

Cerebrovascular Manifestations of Hereditary Hemorrhagic Telangiectasia

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Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu–Osler–Weber disease, is an autosomal-dominant genetic disorder affecting the vasculature in multiple organ systems. The first reports of the disease were published by several English physicians in the 19th century, including Henry Sutton, Benjamin Babington, and John Legg who described families of patients with recurrent nosebleeds. Between 1896 and 1907, Marie Rendu, William Osler, and Frederick Parkes Weber further described the disease by demonstrating the association between epistaxis, mucocutaneous lesions, and visceral arteriovenous malformations (AVMs). In 1909, Frederic Hanes was the first to coin the term HHT; however, the eponym lives on as a tribute to Rendu, Osler, and Weber.¹

The pathognomic vascular lesions in HHT are telangiectasias and AVMs. These are frequently seen on the skin and mucus membranes and also in internal organs, such as the liver, lung, gastrointestinal track, and brain. Patients with HHT often present with a wide range of serious neurological, pulmonary, and gastrointestinal complications, such as cerebral and spinal AVMs, cerebral abscess, stroke, epistaxis, pulmonary AVMs (PAVMs), liver AVMs, and gastrointestinal bleeding.^{2–8} HHT is diagnosed clinically using the Curaçao criteria.⁹ The 4 Curaçao criteria are (1) spontaneous and recurrent epistaxis, (2) mucocutaneous telangiectasias (lips, oral cavity, face, and fingers) (3) visceral AVMs (brain, liver, lung, etc.), and (4) diagnosis of HHT in a first degree relative using the same criteria. Patients who meet ≥ 3 of the 4 criteria are labeled as definite HHT, whereas those with 2 of the 4 criteria are labeled as possible or suspected HHT.¹⁰ Patients with 0 or 1 criterion are considered unlikely to have HHT.

Patients with HHT present a unique challenge to physicians because of the multisystemic nature of the disease. Because of the higher prevalence of cerebral and spinal vascular manifestations and associated complications, these patients are commonly encountered by neurovascular specialists. Importantly, understanding the genetic basis of the disease and the pathophysiological cascade leading to the formation of AVMs in affected individuals may improve our understanding of intracranial AVMs. In this article, we review the epidemiology, genetics, and clinical manifestations of HHT with a focus on neurovascular complications and their management.

Epidemiology

Estimates about the prevalence of HHT in the general population vary widely depending on the methodology and population studied. Current studies suggest a prevalence of $\approx 1:10\,000$ in the United States and United Kingdom, $1:5\,000$ – $1:8\,000$ in Japan and $\approx 1:1\,300$ in The Netherland-Antilles.^{11–14} Clinical symptoms in HHT are variable even among first degree relatives with HHT and often evolve over time. Many of the clinical manifestations, especially the severity of epistaxis and gastrointestinal bleeding, become more prominent in the later decades of life.¹⁴ Approximately 90% of cases are diagnosed by the age of 40 years, and 97% of cases are diagnosed by the age of 60 years.¹⁵

Interestingly, despite the fact that HHT is an autosomal dominantly inherited disorder, its clinical prevalence is higher in women with studies demonstrating a male:female ratio of 1:1.33 to 1:1.54.^{14,16,17} Proposed explanations for this disparity include (1) increased use of healthcare resources by women resulting in higher detection rates, (2) epigenetic and environmental factors, and (3) hormonal factors.¹⁴ Some data suggest that alterations in estrogen and progesterone levels during pregnancy result in worsening of the clinical manifestation of HHT in females.¹⁸

Genetics and Pathophysiology

Tremendous progress has been made during the past 2 decades in understanding the genetic underpinnings of HHT. It is now well recognized that HHT primarily occurs because of mutations in genes regulating signaling via the TGF- β pathway. This pathway is essential in regulating angiogenesis and vascular integrity.

The vast majority of patients with HHT harbor mutations in either the ENG gene (HHT1) or the ACVRL1 gene (HHT2). ENG encodes endoglin, a transforming growth factor (TGF)- β type III receptor and ACVRL1 encodes activin receptor-like kinase type 1, a TGF- β type I receptor.¹⁹ ENG and ACVRL1 mutations are found in $>80\%$ to 90% of patients with definite HHT.¹⁰ There are >700 disease causing mutations described in ACVRL1 and ENG spanning across all coding regions of these genes.¹⁰ Several other genes have been linked to HHT including MADH4, which results in juvenile polyposis and HHT, BMP9 (HHT5), and GDF2. These account for $<2\%$ of patients with HHT.¹⁰ A minority of patients with definite

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HHT have variants of unknown significance or no detectable mutations in any of the above-listed genes suggesting involvement of alternative pathways and mechanisms. De novo mutations in HHT are rare but have been reported. One series of 126 patients found only 3 patients with de novo mutations.²⁰ Although HHT1 and HHT2 are both related to TGF- β signaling defects, the phenotype is slightly different with increased incidence of PAVMs, brain AVMs, and gastrointestinal bleeding in HHT1, whereas HHT2 has increased incidence of liver vascular malformations and high output cardiac failure. Epistaxis tends to be seen equally in both the phenotypes.

The classic HHT-associated vascular lesions are telangiectasias and AVMs. Telangiectasias are focal dilations of post-capillary venules, which connect with dilated arterioles in the absence of an intervening capillary bed. Thus, these represent the smallest forms of direct arteriovenous communications. Telangiectasias can be found in many locations, including the skin, pulmonary vasculature, gastrointestinal tract, liver, and other visceral organs.²¹ Larger AVMs start out as telangiectasias and are likely a result of continued vascular remodeling and inappropriate endothelial cell proliferation responses.²²

The development of vascular lesions in HHT can be understood via a haploinsufficiency model with reduced signaling in the ENG- and activin receptor-like kinase type 1-mediated TGF- β pathways and preserved signaling through alternative TGF- β pathways. Activin receptor-like kinase type 1 and endoglin are involved in balancing the activation phase and resolution phases of angiogenesis.^{23,24} The activation phase involves a proangiogenic stimulus, which increases endothelial cell layer permeability, basement membrane degradation, and sprouting of endothelial cells. Lumen formation from endothelial sprouts then occurs followed by the resolution phase, which entails vessel maturation and basement membrane reconstruction. AVMs in this setting are not congenital but considered to develop early in infancy when arteriovenous maturation occurs and vessels are continuously being developed.²⁵ It is conceivable that the ENG and ACVR1 mutations also result in a hyper response to proangiogenic stimuli.²² One recent mouse study demonstrated that the absence of endoglin results in developing vessels having delayed remodeling of capillary plexuses, increased endothelial cell proliferation, and local venous enlargement, thus resulting in arteriovenous shunt formation.²² The triggering event leading to the formation of these AVMs in humans remains unknown although several mechanisms have been proposed, including inflammation/infection, endoluminal shear stress, and hypoxemia.

Systemic Manifestations

For the purposes of this review, we will present a brief review of the non-central nervous system (CNS)-related vascular lesions associated with HHT followed by a more in-depth description of the CNS-related lesions. A majority of vascular malformations affecting patients with HHT are non-CNS lesions.

Non-CNS Manifestations

Pulmonary Manifestations

PAVMs are more frequently seen in patients with HHT1. Current recommendations state that all patients with HHT

should be screened for PAVMs using transthoracic contrast echocardiography with high resolution chest computed tomography for confirmation.²⁶ PAVMs can be either single, multiple, or diffuse. A PAVM is labeled as simple when it has a single feeding artery and is considered complex when it has ≥ 2 feeding vessels. PAVMs are more common in HHT1 and may be seen in $\leq 50\%$ to 70% of these patients. PAVMs may be asymptomatic (if small) or may result in infectious and ischemic complications, such as brain abscess and transient ischemic attack/stroke. Similarly dyspnea, orthodeoxia, platypnoea, and hypoxemia can also occur in patients with diffuse or large PAVMs especially when present at the lung bases. The risk for these complications may be increased in patients with large PAVMs. Hemorrhagic complications from PAVMs are rare but serious and include hemoptysis and hemothorax. HHT-associated PAVMs are generally considered for therapeutic embolization when the feeding artery is 3 mm or larger, although some authors have advocated treating smaller AVMs with a feeding artery diameter of 2 to 3 mm as well.²⁶

Gastrointestinal Manifestations

Vascular manifestations of HHT include gastrointestinal telangiectasias and hepatic vascular malformations. Gastrointestinal telangiectasias can involve the entirety of the gastrointestinal tract from the esophagus to the rectum. Although intestinal telangiectasias are present in $\leq 80\%$ of patients with HHT, only $\approx 20\%$ to 30% go on to develop symptomatic gastrointestinal bleeding. Gastrointestinal bleeding typically becomes problematic after the fifth decade of life and is more common in patients with HHT1, whereas diffuse liver vascular involvement is more common in patients with HHT2. A screening upper endoscopy is recommended in cases where the degree of anemia is disproportionate to the amount of blood loss from epistaxis and annual hemoglobin and ferritin checks are recommended for all patients starting at the age of 35 years.²⁶ Bleeding lesions can generally be treated endoscopically using argon photocoagulation or neodymium-doped yttrium aluminium garnet laser application. Intravenous bevacizumab has been recently shown to be effective in reducing gastrointestinal bleeding in some patients with HHT.^{27,28}

Hepatic vascular malformations include telangiectasias as well as AVMs. Hepatic vascular malformations affect 30% to 70% of patients with HHT and can be associated with high output cardiac failure, portal hypertension, biliary ischemia, and rarely, acute liver failure. These lesions are typically evaluated with contrast enhanced triple phase computed tomographic scans or Doppler ultrasound in settings where there is a high clinical suspicion.²⁶ Arterial embolization or other local approaches in the liver are not recommended because of high rates of complications. Liver transplantation remains the definitive treatment in cases of intractable liver failure, high output cardiac failure, or biliary complications.²⁶ Interestingly, there are cases where AVMs have recurred in the transplanted liver.²⁹ In patients with severe hepatic vascular malformations and high cardiac output, bevacizumab has been shown to be effective in reversing the cardiac output cardiac failure and preventing the need for a liver transplantation.^{30,31} In 1 case, systemic bevacizumab treatment was shown to reverse the need for a liver transplant in an HHT patient with liver failure.³¹

Epistaxis

Recurrent and spontaneous epistaxis is an almost universal finding in HHT affecting >95% of individuals.²⁶ Epistaxis is often the first manifestation of the disease and is present in ≤50% of patients by the age of 20 years.²¹ Recurrent and severe epistaxis plays a significant role in reducing quality of life and is associated with chronic anemia and increased need for both iron infusions and RBC transfusions.³²

Many different treatments are available for epistaxis and patients should be ideally managed in experienced HHT centers. Conservative measures to prevent epistaxis should be encouraged in all patients and include humidification and topical lubricants.²⁶ Tranexamic acid has been shown to be modestly effective in reducing epistaxis frequency and severity in patients with HHT in randomized controlled trials.^{8,33} Thermal and chemical coagulations are effective but less favored because of higher rates of complications, such as scarring and septal perforations. Endoscopic application of potassium titanyl phosphate or neodymium-doped yttrium aluminium garnet laser has been shown to be effective but repeated applications are necessary to maintain benefit. Septodermoplasty has also been shown to help with severe epistaxis. In refractory cases, nasal closure (Young procedure) can be performed.²⁶ Epistaxis can also be managed through surgical ligation of the feeding artery as well as endovascular embolization.^{34–36} Intranasal and intravenous bevacizumab has been shown to be effective in reducing epistaxis frequency and severity in patients with HHT and is currently a focus of studies in these patients.^{37–39}

CNS Manifestations of HHT

Patients with HHT can present with a myriad of CNS complications. These can be broadly classified as being (1) primary: because of the presence of vascular malformations in the brain and spinal cord and (2) secondary: because of embolic phenomenon from right to left shunting in the pulmonary vascular bed (from AVMs), resulting in hemorrhagic, ischemic, and infectious complications (eg, brain abscesses). Below is a detailed description of the CNS manifestations of HHT.

Cerebral Embolic Complications

Cerebral abscesses are exceedingly rare in the general population affecting <1 in 100 000 people per year. However, in individuals with HHT, cerebral abscesses are not uncommon and are universally associated with PAVMs. These are thought to be more prevalent in patients with ENG mutations (HHT1) because of higher prevalence of moderate- to large-sized PAVMs. Cerebral abscesses can result in permanent neurological sequelae⁴⁰ and are usually secondary to septic emboli passing through right to left intrapulmonary and intracardiac shunts. Careful prevention is critical and consists of prophylactic antibiotic administration before invasive procedures with a potential for bacteremia (ie, dental procedures, colonoscopy, etc.) as well as coil embolization of PAVMs. In addition, the use of micro filters during intravenous therapy is strongly recommended to prevent air/particulate embolization. Cerebral abscesses in patients with treated and occluded PAVMs are exceedingly rare.⁴⁰

Acute ischemic stroke is a common complication of HHT affecting ≤30% of individuals with PAVMs.^{41,42} Patients with

HHT-associated stroke are generally younger than the general stroke population and lack conventional neurovascular risk factors.⁴² Stroke in the setting of HHT is usually secondary to aseptic thromboemboli passing through PAVMs.⁴² Other potential mechanisms for stroke in patients with HHT include hyperviscosity secondary to chronic hypoxemia from right to left shunts and gas emboli secondary to excess cough and communication between the airway and pulmonary circulation.⁴³ Obliteration of PAVMs significantly reduces stroke rates in these patients.⁴² Cerebral AVMs are rarely a cause of ischemic strokes in HHT.⁴⁴

There are no current guidelines about the use of thrombolytics in the treatment of acute ischemic stroke in patients with HHT. This question is an important one as patients with HHT are at higher risk of acute ischemic stroke.⁴⁵ Although known cerebral AVMs and active gastrointestinal bleeding are contraindications to thrombolysis, the risk of thrombolysis in patients with nonbleeding extracranial AVMs has not been established. Ischemic stroke is often the first manifestation of HHT so it is likely that a substantial number of patients with HHT have received thrombolysis before diagnosis of HHT. Currently, HHT is not considered a contraindication to thrombolysis, however, some have advocated screening stroke patients for a history of nose bleeds before administering thrombolysis.⁴⁶

Cerebral Vascular Malformations

Arteriovenous Malformations

Approximately 10–20% of patients with HHT are affected by a cerebral vascular malformation (CAVM) of some sort with a higher prevalence noted in patients with HHT1.⁴⁷ CAVMs seen in patients with HHT can be classified into three types (1) large single-hole pial arteriovenous fistulae (AVF; Figure 1), (2) AVMs with a nidus (Figures 2 and 3), and (3) micro-AVMs or capillary vascular malformation⁴⁸ (Figure 4). The large AVMs/AVFs typically but not exclusively become clinically manifest in young children, whereas small AVMs are typically discovered in older age groups.⁴⁸ Micro-AVMs are typically found in older children and young adolescents. AVFs represent ≈10% of CAVMs, whereas nidus type AVMs represent ≈50% of CAVMs.⁴⁸ Approximately 60% of patients with CAVMs have micro-AVMs/capillary vascular malformations.

The angioarchitecture of each of these lesions differ substantially. Pial AVFs are typically defined by a lack of a nidus between the feeding artery and draining vein, that is, a single hole with a pouch. These lesions are usually superficially located with only a tiny minority located in the deep portions of the brain.⁴⁸ Over 90% of these lesions have a supratentorial location. Pial AVFs generally have high shunt volumes, which result in marked feeding artery enlargement and local hypoxemia. These lesions have many other features that portend a poorer natural history, including arterial stenoses, feeding artery aneurysms, multiple draining veins, venous ectasia, and a pseudophlebitic pattern.⁴⁸ The angioarchitecture of pial AVFs is also thought to differ by age. One series of 41 patients with supratentorial pial AVFs, Hetsch et al⁴⁹ noted that patients ≤2 years of age were more likely to have large, complex, multihole AVFs, whereas patients >2 years of age were more likely to harbor single-hole pial AVFs.

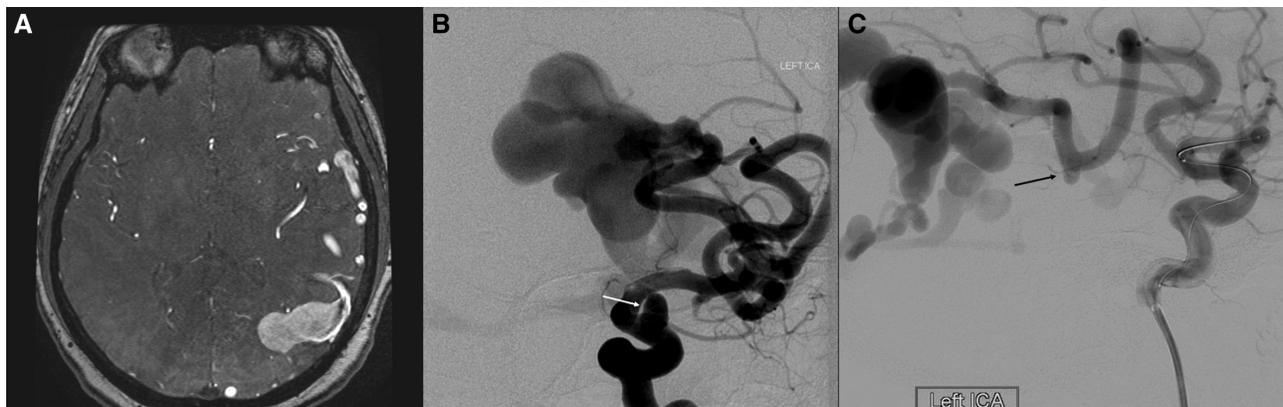


Figure 1. Cortical pial arteriovenous fistula in a 53-year-old female. **A**, T1 contrast enhanced magnetic resonance imaging demonstrates an enhancing vascular lesion in the left inferior parietal lobe with a large venous varix. **B**, Cerebral angiogram demonstrates the left inferior parietal pial arteriovenous fistula, fed by the left middle cerebral artery, and with a large amount of superficial venous drainage, including a 4.5-cm venous varix and a 7-mm internal carotid artery (ICA) feeding aneurysm (arrow; **C**) lateral view demonstrates an additional feeding artery aneurysm of the middle cerebral artery (arrow).

Nidus type AVMs are arteriovenous connections with an intervening nidus with the presence of a shunt/early draining vein. One recent study found that 40% of these lesions are located in eloquent areas and $\approx 15\%$ have deep venous drainage.⁴⁸ Several studies have demonstrated that $>90\%$ of these lesions have a Spetzler–Martin score of ≤ 2 and they are typically located in a supratentorial location.^{25,48,50} Feeding arteries are generally pial vessels. The angioarchitecture of these lesions is typically benign. These lesions tend to measure 1 to 2 cm and tend to lack features such as arterial stenoses, associated aneurysms, multiple draining veins, venous ectasia, and venous reflux. Associated aneurysms are exceedingly rare as are signs of long-standing venous hypertension.⁴⁸

Micro-AVMs are known as capillary vascular malformations. These lesions lack definite shunting on angiography and have no dilated feeding arteries or veins. Rather, these are characterized by a blush of abnormal vessels in the arterial phase that persists into the late arterial and capillary phase.⁴⁸ Angiographically, these lesions are distinct from both capillary telangiectasia and AVMs as these are characterized by the presence of a capillary bed that is abnormally dilated. About 80% of these lesions are superficially located with $<5\%$ having a deep location. A majority are located supratentorially. These lesions are small measuring ≈ 5 mm in maximum diameter.^{25,48,50}

There are many salient features of HHT AVMs that should lead one to consider a diagnosis of HHT if one has not already been established. While also seen in the sporadic AVM population, micro-AVMs/capillary vascular malformations are primarily described in HHT, thus the presence of these lesions should lead one to consider a diagnosis of HHT. Pial AVFs are thought to be an exceedingly rare in the sporadic AVM population, but are seen in $\leq 10\%$ of HHT AVM patients, thus the presence of these lesions should trigger an investigation for HHT.^{51,52} Features of nidus type AVMs that should trigger an investigation for HHT are lesion multiplicity, especially when seen in superficial locations. Lesion multiplicity is thought to be a hallmark of HHT as according to 1 recently published study, 44% of patients with CAVMs had at least 2 different brain AVMs.

On the basis of the angioarchitecture of these lesions, the natural history and presentation also differ substantially. Capillary vascular malformations are often detected incidentally and are not associated with symptoms, such as seizures, headache, or hemorrhage. Nidus type AVMs are typically asymptomatic with $>60\%$ either detected incidentally or during screening.^{48,53} About 25% of AVMs in patients with HHT present with hemorrhage and in a majority of cases, the AVM was unknown or had not manifested itself until the time of hemorrhage.^{48,53} Seizure is another common presentation of

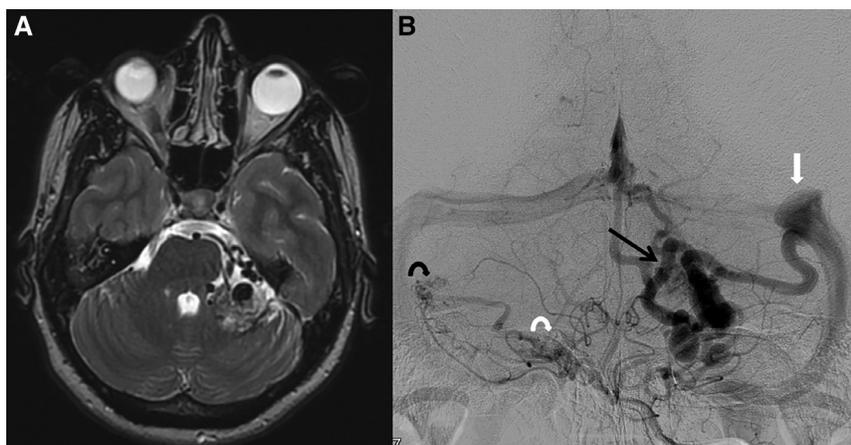


Figure 2. Nidal-type arteriovenous malformation (AVM) in a 32-year-old female with hereditary hemorrhagic telangiectasia (HHT). **A**, Axial T2-weighted magnetic resonance image demonstrates a diffuse AVM involving the left cerebellar hemisphere. **B**, Left vertebral artery injection demonstrates a diffuse AVM fed primarily by branches of the superior cerebellar artery. There is dilatation of the transverse sinus at the point of entrance of a large venous varix (white arrow). There are 2 smaller shunting AVMs. One in the lateral right cerebellar hemisphere (curved black arrow) and 1 just lateral to the pons (curved white arrow).

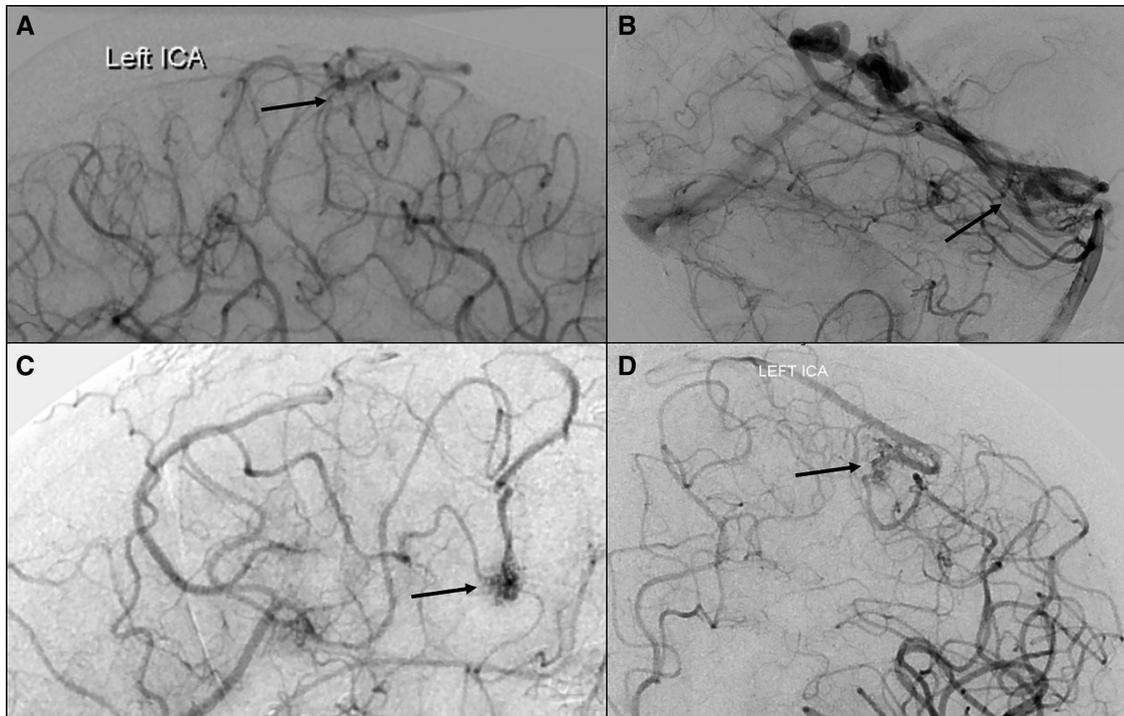


Figure 3. Nidus-type arteriovenous malformations (AVMs) in patients with hereditary hemorrhagic telangiectasia (HHT). **A**, Supratentorial AVM with superficial venous drainage, small nidus, and no worrisome angioarchitectural features. **B**, Infratentorial AVM with deep venous drainage. The nidus is small (black arrow) and there were no feeding aneurysms or venous outflow stenosis. **C** and **D**, Two examples of supratentorial AVMs with superficial venous drainage, small niduses, and no worrisome angioarchitectural features. These lesions are typical of the nidus AVMs seen in HHT.

AVMs in HHT, seen in $\approx 10\%$ of cases.^{48,53} Because of their size and poor angioarchitecture, pial AVFs can present with hemorrhage, seizure, or bruit. Infants with these large lesions can present with heart failure and increased intracranial pressure as well as developmental delay.⁵⁴

Studies of natural history of cerebral AVMs in patients with HHT are few in number and are limited by the fact that the angiographic characteristics of the lesions are sometimes not well characterized. In a study of 29 patients with CAVMs including 22 patients with AVMs, Willemse et al⁵⁵ found a bleeding risk of 0.4% to 0.7% for all CAVMs and a bleeding risk of 0.4% to 0.7% specifically for AVMs. However, it is unclear from this study whether there was any difference in bleeding rates between nidus type AVMs and single-hole pial AVFs.⁵⁵ In a recently published study from the Brain Vascular Malformation Consortium HHT Investigator Group, 153 HHT brain AVM patients were followed for a mean of 3 years. The authors found an overall bleeding rate of 1% per year with a rupture rate of 0.4% per year (95% confidence interval [CI], 0.1–1.7%) for unruptured AVMs and 10% per year for ruptured AVMs (95%CI, 3.3–31.2%). It is important to point out that this study did not stratify natural history by AVM type, a factor which is important in risk stratification of these patients. Nevertheless, this study was the first to demonstrate that the brain AVM rupture rate is similar to that of sporadic AVMs, when considering the upper limit of the confidence interval of 1.7%. The ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) study found rupture rates of 2.2% per year (95%CI, 0.9–4.5%) for unruptured AVMs,⁵⁶ whereas a recently published meta-analysis performed by

Gross and Du⁵⁷ found rupture rates of 2.2% (95%CI, 1.7–2.7%) for unruptured AVMs.

No studies, to date, have reported the natural history of only nidus AVMs in HHT, however, given the typical angioarchitecture and location of these lesions (ie, superficial location, superficial venous drainage, no associated aneurysm, and small size), it is likely that most HHT-associated unruptured AVMs have a benign natural history. This is supported by a meta-analysis performed by Gross and Du,⁵⁷ which demonstrated that factors associated with hemorrhage of AVMs were deep location, deep venous drainage, and an associated aneurysm; features which these lesions typically lack.⁵⁷ Nonetheless, further studies are needed to determine the natural history of cerebral AVMs, stratifying outcomes by type of AVM.

Little is known about the natural history of single-hole pial AVFs. Case series are generally limited to <10 patients and follow-up periods are generally brief. Small studies on the natural history of superficial single-hole pial AVFs in patients with HHT have demonstrated high rates of neurological deficit and hemorrhage.⁵⁸ One study of 8 patients receiving conservative management of pial AVFs demonstrated mortality in 63% of patients because of bleeding of the AVF.⁵⁴

Capillary vascular malformations are thought to have a benign prognosis with no reports of hemorrhage or growth of these lesions to date. As such, they are considered do not touch type lesions by many investigators.^{25,48,51}

Precise guidelines about screening and management of CAVMs are not available because of lack of high-quality evidence.²⁶ Most experts (77%) agree that clinicians should screen adult patients with possible or definite HHT for CAVMs. There is

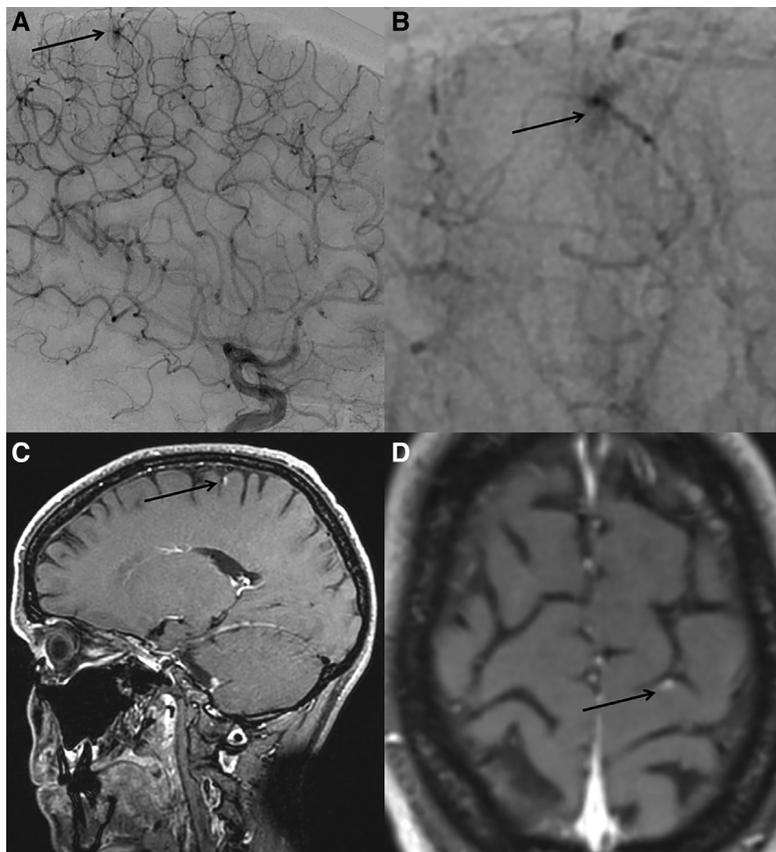


Figure 4. Capillary vascular malformation. **A**, Left internal carotid artery injection in a 43-year-old male with hereditary hemorrhagic telangiectasia 1 demonstrates a small capillary vascular malformation without definite evidence of arteriovenous shunting (black arrow; **B**). **C** and **D**, Sagittal and axial T1 postgadolinium images demonstrate a 3-mm area of enhancement in the vertex of the left frontal lobe corresponding to the capillary vascular malformation.

less consensus about screening for children with 64% of experts advocating for screening in the first 6 months of life. Those who did not agree to this recommendation cited lack of evidence for benefit of screening in children and lack of evidence of treatment efficacy for asymptomatic CAVMs in children. There is consensus, however, that once diagnosed with a CAVM, patients should be referred to centers with neurovascular expertise and that patients with hemorrhage secondary to a vascular malformation receive definitive treatment at these centers.²⁶

Most HHT centers do not rescreen patients after an initial negative magnetic resonance imaging/magnetic resonance angiogram scan done in adulthood. The role of serial imaging, particularly at young ages where AVMs may be developing, has yet to be established. This is based on the assumption that cerebral AVMs in this population are congenital and that de novo formation of AVMs either does not occur or is exceedingly rare. However, it is important to point out that there is a growing body of evidence suggesting that de novo formation of AVMs can occur at any stage of life.⁵⁹ There are growing reports of progression and regression of nidus AVMs, both in the sporadic AVM population and among those with HHT.⁶⁰ Several mechanisms have been proposed for de novo formation of nidus AVMs, both sporadic and HHT-associated including a hyperangiogenic environment secondary to cerebral infarction, hemorrhage, venous thrombosis or neoplasm, as well as inflammation.⁵⁹ These hypotheses are supported by the fact that nidus AVM specimens demonstrate increased expression of angiogenic factors, such as vascular endothelial growth factor and TGF- α , active endothelial proliferation and

surrounding inflammation.⁵⁹ Aside from vein of galen malformations, the only in-utero/congenital AVMs that have been reported in the literature are large pial AVFs. It is possible that these lesions form in utero or during early neonatal life as these lesions often manifest themselves in the first 2 years of life.⁶¹

Treatment of AVMs should be considered on a case by case basis with careful consideration of the angioarchitecture of the lesion, natural history, and patient comorbidities.²⁶ Effective treatment strategies include endovascular embolization, stereotactic radiation, and microsurgery as well as combined treatment approaches. There are no studies demonstrating the superiority of one treatment over the other.⁵² For nidus AVMs, single-modality treatment is generally feasible given the small size of these lesions and treatment decisions should be guided based on local expertise. Definitive treatment of high-flow pial fistulae has been advocated because of their poor natural history.⁵⁸ Given the angioarchitecture of these lesions, most high-flow pial fistulae can be treated with endovascular therapy alone.^{50,52} As mentioned previously, micro-AVMs are considered do not touch lesions. No pharmacological therapies have been shown to be effective in treatment of AVMs in humans. However, 1 recently published study of an activin receptor-like kinase type 1 knockout mouse model demonstrated that bevacizumab did reduce the amount of dysplastic vessels.⁶²

Spinal Vascular Malformations

The exact prevalence of spinal vascular malformations in patients with HHT is unknown; however, it is generally accepted to be substantially higher than in the general



Figure 5. Spinal pial arteriovenous fistulae in a 38-year-old female with left lower extremity spasticity and back pain. Patient had a history of epistaxis and cerebral arteriovenous malformations as well. Spinal angiogram demonstrates a large perimedullary spinal arteriovenous fistula fed by the left T9 intercostal artery (A and B). The site of the fistula is in the subarachnoid space at the level of T6 (black arrow). The fistula, including the site of the arteriovenous connection (black arrow) was embolized with coils and the patient made a full recovery (C).

population. One literature review of 200 HHT patients with CNS involvement found a prevalence of 8%, however, this number is thought to reflect publication bias and is likely a gross overestimate.⁶³ Current recommendations do not support routine screening for spinal vascular malformations, thus most of these lesions are detected when symptomatic.²⁶ Spinal vascular malformations are found primarily in children and are thought to have a poor natural history.^{51,64} In their review of 31 children with neurovascular manifestations of HHT, Krings et al⁵¹ found that patients with spinal AVF had a mean age of 2.2 years old. In fact, HHT is the most common cause of a spinal vascular malformation in children <2 years of age according to 1 small series.⁶⁵ These lesions have a universally poor prognosis.^{51,66–68} In the Krings et al⁵¹ series, all 7 treated patients had severe neurological deficits, including tetra- or paraplegia or spinal subarachnoid hemorrhage before treatment. These findings have been echoed in numerous case reports on treatment of spinal vascular malformations in patients with HHT.^{66–68}

Although the most common type of spinal vascular malformation is a type I spinal dural AVF, in the population with HHT, intradural perimedullary type IV fistulas are most commonly encountered.^{51,66–68} Perimedullary AVF are found along the surface of the spinal cord and have direct arterial supply from the posterior or anterior spinal arteries. Like all fistulae, they lack an intervening capillary bed. These fistulae do not penetrate the spinal cord. Symptoms are generally the result of congestion of the coronal venous plexus. In their review of 7 cases, Krings et al⁵¹ noted that all spinal cord AVFs were located on the cord surface and had direct connections between the anterior/spinal artery and medullary veins. These lesions all had poor angioarchitectural prognostic characteristics, including venous stenosis, venous ectasias, and pial reflux.⁵¹

Endovascular embolization is the preferred treatment modality for spinal vascular malformations seen in HHT (Figure 5). In their series of 7 patients, Krings et al⁵² noted complete or near complete occlusion of the fistulae with endovascular treatment

in all cases. No patients had worsening of symptoms after intervention and 2 patients improved. Calhoun et al⁶⁴ reported successful surgical treatment in 1 case and successful combined endovascular and surgical treatment in another. Mont'Alverne et al⁶⁹ report successful coil embolization of a giant perimedullary fistula with complete resolution of symptoms. In their review of 213 patients treated for perimedullary fistulas, Gross et al⁷⁰ reported similar obliteration and symptom resolution rates between surgical and endovascular groups.

Conclusions

HHT is a relatively common genetic disease associated with a wide variety of systemic and CNS vascular pathologies. Thus, awareness and understanding of this disease is important for neurovascular specialists. Neurovascular complications of HHT often require a multidisciplinary specialized team because of the complexity of the lesions as well as the need to address the multisystemic aspects of the disease (ie, embolization of the PAVM in patients having ischemic stroke). With the expanding role of antiangiogenesis medications in the treatment of HHT, it will be interesting to see what effect, if any, they have on the CNS manifestations of the disease.

Disclosures

None.

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KEY WORDS: arteriovenous malformations ■ brain ■ hereditary hemorrhagic telangiectasia ■ mucus ■ stroke

Correction

In the article by Brinjikji et al (Brinjikji W, Iyer VN, Sorenson T, Lanzino G. Cerebrovascular manifestations of hemorrhagic hereditary telangiectasia. *Stroke*. 2015;46:3329–3337. DOI: 10.1161/STROKEAHA.115.010984.), which published online ahead of print on September 24, 2015, and appears in the November 2015 issue of the journal, a correction was needed.

The title, “Cerebrovascular manifestations of hemorrhagic hereditary telangiectasia,” has been changed to read, “Cerebrovascular manifestations of hereditary hemorrhagic telangiectasia.”

The authors regret the error.

This correction has been made to the online and print version of the article, which is available at <http://stroke.ahajournals.org/content/46/11/3329>.

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