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Exceptional multiplicity of cerebral arteriovenous malformations associated with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome).

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This information is current as of April 22, 2024.

AJNR Am J Neuroradiol 1996, 17 (9) 1733-1742
<http://www.ajnr.org/content/17/9/1733>

Exceptional Multiplicity of Cerebral Arteriovenous Malformations Associated with Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

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PURPOSE: To describe the clinical and imaging features of seven patients with hereditary hemorrhagic telangiectasia and an exceptional number of cerebral arteriovenous malformations (AVMs). **METHODS:** One hundred thirty-six patients from a dedicated hereditary hemorrhagic telangiectasia clinic were screened systematically for cerebral AVMs by means of MR imaging. Thirty-one were found to have abnormalities suggestive of a vascular malformation. Eighteen of these 31 patients subsequently underwent diagnostic cerebral angiography. **RESULTS:** Of the 18 patients who had cerebral angiography, all were found to have at least one AVM and seven were found to have three or more AVMs. The number of cerebral AVMs detected ranged from three to nine. At angiography, the AVMs varied in size from 3 to 25 mm in maximal dimension and consisted of a poorly defined plexiform nidus that typically had a single arterial feeding pedicle and a single draining vein. The two largest AVMs (20- and 25-mm nidus, respectively) contained intranidal aneurysms. Treatment included embolization, surgical excision, or follow-up management. **CONCLUSIONS:** Multiple cerebral AVMs are associated with hereditary hemorrhagic telangiectasia and further highlight the uniqueness of central nervous system involvement by this systemic angiodyplasia. MR imaging can underestimate the number and size of cerebral AVMs; therefore, catheter angiography is necessary to establish the extent of central nervous system involvement in this disorder.

Index terms: Arteriovenous malformations, cerebral; Telangiectasia

AJNR Am J Neuroradiol 17:1733-1742, October 1996

Multiple concurrent cerebral arteriovenous malformations (AVMs) are rare; a few such cases have been reported in large series of patients (1-7). The finding of more than three concurrent cerebral AVMs in a single patient is considered exceptionally rare; we found three cases described (1, 7, 8).

Hereditary hemorrhagic telangiectasia (HHT), otherwise known as Osler-Weber-Rendu

syndrome, is an uncommon angiodyplastic disorder with autosomal dominant inheritance. It is characterized by so-called telangiectasia of the skin, mucous membranes, and viscera, which have a propensity for hemorrhagic complications. Most patients with HHT have recurrent epistaxis from these lesions, although gastrointestinal bleeding, hemoptysis, hematuria, and intracranial hemorrhage are also observed (8, 9). In fact, evidence has been mounting that HHT frequently produces significant vascular abnormalities within the brain and spinal cord that may result in hemorrhage (1, 6-8, 10-30).

We describe seven patients in whom multiple cerebral AVMs were found, including three patients in whom the number of lesions either matched or exceeded that previously reported within a single patient. All AVMs in this series occurred in association with HHT. The marked

Received December 26, 1995; accepted after revision April 18, 1996.
Presented at the annual meeting of the American Society of Neuroradiology, Chicago, Ill, April 1995.

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AJNR 17:1733-1742, Oct 1996 0195-6108/96/1709-1733

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multifocality of the AVMs in these patients highlights the potential widespread nature of angiodyplasia affecting the central nervous system.

Subjects and Methods

Between 1988 and 1995, 136 patients referred to a dedicated HHT clinic were systematically screened with magnetic resonance (MR) imaging of the brain. The diagnosis of HHT was confirmed if the patient met two of three major criteria: presence of telangiectasia, recurrent hemorrhagic episodes, and family history of HHT (31). All patients were examined by a multidisciplinary team consisting of a neurologist, a neurosurgeon, and an interventional neuroradiologist. All sequential patients seen in the clinic underwent MR imaging. Screening MR consisted of standard axial spin-echo T1-, proton density-, and T2-weighted imaging; axial gradient-echo imaging; and contrast-enhanced axial spin-echo T1-weighted imaging. Two neuroradiologists evaluated the images for evidence of vascular malformations with arteriovenous shunting (dural arteriovenous fistula, pial arteriovenous fistula, or cerebral arteriovenous malformation) (32). Abnormal vessel enlargement (venous or arterial), an abnormal number or clustering of vessels, and increased venous velocity were considered evidence of arteriovenous shunting and sufficient to refer the patient for angiography. In addition, areas of linear enhancement, hemorrhage, or hemosiderin deposition were regarded as grounds for angiography. All patients with imaging findings suggestive of a cerebral vascular malformation were referred for diagnostic cerebral angiography. High-resolution digital subtraction angiography (1024 × 1024 matrix) with magnification views was performed after selective injection of both internal carotid arteries and at least one vertebral artery. All angiograms were obtained with the smallest possible focal spot (0.3 cm) at a standard frame rate (1.9 to 2.5 frames per second). Filming was carried out to the late venous phase. The clinical history, findings at physical examination, and imaging findings of patients with multiple cerebral AVMs were reviewed with special attention to comparing the MR findings with results of cerebral angiography.

Results

Of 136 patients examined with MR imaging, 31 had imaging findings suggestive of a cerebral vascular malformation. Of these, 18 had cerebral angiography. The remaining 13 patients are either awaiting cerebral angiography or have been lost to follow up.

Cerebral angiography showed 48 AVMs in 18 patients. Eleven patients had a single AVM. Seven patients had a total of 37 AVMs, with each having three or more. No dural arteriovenous fistulas or pial arteriovenous fistulas

were found. The clinical and imaging findings of these seven patients are summarized in the Table. None were from the same family, and five had family histories of cerebral AVMs. Only two were symptomatic at presentation. Patient 3 had seizures, which could not be reliably attributed to the AVMs owing to insufficient diagnostic evaluation. Patient 6 had an acute neurologic deficit, which was believed to be due to one of four separate foci of intraparenchymal hemorrhage seen on MR images. None of the other patients has had documented intracranial hemorrhages. Patients 4, 5, and 7 each had four separate AVMs. Patients 1, 2, 3, and 6 had five, nine, eight, and three separate AVMs, respectively. MR imaging revealed lesions suggestive of vascular malformations in a minority of the total number of cerebral AVMs detected at angiography (8 of 37) (Fig 1). Only eight of 17 lesions seen on MR images had the classic appearance of a cerebral AVM. The majority of lesions had nonspecific imaging features (eg, abnormal focal enhancement on contrast-enhanced spin-echo T1-weighted images) or had features suggestive of small venous malformations (Fig 2). In only three instances (patient 6) were abnormalities seen on MR images that were not detected at cerebral angiography (Fig 3).

At angiography, the AVMs varied in size from 3 to 25 mm in maximal dimension, and consisted of a plexiform nidus (ie, a network of interconnected microvasculature) that typically had a single arterial feeding pedicle and a single draining vein. Venous drainage was through superficial cortical veins to the dural sinuses in all cases. In several instances, because of their small size and relatively small amount of associated arteriovenous shunting, the AVMs were best seen in the late arterial phases of angiography (Fig 4). The AVMs were found in both supratentorial and infratentorial locations. There were no AVMs in periventricular or intraventricular locations. In patient 7, the largest AVM, in the right cerebellar hemisphere, could only be seen on the ipsilateral vertebral injection because the primary arterial supply was from the right posterior inferior cerebellar artery. The two largest lesions (20 and 25 mm, respectively), which were detected in two different patients (patients 1 and 2), contained intranidal aneurysms. These AVMs were treated with endovascular therapeutic embolization followed by surgical excision. One additional smaller

TABLE 1: Clinical and imaging findings in seven patients with hereditary hemorrhagic telangiectasia

	Patient						
	1	2	3	4	5	6	7
Age/Sex	28 y/M	27 y/M	29 y/M	41 y/F	9 y/M	6 wk/F	19 y/F
No. of AVMs	5	9	8	4	4	3	4
Signs and symptoms	None	None	Seizures	None	None	ICH, deficit	None
Medical history	Cerebral palsy, seizures	None	None	Pulmonary AVM	Epistaxis, scalp AVM	Vocal cord paralysis	Epistaxis
Findings at neurologic examination	L hemiparesis with sensory loss	Normal	Normal	Normal	Normal	L visual field defect	Normal
MR findings	3 AVMs: Focal lesions c/w AVMs: L medial precentral gyrus, L lateral supramarginal gyrus, L medial superior frontal gyrus	2 AVMs: 5 × 7-mm lesion in middle frontal gyrus and 7-mm lesion in R sylvian fissure c/w AVMs	2 AVMs, 2 IVAs: 2 × 1.5-cm lesion in posterior L inferior frontal gyrus, 10-mm lesion in R insula c/w AVMs; 2 focal regions of abnormal enhancement in R cerebellar hemisphere and a possible venous malformation in R colliculus	1 IVA: Hemosiderin in R frontal lobe with encephalomalacia; small foci of enhancement in L parietal lobe	1 AVM: L posterior parietal lobe infarct, L sylvian fissure AVM	5 IVAs: Subacute parenchymal hemorrhage in L sylvian fissure, L occipital lobe, R brachium pontis, L side of cerebellum; enlarged vessel R parietal lobe	1 IVA: Focus (1 cm) of enhancement in R cerebellar hemisphere
Angiographic findings	5 AVMs: 3 in L paramedian frontal lobe, 2 in L lateral frontal lobe (operculo frontal region and precentral gyrus)	9 AVMs: 3 in R frontal lobe, 2 in B parietal lobes, 3 in L frontal lobe, 1 in L occipital lobe	8 AVMs: 2 in L frontal lobe, 1 in L parietal lobe, 1 in R colliculus, 1 on R side of cerebellum, 2 in B occipital lobe	4 AVMs: 1 in R frontal lobe, 1 in L frontal lobe, 1 in L temporal parietal lobe (R side of scalp)	4 AVMs: 1 in R occipital lobe, 1 on R side of cerebellum, 1 in L frontal lobe, 1 in L parietal lobe (R side of scalp)	3 AVMs: 1 in R frontal lobe, 1 at R pontomedullary junction, 1 in R occipital pole	4 AVMs: 1 in L frontal lobe, 1 in L temporal lobe, 2 on R side of cerebellum

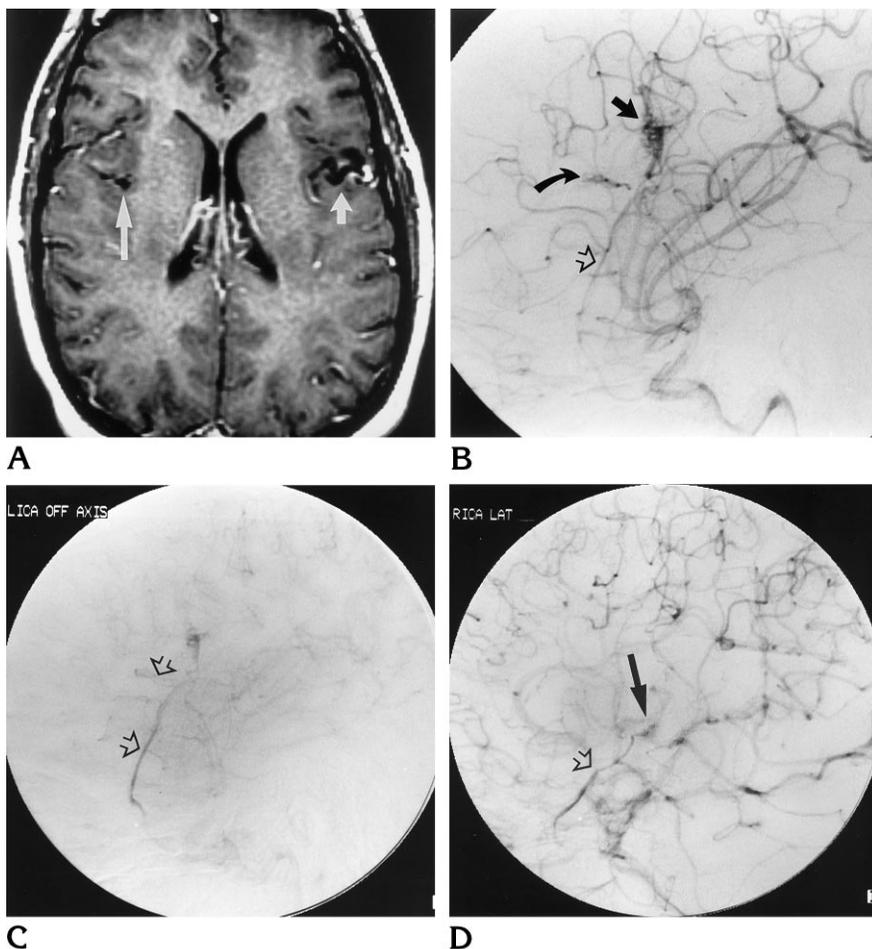
Note.—AVM indicates arteriovenous malformation; B, bilateral; c/w, consistent with; ICH, intracranial hemorrhage; and IVA, indeterminate vascular abnormality.

Fig 1. A, Contrast-enhanced T1-weighted MR image shows a serpiginous flow void in the left sylvian fissure compatible with a cerebral AVM (*short arrow*). A second small lesion is present in the right sylvian region (*long arrow*).

B, A left internal carotid artery (ICA) angiogram shows the cerebral AVM in the left sylvian fissure (*straight solid arrow*) and a second smaller lesion that was not seen on the MR image (*curved arrow*). The early draining vein is difficult to see in this late arterial phase (*open arrow*).

C, Capillary phase of a left ICA angiogram more clearly shows the draining veins (*arrows*).

D, A right ICA angiogram shows the smaller left sylvian cerebral AVM nidus (*solid arrow*) and draining vein (*open arrow*).



AVM, adjacent to one of the larger lesions that was embolized, also was surgically excised because of its proximity to and accessibility through the craniotomy. The remaining AVMs found in the other five patients are being followed up with serial MR imaging and cerebral angiography.

Discussion

Cerebral arteriovenous malformations are congenital vascular anomalies that most likely represent the abnormal persistence of embryonic arteriovenous connections that fail to differentiate properly into arteriolar, capillary, and venular channels (33). These persistent connections result in abnormal arteriovenous shunting. Such a congenital disturbance in vasculogenesis might be expected to be widespread, producing multiple malformations; however, multiple cerebral AVMs are distinctly uncommon. A few large case series have noted

that multiple cerebral AVMs occur in approximately 1% of all cases (2–5), although many other clinical series have not reported any cases of multiplicity (34–40). In contrast, Willinsky et al (1) reported 11 cases of multiple concurrent cerebral AVMs in 203 consecutive patients with cerebral AVMs (6%), which is the largest recorded frequency in a large case series. These authors attributed this increased preponderance in their series in part to their meticulous angiographic technique with magnification and re-evaluation after endovascular embolization.

The occurrence of an exceptional number of multiple cerebral AVMs, which we have arbitrarily defined as three or more lesions, appears to be rare. In reviewing the literature, we found six previous reports (1, 7, 8, 20, 23, 26) in which most patients had three concurrent AVMs. Willinsky et al (1) and Iizuki et al (7) reported the most number of cerebral AVMs (five separate lesions) occurring in a single pa-

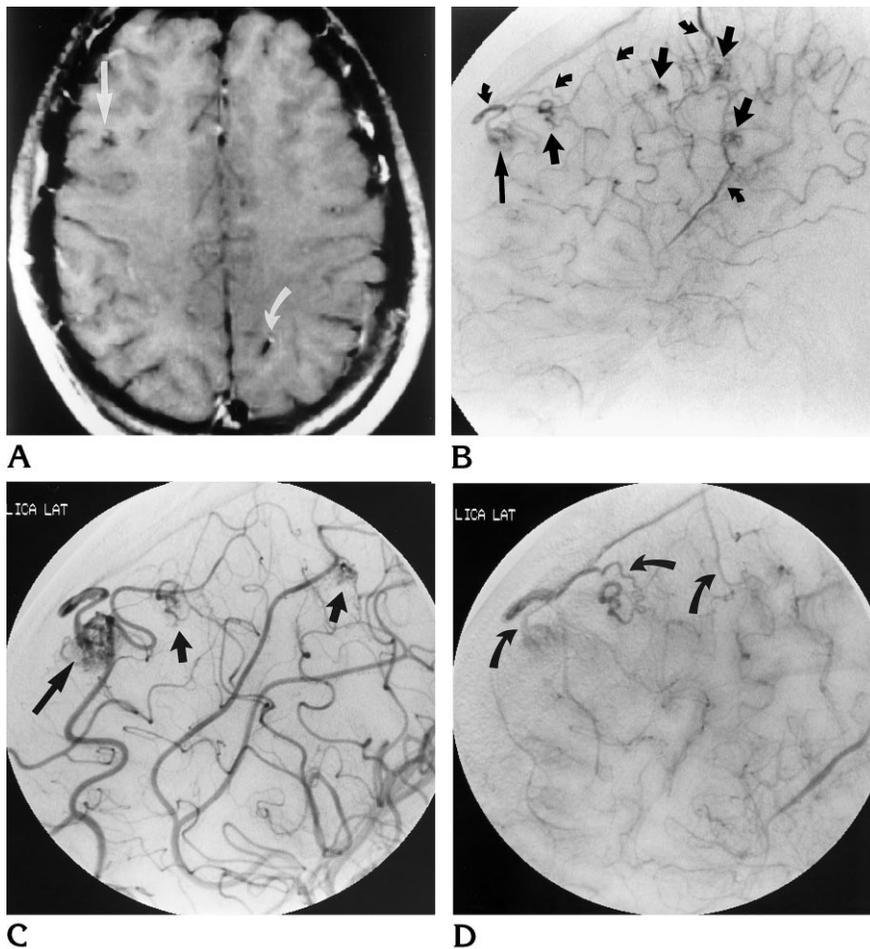


Fig 2. A, Axial contrast-enhanced T1-weighted MR image shows two signal voids, one in the right frontal and one in the left parietal lobes, compatible with cerebral AVMs (arrows).

B, Late arterial phase of the left internal carotid artery (ICA) angiogram shows five separate cerebral AVMs (straight arrows) with slightly enlarged cortical draining veins (curved arrows).

C and D, Magnification views from a left ICA angiogram better show three frontal cerebral AVMs (straight arrows) with draining veins (curved arrows).

tient. Our current series of seven patients is most noteworthy because all had concurrent cerebral AVMs and, in three patients, the number of lesions either equaled or substantially exceeded that which has previously been reported in a single patient.

HHT is an uncommon multisystem vascular disease of autosomal dominant inheritance, characterized by so-called telangiectatic malformations of the skin, mucous membranes, and viscera. These vascular malformations have various pathophysiological consequences, depending on which organ system is involved. For example, lesions in the nasal and gastrointestinal mucosa characteristically manifest by episodic hemorrhage, whereas lesions in the lung and liver produce clinical sequelae related to pathologic arteriovenous shunting (9, 41). A recent pathoanatomic study of skin telangiectasia showed that these malformations are actually plexiform arteriovenous fistulas with significant arteriovenous shunting (42).

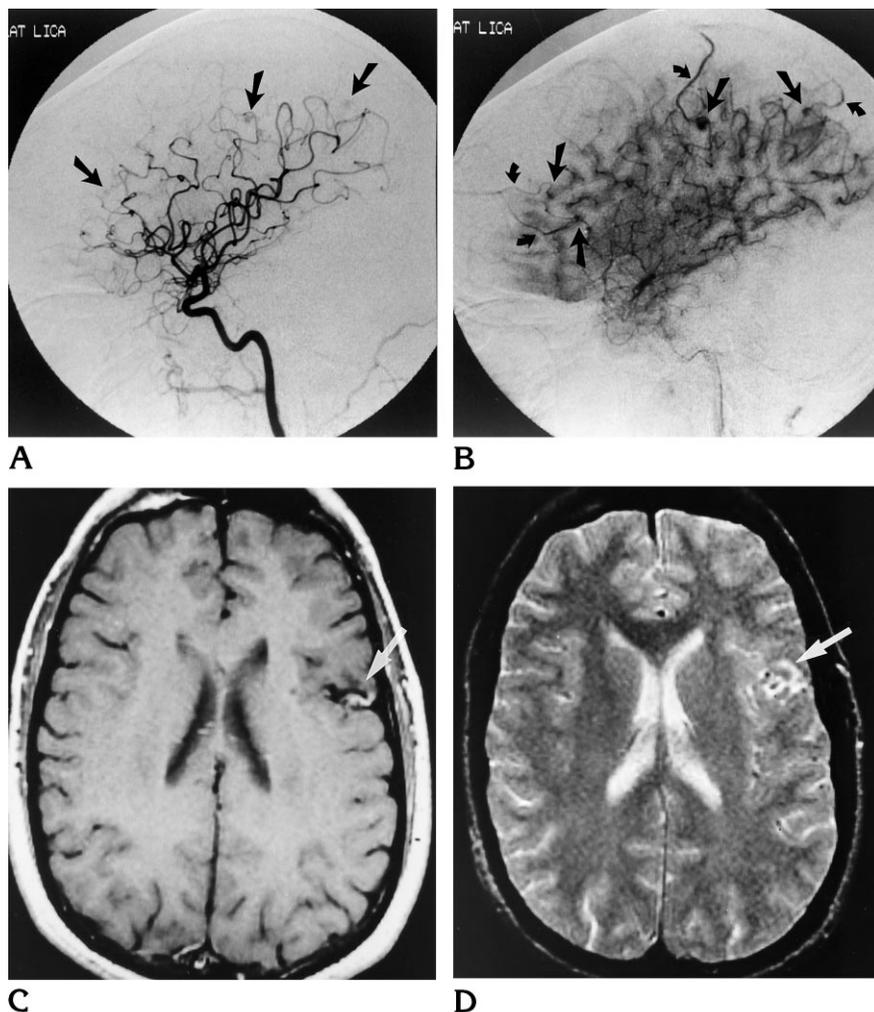
Similarly, pulmonary lesions associated with this disease also represent plexiform arteriovenous malformations. The descriptions by Rendu, Osler, and Weber in the 1890s stressed the association of cutaneous telangiectasia with epistaxis and their hereditary occurrence, while more recent literature has shown a widespread angiodysplasia associated with this syndrome. Vascular malformations of various types have been described in the retina, thyroid, heart, lungs, intestine, liver, spleen, pancreas, kidneys, prostate, cervix, bladder, urethra, diaphragm, vertebrae, major arteries, and aorta (9).

A gene defect associated with HHT has been identified on chromosome 9q33-34, involving the transforming growth factor- β binding protein, endoglin (43). Other cases of non-endoglin-linked families with HHT have recently been reported, and it remains unknown how any gene defect or other factors interact to cause the genesis or clinical progression of AVMs.

Fig 3. A, The arterial phase of a left internal carotid artery angiogram shows several faint vascular blushes of the multiple cerebral AVMs (*arrows*).

B, The cerebral AVMs (*straight arrows*) are more easily seen in the later (capillary) phase. The draining veins are only slightly enlarged (*curved arrows*).

C and D, Axial T1-weighted and T2-weighted MR images, respectively, show a flow void in the left frontal lobe corresponding to the largest cerebral AVM seen on angiography (*arrows*). The other lesions were not seen.



Neurologic complications of HHT, in which the majority of events have been attributed to paradoxical emboli through pulmonary AVMs, resulting in either cerebral infarction or brain abscess, have been well known for decades (9, 31, 41, 44–47). Other potential mechanisms of cerebral injury related to pulmonary AVMs are systemic hypoxia related to right-to-left arteriovenous shunting, air embolism, and secondary polycythemia (9, 44, 48). Polycythemia resulting from a pulmonary AVM may predispose to cerebrovascular thrombosis due to a combination of increased blood viscosity, large total blood volume, and thrombocytosis. A previous study has shown significant reduction of regional cerebral blood flow in patients with polycythemia (49).

Several anecdotal reports of symptomatic cerebral AVMs associated with HHT also have been described, in which patients presented

with apoplectic hemorrhage, seizures, and progressive neurologic deficits, similar to patients with sporadic cerebral AVMs (1, 6, 7, 10, 14–16, 18, 23, 27, 50, 51). Because of reports of such presentations, it has been assumed that the natural course of cerebral AVMs in HHT is similar to that of cerebral AVMs in patients in the general population.

In reviewing the several case reports of multiple cerebral AVMs, it appears that most of them have been associated with either so-called peripheral telangiectasia or a specific diagnosis of HHT (8, 11–27, 42, 52) (J. C. Chaloupka, R. K. Fulbright, P. B. Fayad, et al, “The Detection of Cerebral Vascular Malformations 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). By our count, 14 of 44 such cases occurred in

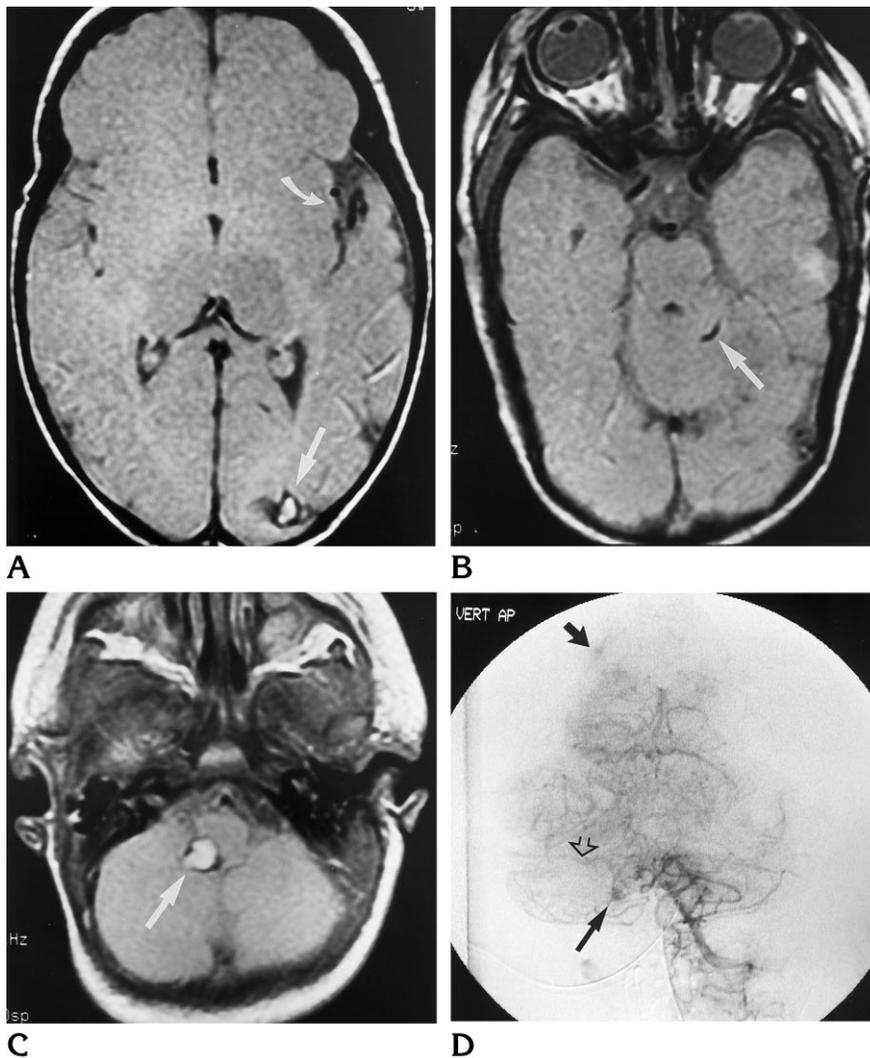


Fig 4. A, An axial proton density-weighted MR image shows abnormal signal in the left sylvian fissure (*curved arrow*) and left occipital lobe (*straight arrow*), compatible with hemorrhage.

B, An axial image from the same sequence shows a linear region of decreased signal on the left side of the cerebellum (*arrow*). None of the three lesions had corresponding cerebral AVMs at angiography.

C, A third axial image shows a lesion on the right side of the pontomedullary junction (*arrow*).

D, Late arterial phase of a left vertebral angiogram shows the corresponding small cerebral AVM (*long solid arrow*) with a subtle draining vein (*open arrow*). A cerebral AVM is faintly seen in the right occipital lobe (*short solid arrow*), and was confirmed on magnification views (not shown).

patients with HHT or peripheral telangiectasia. Indeed, Reddy et al (23) reported a patient with three cerebral AVMs in whom HHT was subsequently diagnosed. Of the 11 cases of multiple cerebral AVMs reported by Willinsky et al (1), three patients had HHT or peripheral telangiectasia. Considering HHT is a relatively uncommon disorder with a frequency estimated at 1 to 2 per 100 000 people, these reports suggest a significantly increased rate of occurrence of multiple cerebral AVMs associated with HHT.

Owing to the frequency of neurologic complications associated with HHT, our institution has initiated a screening program for selected patients with the syndrome to detect various central nervous system manifestations using cerebral MR imaging. Our preliminary experience with such screening has shown that there is a remarkable prevalence of both ischemic brain

injury (27%) and vascular malformations (23%) in these patients (52) (Chaloupka et al, "Detection") (P. B. Fayad, R. K. Fulbright, J. C. Chaloupka, "A Prospective Neurological and Magnetic Resonance Imaging Evaluation of Hereditary Hemorrhagic Telangiectasia," presented at the 20th International Joint Conference on Stroke and Cerebral Circulation, San Antonio, Tex, January 1995).

In all seven of our patients, MR of the brain showed evidence of cerebral vascular malformations, prompting cerebral angiography. However, in all cases the number and specific nature of these cerebral malformations were significantly underestimated by MR imaging. In our first patient, only the largest AVM of the five shown at angiography was identified by MR imaging. In the second and third patients, only two of nine and four of eight AVMs, respectively,

were detected prospectively by MR imaging. In the fourth patient, evidence of prior hemorrhagic infarction resulted in referral for angiography. None of the four AVMs identified angiographically was identified prospectively on MR images.

The exceptional multiplicity of cerebral AVMs in our patients posed unique and difficult challenges in management. Our current management approach is based on the natural course of solitary, sporadic cerebral AVMs. It is generally agreed that such lesions tend to undergo a gradual pathophysiological and consequent pathohistologic evolution, which affects the feeding arteries, nidus, and draining veins. This process often produces degenerative weakening within the walls of these vessels, predisposing to rupture. Natural history studies have shown that the cumulative annual hemorrhagic risk of sporadic cerebral AVMs is approximately 3% to 4% (53–55). Other complications of cerebral AVMs include local ischemia and gliosis, resulting in either a progressive neurologic deficit or seizures. Although the natural course of sporadic cerebral AVMs has been well documented, the specific natural course of the cerebral AVMs associated with HHT is not known.

Current clinical practice favors definitive treatment of a cerebral AVM with one or more techniques, including embolization, surgical excision, and stereotactic radiosurgery to prevent catastrophic hemorrhagic complications. In previous reports of multiple cerebral AVMs, others have applied this practice by evaluating each lesion as if it were an isolated occurrence. The size of each lesion, its accessibility, and the structures involved have been stressed as important factors in determining the feasibility of open resection. Staged embolization and surgical excision were performed in all accessible lesions in previous reports. Tada et al (21) favored definitive surgical management in all lesions but also stressed the importance of hemodynamic changes in cerebral blood flow, especially venous outflow, in determining the timing of the procedures, indicating the need to incorporate information regarding other lesions before operating on an individual AVM. Overall, the consensus has been for definitive therapy in all lesions when possible in patients with multiple cerebral AVMs.

Such an approach in our patients, however, would appear to be either impractical or untenable, owing to a variety of factors. The excep-

tional number of lesions would require several craniotomies to approach them all, such as in patients 2 and 3. Some of the lesions are in or near eloquent areas of the brain or are not easily accessible either by an endovascular or surgical approach, such as the inferior collicular lesion in patient 3. The small size of many of the AVMs makes locating them difficult, especially in view of the subtle changes identified at MR imaging. Stereotactic location with angiography could be performed but would require multiple angiograms, which carry a small but additional risk. Stereotactic radiosurgery could be offered for lesions in which surgical risk was considered too high; however, as in patients 2 and 3, treatment would be required at several locations, and the risks and benefits of stereotactic radiosurgery for AVMs at numerous locations have not been defined. Because the natural course of cerebral AVMs in HHT is not known, the risk versus benefit of extensive interventions cannot be justified.

Given the lack of symptoms directly referable to the cerebral AVMs in the patients in our series, the risk of multiple craniotomies, multiple angiograms with or without embolization, and possible stereotactic radiosurgery appear unwarranted at this time. Our current approach in these patients is to consider the size of the lesions, their location, and their accessibility to embolization or open resection, and to compare these factors with evidence of prior hemorrhage, referable symptoms, and the specific angioarchitecture to identify lesions at high risk for hemorrhagic complications. Cerebral AVMs that are large or easily accessible or that have dangerous angioarchitectural features (such as intranidal aneurysm, high shunt flow, or venous outlet obstruction) are treated with preoperative embolization and surgery. If they are not surgically approachable, these high-risk lesions are treated with stereotactic radiosurgery (and embolization if necessary). Other lesions (ie, those smaller than 1 cm or those with modest arteriovenous shunting or no intranidal aneurysms) are followed up with serial imaging—MR imaging yearly and cerebral angiography at 5-year intervals. If a lesion enlarges or becomes symptomatic, cerebral angiography would also be performed. We recognize that the choice of 1 cm as a size threshold appears arbitrary, and it does not guarantee that lesions smaller than 1 cm in diameter will not bleed during the follow-up period; however, in our experience, such

smaller lesions have not exhibited a well-defined nidus or any associated unfavorable angioarchitectural features. If any lesion increases in size, develops evidence of hemorrhage (ie, surrounding hemosiderin) or worrisome architecture (ie, intranidal aneurysms, high shunt flow, or venous outlet obstruction), or becomes symptomatic, definitive therapy would be undertaken.

In summary, our experience with patients with HHT and a review of the literature suggest an increased risk for multiple cerebral AVMs in these patients. The exceptional number of lesions seen in patients with HHT further highlights the possible primary involvement of the central nervous system by the widespread angiodysplasia in HHT. The numerous and widely distributed cerebral AVMs pose a difficult challenge to the current paradigms of management of these lesions. Further studies of their natural course and pathophysiology is required so that therapeutic options can be better formulated.

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