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MR of Hereditary Hemorrhagic Telangiectasia: Prevalence and Spectrum of Cerebrovascular Malformations

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PURPOSE: **Our goal was to describe the prevalence and types of cerebral vascular malformations (CVMs) seen with MR imaging in patients with hereditary hemorrhagic telangiectasia (HHT).**

METHODS: **We reviewed retrospectively the brain MR images of 184 consecutive patients with HHT. Catheter angiography was performed in 17 patients with CVMs detected on MR images.**

RESULTS: **MR imaging revealed 63 CVMs in 42 patients. Classic arteriovenous malformations (n = 10) had a conspicuous network of vessels with flow voids and enlarged adjacent pial vessels. Apparent venous malformations (n = 5) were best seen after administration of contrast material as a prominent vessel coursing through normal brain parenchyma. Indeterminate vascular malformations (n = 48) had a spectrum of appearances characterized by variable combinations of heterogeneous signal intensity, enhancement, or hemosiderin. Angiography in 17 patients revealed 47 CVMs. Forty-six were arteriovenous malformations (AVMs), including 25 CVMs not seen with MR imaging and 21 CVMs that by MR criteria included 8 AVMs and 13 indeterminate vascular malformations. Angiography confirmed 1 venous malformation seen with MR imaging but failed to detect 3 indeterminate lesions revealed by MR imaging.**

CONCLUSION: **MR imaging of a large cohort of consecutive patients with HHT revealed a CVM prevalence of 23% (42/184). Most CVMs (48/63) have an atypical appearance for vascular malformations on MR images. Angiographic correlation suggests that MR imaging underestimates the prevalence of CVMs and that the majority of indeterminate CVMs, despite their variable MR appearance, are AVMs.**

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is an autosomal dominant vascular dysplasia. Although the original descriptions of this syndrome emphasized the association of epistaxis with mucocutaneous telangiectasia (1–4), subsequent reports have shown that multiple organs can harbor vascular abnormalities, including the brain, lungs, and gastrointestinal tract (5–10). Ten percent of patients are estimated to suffer serious morbidity or die prematurely from arteriovenous malformations (AVMs) of these three organ systems (7–9, 11). Recent genetic studies have linked HHT to chromosome 9q33-q34 in some families and to chromosome 12q in others (12–17). It remains unknown, however, how gene defects or other factors interact to cause vascular malformations.

Cerebral vascular malformations (CVMs) in patients with HHT are a manifestation of the underlying vascular dysplasia. These lesions represent abnormal arteriovenous connections that fail to differentiate properly into arteriolar, capillary, and venular channels (18, 19). Because CVMs can lead to neurologic deficits when they hemorrhage, it is important to recognize their imaging features, especially since evidence suggests a higher prevalence of HHT than previously recognized (9, 20–23).

Our institution established a screening program for patients with HHT by using standard magnetic resonance (MR) imaging techniques to test the hypothesis

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that CVMs are common in this patient population. We report our findings as to the prevalence and types of CVMs seen with MR imaging in a large number of HHT patients, and compare the MR findings with those of conventional cerebral angiography in a subset of patients.

Methods

From 1988 to 1995, 184 consecutive patients were examined in a specialized multidisciplinary clinic at a single institution. They were referred for screening MR imaging as part of their initial clinical assessment. Two of the three following criteria needed to be present to establish the diagnosis of HHT: nosebleeds at least four times a month, telangiectasia of the skin, and a mother or father with HHT (10). All patients had MR imaging consisting of axial T1-weighted sequences with parameters of 500/12/1 (repetition time [TR]/echo time/excitation), a matrix of 256 × 192, a 24-cm field of view (FOV), and 5-mm-thick sections with a 1-mm gap; dual-echo long-TR sequences (2000/30,80/1) with a 256 × 192 matrix, 5-mm-thick sections with a 2.5-mm gap, and a 24-mm FOV; axial or coronal gradient-recalled echo sequences (750/50) with a 10° flip angle, a 20-mm FOV, and 5-mm-thick sections with a 1-mm gap; and 128 patients had an axial T1-weighted sequence following administration of a standard dose of intravenous contrast material. All cases were reviewed retrospectively by three neuroradiologists to identify and classify vascular malformations. A consensus reading determined final categorization.

The AVMs were defined as those CVMs with one or more of the following MR features: a collection of enlarged vessels easily seen on both T2- and T1-weighted (without and with contrast enhancement) sequences; associated enlargement or ectasia of adjacent pial arteries and draining veins; a well-defined, relatively large nidus (>15 mm); and such secondary features as dilated proximal intracranial or extracranial arteries (angiomatous change) (24–27). Brain adjacent to AVM might show old hemorrhage, gliosis, or both.

Venous malformations were defined as those CVMs with all the following MR imaging features: a single enlarged vascular channel usually in a subcortical location (periventricular white matter, mesencephalon, deep cerebellum); no discernible enlargement of adjacent arteries; best seen after administration of contrast material; could be associated with smaller linear vascular channels orthogonal to the axial plane of the single enlarged vascular channel (caput medusae appearance); and normal adjacent brain (28, 29).

Cavernous malformations were lesions with a complete, concentric ring of curvilinear hypointensity on long-TR sequences that appeared to enlarge or "bloom" on gradient-recalled echo sequences; a complex multilobular center with septa and a speckled or reticulated appearance on T2-weighted sequences owing to a combination of hypointensities and hyperintensities; and no or minimal enhancement after administration of contrast material (30–33).

Indeterminate CVMs were lesions that did not fit into one of the three categories of cerebral AVMs, venous malformations, or cavernous malformations. Their MR features included a small, localized tangle of curvilinear structures (10 to 15 mm) without a discernible nidus; no enlargement of adjacent arteries and veins; curvilinear or punctate structures with variable combinations of localized hypointensity or hyperintensity on short- and long-TR images; curvilinear or punctate hypointensity on long-TR sequences that could bloom on gradient-recalled echo sequences but that did not form a complete, concentric ring; and improved visualization on contrast-enhanced T1-weighted sequences.

Conventional cerebral angiography was indicated in 17 patients with CVMs seen at MR imaging and who had focal neurologic (motor, sensory, visual, or language) deficits, seizures, or both. Catheter angiography was performed by selective hand injection of iohexol (4 to 6 mL) into each internal carotid artery, and at least one vertebral artery. High-resolution (1024 × 1024 matrix) digital subtraction angiography with magnification views or film-screen technique was used. AVMs were defined as lesions with a focal collection of abnormal vessels (nidus) located within the brain parenchyma that were associated with early visualization of veins during either the arterial or late capillary phase (ie, arteriovenous shunting). Venous malformations were lesions defined as aberrant, small branching vessels that coalesced into a larger single vessel that in turn connected to either a subcortical or subependymal vein. These malformations were always seen during the normal venous phase of angiography. Cavernous malformations usually do not have angiographic findings, although focal pooling of contrast material in the late capillary or venous phase can be seen, without evidence of arteriovenous shunting.

Results

MR Imaging Features

MR imaging revealed 63 CVMs in 42 patients. The types of CVMs included 10 AVMs in nine patients; five apparent venous malformations in five patients; and 48 indeterminate CVMs in 31 patients. Nine patients had multiple CVMs, ranging in number from two to five. Six of these patients had multiple indeterminate lesions and three had a combination of CVMs: one patient had two AVMs and one indeterminate lesion, and two patients had three indeterminate lesions and one AVM. No patient had classical MR imaging characteristics of cavernous malformations.

AVMs (Fig 1) had prominent dilatation of afferent and efferent vessels and nidus components (>15 mm) consisting of serpentine flow voids of various sizes on T1- and T2-weighted sequences. The observed flow voids were most likely caused by a combination of high-velocity blood flow and the dephasing effects related to laminar flow disturbance. The abnormal vessels of these cerebral AVMs tended to insinuate themselves within brain tissue rather than cause an encapsulated mass. Evidence of associated hemorrhage was occasionally identified in the form of hemosiderosis.

Apparent venous malformations had imaging features that most closely resembled those described for classic venous malformations of the brain. They were best seen or only seen on T1-weighted contrast-enhanced sequences and manifested as enhancing linear or punctate structures within a subcortical or subpial location (Fig 2). Occasionally, smaller vascular structures radiating into a larger, central vessel were observed. These CVMs were not associated with any signal abnormalities of adjacent brain. Since they had an MR imaging appearance very much like that described for venous malformations yet did not always have conventional angiographic correlation, we designated them as apparent venous malformations.

Indeterminate CVMs (n = 48) were a heterogeneous group of vascular lesions with a spectrum of MR appearances: some had features that resembled small cavernous malformations, others resembled venous malformations, mixed vascular malformations,

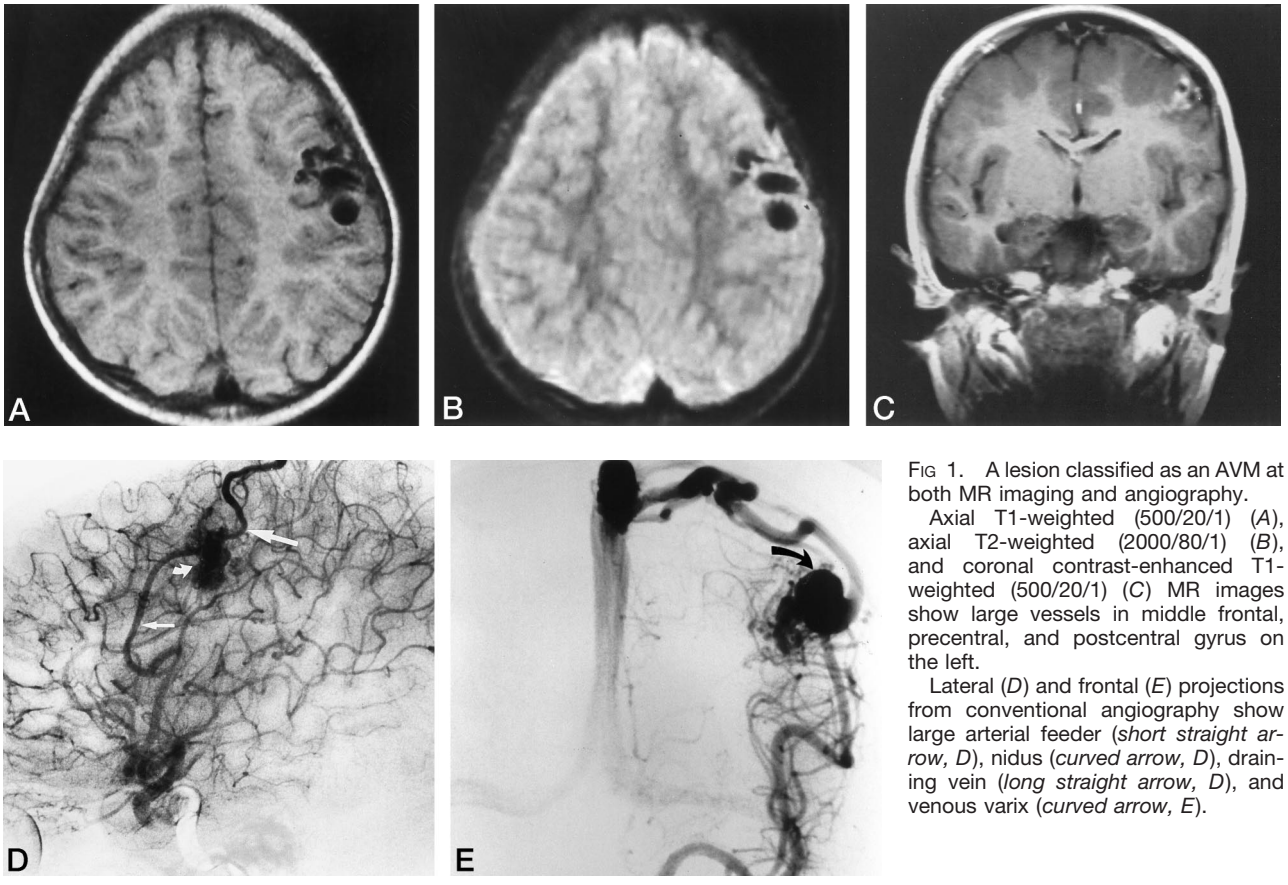

FIG 1. A lesion classified as an AVM at both MR imaging and angiography.

Axial T1-weighted (500/20/1) (*A*), axial T2-weighted (2000/80/1) (*B*), and coronal contrast-enhanced T1-weighted (500/20/1) (*C*) MR images show large vessels in middle frontal, precentral, and postcentral gyrus on the left.

Lateral (*D*) and frontal (*E*) projections from conventional angiography show large arterial feeder (*short straight arrow, D*), nidus (*curved arrow, D*), draining vein (*long straight arrow, D*), and venous varix (*curved arrow, E*).

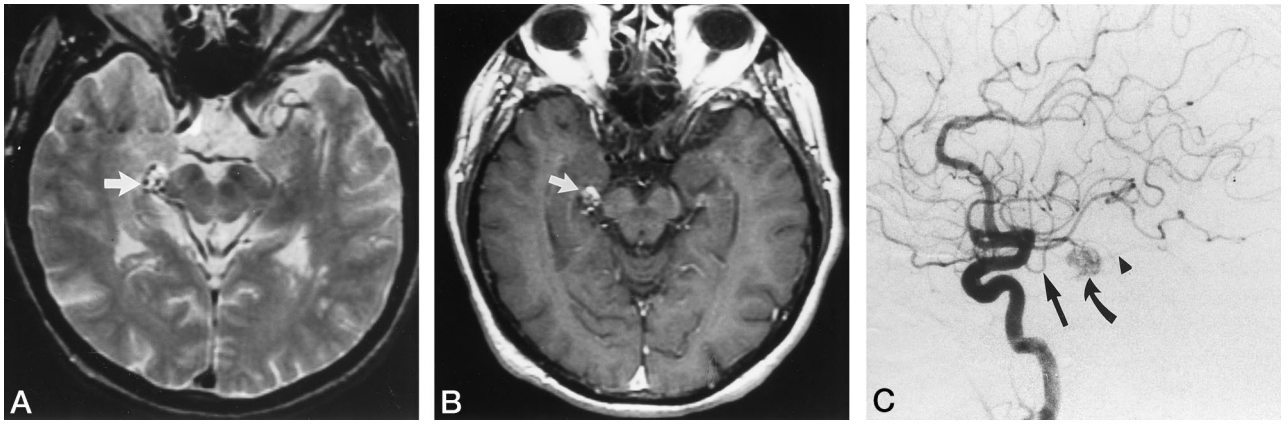

FIG 2. At MR imaging, this lesion was classified as an indeterminate malformation, but angiographic imaging revealed an AVM.

Axial T2-weighted (2000/80/1) (*A*) and axial contrast-enhanced T1-weighted (500/20/1) (*B*) images reveal a partially enhancing lesion with heterogeneous signal in the right perimesencephalic cistern (*arrows*).

C, Frontal oblique angiogram shows that this is an AVM with a feeding artery (*straight arrow*), nidus (*curved arrow*), and early draining vein (*arrowhead*).

or poorly defined vascular anomalies. Thirteen indeterminate lesions had angiographic correlation (see below). Indeterminate CVMs were small (5 to 15 mm) and appeared as ovoid lesions or as focal, curvilinear or patchy structures (Figs 3–6). The signal intensity on T2-weighted images was variable, appearing bright, dark, or both, and distributed in no particular pattern. Lesions were surrounded partially or interspersed by focal or curvilinear structures that had decreased signal intensity on both T1- and T2-weighted sequences. These hypointense structures sometimes bloomed on gradient-recalled echo sequences, but a complete ring of hypointensity was not seen. Indeterminate lesions had variable enhancement with contrast administration, with small lesions best seen on contrast-enhanced images as enhancing curvilinear structures (Figs 3 and 5). Although some indeterminate malformations had features suggestive of cavernous malformations (Fig 4), they did not have the classic pattern of a reticulated center of variable

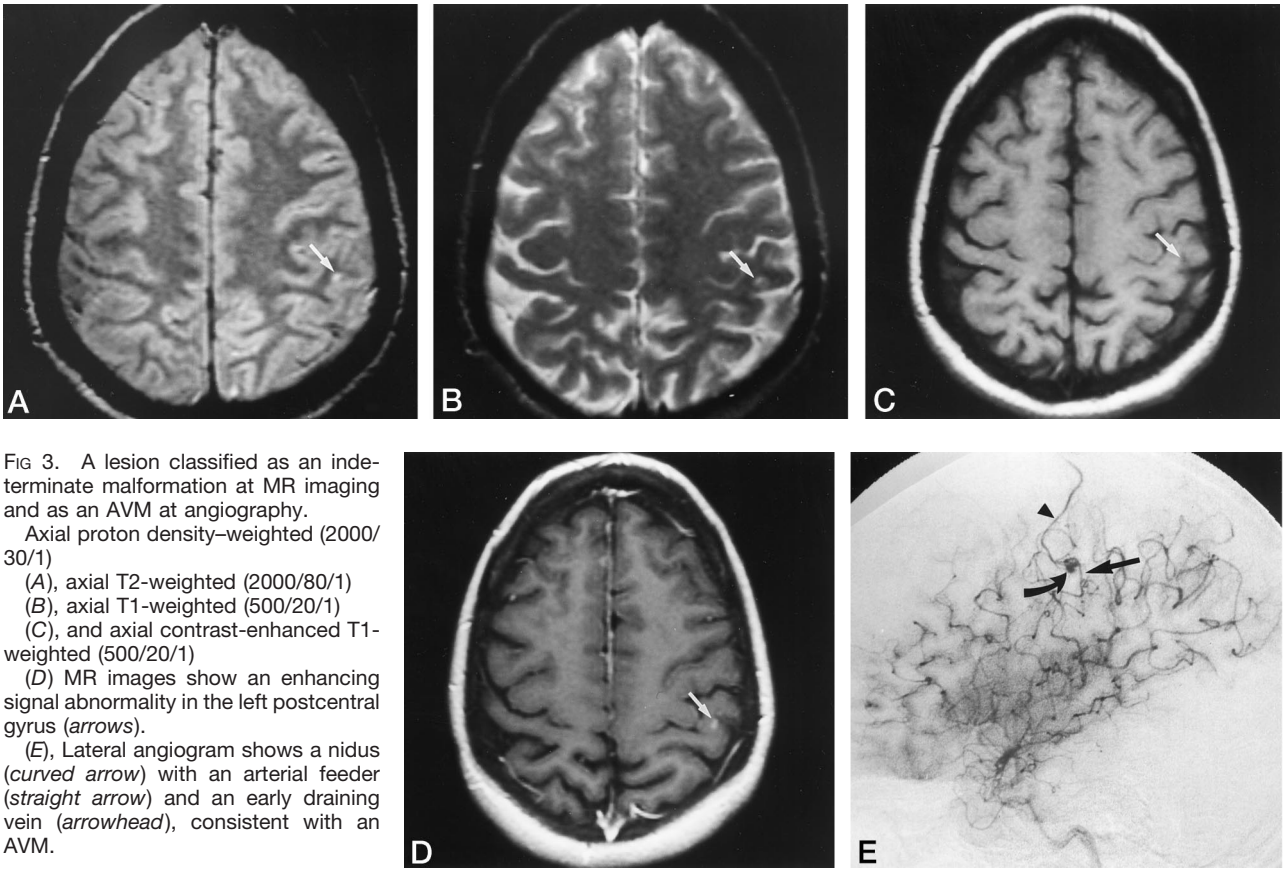

FIG 3. A lesion classified as an indeterminate malformation at MR imaging and as an AVM at angiography.

Axial proton density–weighted (2000/30/1) (*A*), axial T2-weighted (2000/80/1) (*B*), axial T1-weighted (500/20/1) (*C*), and axial contrast-enhanced T1-weighted (500/20/1) (*D*) MR images show an enhancing signal abnormality in the left postcentral gyrus (*arrows*).

(*E*), Lateral angiogram shows a nidus (*curved arrow*) with an arterial feeder (*straight arrow*) and an early draining vein (*arrowhead*), consistent with an AVM.

signal intensity surrounded by a peripheral ring of hemosiderin deposition. Because of this atypical appearance and lack of pathologic confirmation, we were reluctant to designate these lesions as cavernous malformations.

Conventional Angiographic Correlation

Among the 17 patients who underwent catheter angiography, 16 had at least one CVM, and a total of 47 CVMs were found. Multiple CVMs (ranging in number from two to nine) were seen in nine patients. Of 47 CVMs identified at angiography, 46 were categorized as AVMs, including 25 CVMs not seen with MR imaging and 21 CVMs that by MR criteria included eight AVMs and 13 indeterminate vascular malformations (Table). One venous malformation observed with MR imaging corresponded to a venous malformation seen at angiography. Three indeterminate CVMs detected by MR imaging in three patients were not seen with conventional angiography. The 46 AVMs identified at angiography typically consisted of a relatively small nidus (3 to 25 mm in maximal dimension), usually with a single feeding artery and a single draining vein (Figs 3–5). Because of their small size and relatively small amount of associated arteriovenous shunting, these AVMs were seen best in the late arterial phases of angiography (Fig 3). No angiographic findings suggesting a cavernous malformation were seen.

Discussion

Early reports of HHT date back to the middle of the 19th century (1), followed by separate reports by Rendu, Osler, and Weber near the turn of the century documenting hereditary epistaxis and telangiectases (2–4). The term hereditary hemorrhagic telangiectasia was first used by Hanes in 1909 (34). Subsequent reports in this century showed that many organ systems can be involved by the vascular dysplasia (5–9). HHT occurs worldwide in different racial and ethnic groups and is more common than previously recognized (9, 20–23). With recent studies in genetics showing that HHT is a group of autosomal dominant disorders (12–17), continued advances at the molecular level may reveal the mechanisms responsible for the vascular dysplasia.

Once considered a rare condition that causes minimal discomfort, HHT is becoming recognized as a cause of substantial morbidity and mortality (6, 8, 9, 35). A number of clinical problems result from arteriovenous shunting; these are especially acute in the nervous system, causing patients to be at risk for a variety of neurologic problems, including migraine headache, seizures, brain abscess, infarct, and intraparenchymal and subarachnoid hemorrhage. For patients with HHT in general, the prevalence of neurologic symptoms ranges from 8% to 27% (36–40) (J. C. Chaloupka, R. K. Fulbright, P. B. Fayad, et al, "The Detection of Cerebral Vascular Malformations

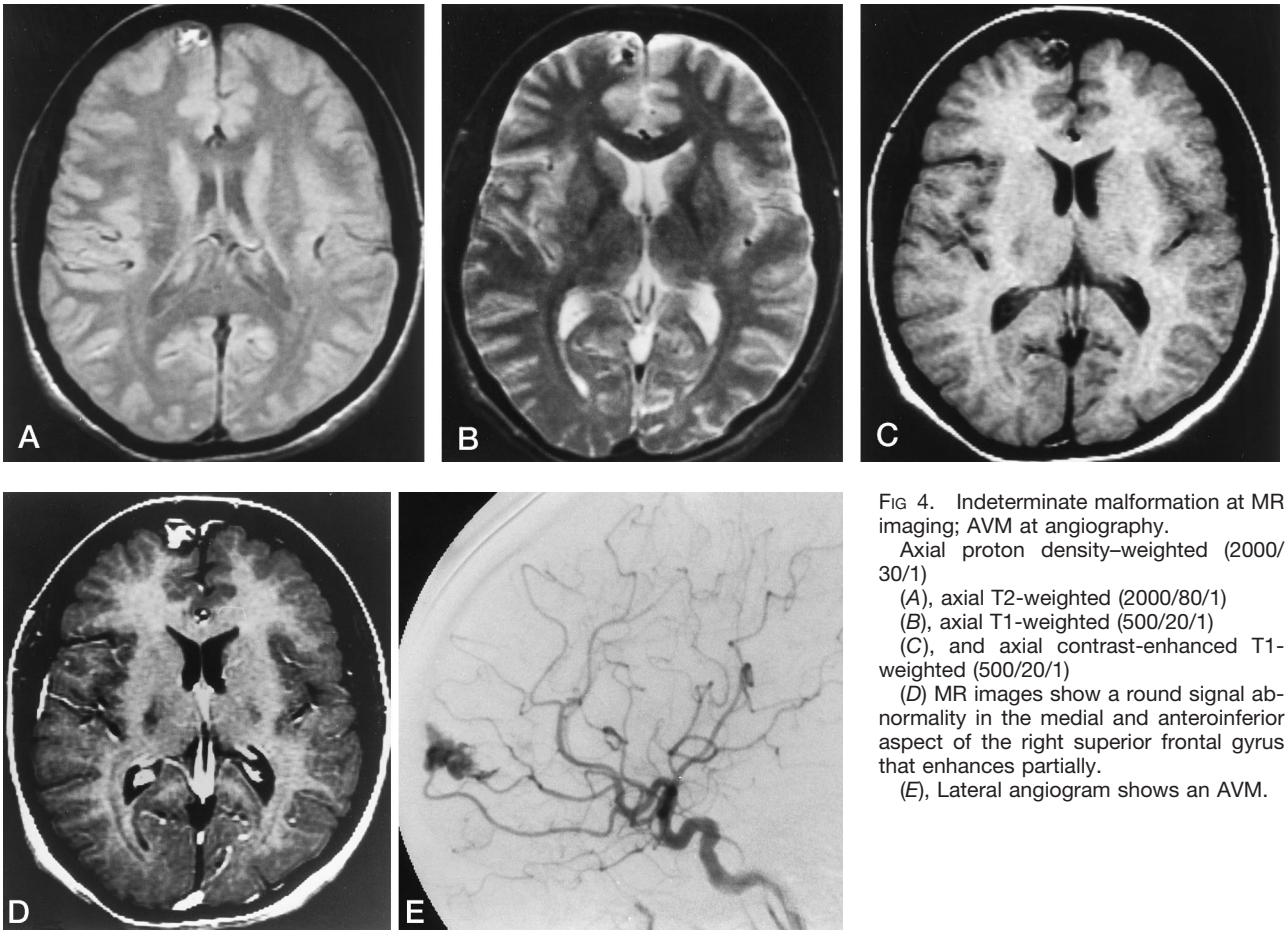

FIG 4. Indeterminate malformation at MR imaging; AVM at angiography.

Axial proton density–weighted (2000/30/1) (*A*), axial T2-weighted (2000/80/1) (*B*), axial T1-weighted (500/20/1) (*C*), and axial contrast-enhanced T1-weighted (500/20/1) (*D*) MR images show a round signal abnormality in the medial and anteroinferior aspect of the right superior frontal gyrus that enhances partially.

(*E*), Lateral angiogram shows an AVM.

in Patients with Hereditary Hemorrhagic Telangiectasia by Screening MRI/MRA," presented at the annual meeting of the American Association of Neurological Surgeons, San Diego, Calif, April 1995). Among patients with neurologic deficits, 61% are due to embolic complications of pulmonary AVMs and approximately 28% result from intracerebral hemorrhage of CVMs (6). Patients with HHT and pulmonary AVMs are 11 times more likely to have imaging evidence of ischemia than are patients without pulmonary AVMs (38).

In our study, a large number of consecutive patients with HHT (n = 184) were studied with MR imaging at a single institution, and among these patients, the prevalence rate of CVMs was 23% (42/184). Of the 63 vascular lesions found in 42 patients, indeterminate lesions with variable signal intensity, enhancement, and hemosiderin were most frequent (48/63, 76%), but lesions resembling classic descriptions of venous malformations (5/63, 8%) and AVMs (10/63, 16%) were also seen.

Compared with conventional angiography, MR imaging underestimated the number and nature of CVMs, unlike in previous reports, which indicated that MR imaging is similar to catheter angiography in the detection of CVMs (41–43). Those studies, however, did not identify AVMs by screening consecutive patients, but were retrospective collections of patients with fairly large AVMs (most were 3 to 7 cm). The CVMs undetected by MR imaging in our study had a small nidus and small efferent and afferent vessels resulting from modest arteriovenous shunting (observed on conventional angiography), and probably fell below the spatial resolution of MR sequences typically used for whole-brain coverage. Figures 3 and 5 exemplify the subtle appearance that small CVMs can have on MR images. Many CVMs did not have associated hemorrhage, infarction, or gliosis—conditions that MR imaging can easily detect. Lack of contrast administration in 56 (30%) of 184 patients also contributed to underestimation of CVM prevalence. Thinner sections, use of background suppression techniques like magnetization transfer, and administration of triple-dose contrast agent might have improved lesion detection.

The exact nature of lesions that had an indeterminate MR appearance remains incompletely defined. The heterogeneous MR signal was probably due to various rates of blood flow and, possibly, to hemorrhagic products. On the basis of correlation with findings at conventional angiography in a small number of patients, these lesions appear to represent small AVMs with abnormal arteriovenous architecture characteristic of vascular malformations found in other organs of patients with this syndrome. A pathoanatomic study of the small skin telangiectasias in patients with HHT showed microscopic plexiform arteriovenous fistulas with substantial arteriovenous

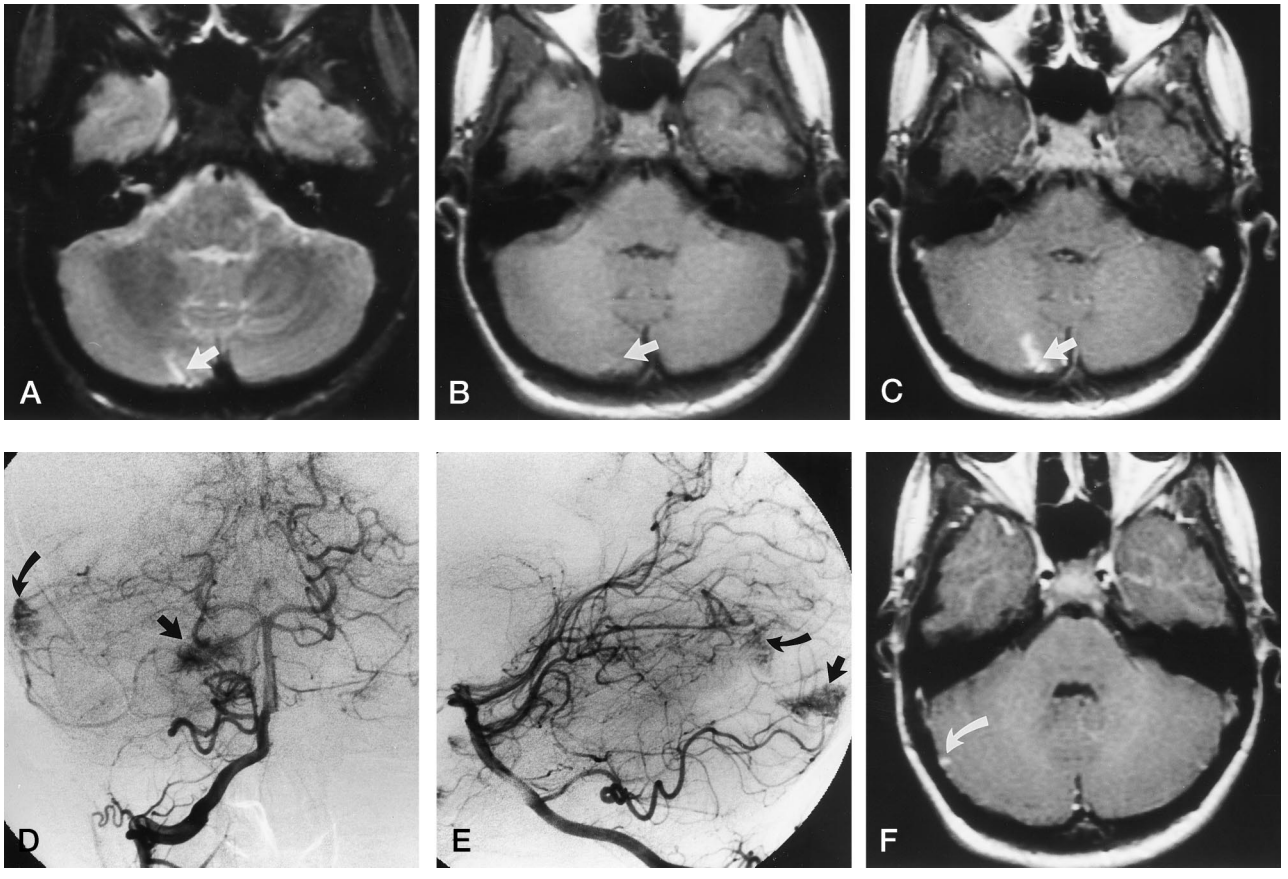

FIG 5. Axial T2-weighted (2000/80/1) (*A*), axial T1-weighted (500/20/1) (*B*), and axial contrast-enhanced T1-weighted (500/20/1) (*C*) MR images show an enhancing signal abnormality in the superior semilunar lobule of the right cerebellar hemisphere that was interpreted as an indeterminate vascular malformation (*arrows*).

Frontal (*D*) and lateral (*E*) angiograms reveal that the lesion is an AVM (*straight arrows*). A second lesion (*curved arrows*) was not reported at MR imaging, but was present in retrospect (*arrow, F*) in a section superior to *A–C*.

shunting (44). Such fistulous malformations have been demonstrated in the nasal mucosa, lung, and liver (7, 45). It is also possible that CVMs with hemosiderin deposits represent the sequela of small AVMs, venous malformations, cavernous malformations, or other lesions that have hemorrhaged, and that some of the small vascular malformations best seen after contrast administration are venous malformations (33, 46, 47). The bias inherent in a retrospective review of patients with suspected vascular lesions could have resulted in indeterminate lesions being classified as CVMs when they might instead have represented neoplasm, infection, inflammation, or old trauma. Additional angiographic and pathologic correlation in a larger number of patients will better define these cerebral lesions.

The clinical significance of CVMs detected in patients with HHT is unclear. If most CVMs represent AVMs, they could have a cumulative annual risk of hemorrhage similar to sporadically occurring cerebral AVMs (3% to 4%) in the general population (48–50). But there is evidence that AVMs in HHT could have a different natural history: pulmonary AVMs in patients with HHT can grow, and with growth there is a higher risk of neurologic complications, such as paradoxical embolic stroke and brain abscess (11). There is also evidence that the number of vascular lesions in the skin, nose, and gastrointestinal tract can increase over time (8). These findings raise the intriguing possibility that CVMs of HHT might grow or increase in number as well. The potential for an increase in size and number of CVMs combined with the frequent occurrence of multiple CVMs in a single patient (51) might translate into an increased cumulative risk of neurologic morbidity in patients with HHT than in those without. Validation of this hypothesis requires a study using life-table analysis of a sufficient number of HHT patients with CVMs.

We advocate screening HHT patients with contrast-enhanced MR imaging. If CVMs are detected, evaluation with conventional angiography will better define the type of vascular malformation. Therapeutic options are based on lesion size and architecture, on how accessible the lesion is to embolization or open resection, and on the patient's symptoms. Preoperative embolization and surgery are used for large AVMs that are accessible or for AVMs with angioarchitectural features like high shunt flow, venous outlet obstruction, and intranidal aneurysms that place the patient at risk for hemorrhage and ischemia (51). If lesions can not be approached surgically, stereotactic radiosurgery and, if necessary, embolization are

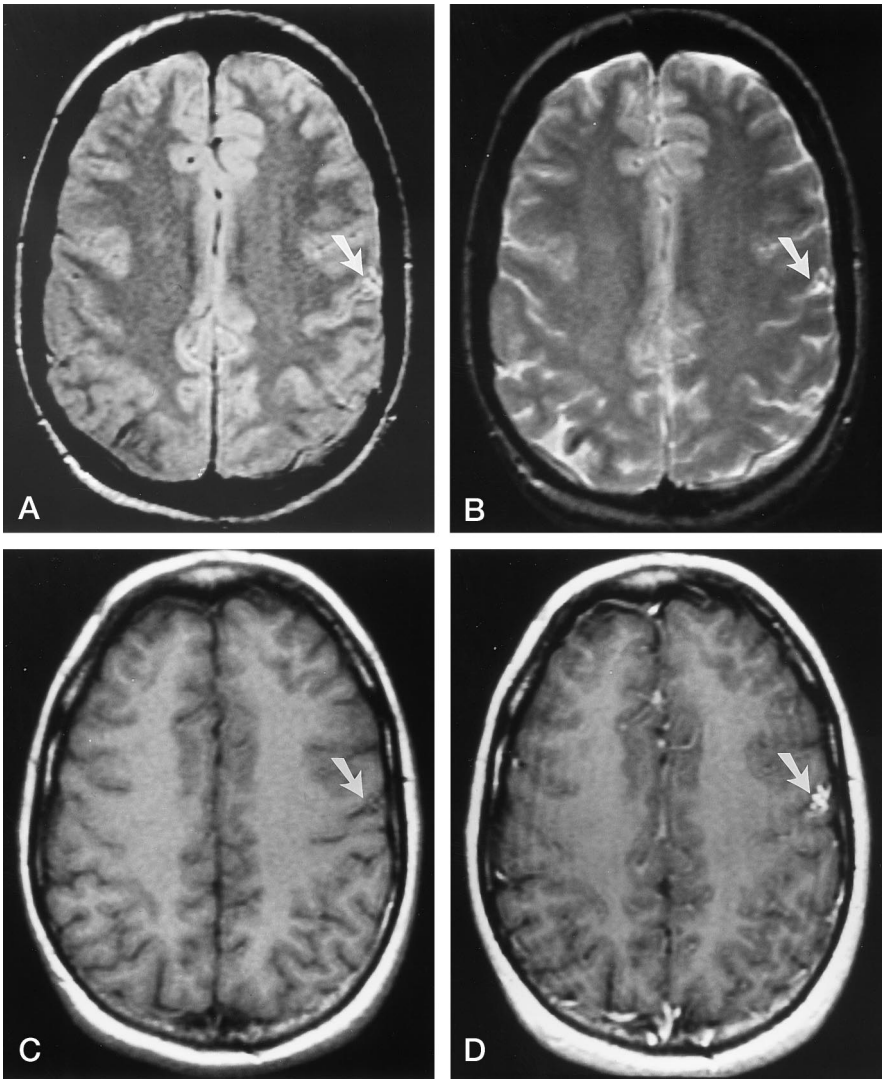

FIG 6. A lesion that was interpreted as an indeterminate vascular malformation at MR imaging; no angiography correlation was available.

Axial proton density–weighted (2000/30/1) (*A*), axial T2-weighted (2000/80/1) (*B*), axial T1-weighted (500/20/1) (*C*), and axial contrast-enhanced T1-weighted (500/20/1) (*D*) MR images show a lesion (*arrows*) in the left central sulcus with heterogeneous signal intensity and enhancement. On the basis of cases with a similar MR appearance that had angiographic correlation, we determined that this lesion was most likely an AVM.

MR and Angiographic Correlation of Number of Cerebrovascular Malformations Seen in 17 Patients with Hereditary Hemorrhagic Telangiectasia

MR Classification		Angiographic Classification			
		Arteriovenous	Venous	Cavernous	Not Seen
Arteriovenous	8	8	0	0	0
Venous	1	0	1	0	0
Cavernous	0	0	0	0	0
Indeterminate	16	13	0	0	3
Not seen	25	25	0	0	0
Total	**50**	**46**	**1**	0	**3**

used. We recommend that other lesions (those smaller than 1 cm or that have modest arteriovenous shunting and no intranidal aneurysms) be followed up with MR imaging every 1 to 3 years, and with cerebral angiography every 5 years. Definitive therapy is recommended if a small lesion increases in size or develops evidence of hemorrhage or worrisome architecture. Until the natural history of CVMs in HHT patients is better defined, and because MR imaging can miss small lesions, patients without CVMs on the initial MR study are examined with subsequent contrast-enhanced MR imaging 3 to 5 years later. Although this study did not evaluate MR angiography, we believe there is no role for MR angiography in screening for CVMs; however, it might supplement the evaluation of select cases of known CVMs, especially as technical advances continue.

Conclusion

MR imaging of a large cohort of consecutive patients with HHT revealed a CVM prevalence of 23%. Most frequent were indeterminate lesions with variable combinations of abnormal signal and enhancement, followed by lesions that resembled classic AVMs and venous malformations. Our preliminary experience with cerebral angiography suggests that, despite a range of MR appearances, most indeterminate lesions appear to represent AVMs and that MR imaging can underestimate the prevalence of CVMs.

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