study is that DSA is typically performed on patients who have a suspicious finding on MR imaging or MRA, not on patients who have normal MR imaging and MRA findings, thus likely undercounting the number of potential cerebral vascular malformations identifiable by DSA. There are, of course, small neurovascular lesions that may not be apparent on brain MR imaging but can be detected on DSA. In the HHT population, it would be expected that many of these very small malformations would be capillary vascular malformations that do not have arteriovenous shunting as opposed to nidus-type AVMs that do, by definition, have arteriovenous shunting. Although capillary lesions likely have a lower risk of hemorrhage than shunting lesions, the rupture rate of small shunting AVMs remains unknown.

Detection of such lesions, thus, remains important for clinical decision-making. Some patients and physicians choose treatment even of small unruptured brain AVMs to prevent future cerebral hemorrhage, particularly if there are angioarchitectural high-risk features, lesional microhemorrhage, genetic predisposition, or a family history of brain AVM hemorrhage.

CONCLUSIONS

This study reinforces the use of MR imaging as a primary screening tool for cerebral AVMs in patients with HHT and suggests that a combination of postgadolinium sequences, specifically 3D-T1 postgadolinium and 2D-T1 postgadolinium, has the highest yield for brain AVM detection in patients with HHT and that MRA, and in particular TOF-MRA, alone is not sensitive enough to be used as a sole screening tool.

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