Cerebral vascular malformations in hereditary hemorrhagic telangiectasia

Clinical article

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Object. Hereditary hemorrhagic telangiectasia (HHT) is a hereditary disorder characterized by mucocutaneous telangiectasias, frequent nosebleeds, and visceral arteriovenous malformations (AVMs). Few reports have outlined the prevalence of the various cerebral vascular malformations found in patients with HHT. The authors set out to define the prevalence of cerebral vascular malformations in a population of HHT patients who underwent imaging with 3-T imaging (MRI/MR angiography [MRA]) of the brain.

Methods. A retrospective review of prospectively collected data was carried out using a database of 372 HHT patients who were seen and examined at the Georgia Regents University HHT Center and screened with 3-T MRI/MRA. Data were tabulated for numbers and types of vascular malformations in this population.

Results. Arteriovenous malformations were identified in 7.7%, developmental venous anomalies in 4.3%, and cerebral aneurysms in 2.4% of HHT patients. The HHT AVMs tended to be supratentorial, small, and cortical in this series, findings consistent with other recent studies in the literature. An arteriovenous fistula, cavernous malformation, and capillary telangiectasia were identified in 0.5%, 1%, and 1.9% of HHT patients, respectively.

Conclusions. Few studies have investigated the prevalence of the various vascular malformations found in HHT patients screened with 3-T MRI/MRA of the brain. Hereditary hemorrhagic telangiectasia AVMs are more likely to be multiple and have a tendency toward small size and cortical location. As such, they are often treated using a single-modality therapy.

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Key Words • hereditary hemorrhagic telangiectasia • Osler-Weber-Rendu • cerebral vascular malformation • brain arteriovenous malformation • vascular disorders

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sler-Weber-Rendu disease or hereditary hemorrhagic telangiectasia (HHT) is a hereditary disorder characterized by mucocutaneous telangiectasias, visceral arteriovenous malformations (AVMs), and epistaxis.1 The prevalence of HHT has been estimated between 1 in 5000 to 1–2 in 100,000, except in particular Dutch, French, and Japanese populations in which prevalence may be as high as 5 in 8000.4,6,7,10,16,20,24 Hereditary hemorrhagic telangiectasia is inherited in an autosomal dominant fashion with high penetrance and variable expressivity. By the age of 16 years, 71% of patients have developed at least one sign of HHT; by age 40, this number increases to greater than 90%.4,24

Hereditary hemorrhagic telangiectasia has been linked to numerous neurological complications including cerebral AVM, spinal AVM, cerebral abscess, ischemic stroke, intracerebral hemorrhage, migraine headache, and seizure.3,7,8,11–15,17,18,21,23,24,26–30,33–35,37–39,41 Cerebral AVMs have been of particular interest in the HHT population as they have an increased frequency and can have potentially devastating consequences if untreated. Cerebral AVMs have been reported to occur in 10% of patients with HHT1 (Endoglin [ENG] deficiency), and in 1% of patients with HHT2 (Activin-like kinase receptor 1 [ACVRL, Alk-1]...
deficiency), compared with an incidence of 1.1–10.3 per 100,000 (approximately 0.01%) of AVMs in the general population.\textsuperscript{3,22,40}

Cerebral AVMs have a reported annual spontaneous hemorrhage rate of 1%–4%, with potentially devastating consequences at the time of rupture.\textsuperscript{3,13,23,40} As such, current consensus guidelines recommend screening patients with possible or definite HHT for cerebral vascular malformations (CVMs) using MRI with and without contrast enhancement, including sequences to detect blood products to increase sensitivity.\textsuperscript{15,35} Debate exists in the literature regarding this recommendation, as some authors argue that cerebral AVMs in HHT have a different natural history and lower spontaneous rupture rate (as low as 0.36%–0.56% per year) than AVMs in the general population.\textsuperscript{21,24,41}

In the present study, we set out to further characterize the types and frequency, as well as the sequelae, of CVMs in the HHT patient population. This study differs from most prior studies in 2 ways. First, we collected data on the full spectrum of CVMs including cavernous malformations, capillary telangiectasias, developmental venous anomalies (DVAs), arteriovenous fistulas (AVFs), and aneurysms. Second, our patient population was screened for CVMs using more powerful 3-T MRI magnets with more sensitive sequences than prior studies (which were circa 2000). A better understanding of the cerebral vascular pathology in HHT patients should guide our diagnostic and treatment choices and may also help us better understand the etiology of CVMs in general. As with any rare disorder, there is value in the presence of multiple large databases in the literature.

**Methods**

A prospectively collected database of 372 patients who were referred to the Georgia Health Sciences HHT center between August 2002 and October 2009 for evaluation of possible HHT was accessed. Data were collected regarding demographic data, presenting symptoms, presence and type of CVMs, and details of systemic disease. Our standard practice in patients who are referred for HHT evaluation is to obtain 3-T MRI/MRA studies of the brain with and without Gd contrast administration that include blood byproduct and calcification-sensitive gradient echo sequences. Magnetic resonance images obtained in patients with HHT were mixed with those obtained in non–age-matched controls and reviewed in a blinded fashion by 2 physicians. Information regarding HHT patients not imaged at our institution was abstracted from radiology reports. Data were tabulated in Microsoft Excel.

The characteristics of the AVMs in the HHT population were analyzed with regard to size, location, and eloquence of cortex. These data were compared with those of historical controls using a Fisher’s exact test.\textsuperscript{5}

Chart review, data collection, and handling of patient information were performed with the approval of and in accordance with the rules set forth by the Georgia Regents University Institutional Review Board.

**Results**

**Data Obtained in HHT Patients**

Of 372 patients referred for evaluation for HHT, 230 were diagnosed with definite HHT. Hereditary hemorrhagic telangiectasia was diagnosed according to the Curacao criteria.\textsuperscript{36} Definite HHT was diagnosed when at least 3 criteria were met or when pathogenic mutation of the ENG or ALK1 genes was present. Possible HHT was diagnosed when 2 criteria were met. The concept of probable HHT is a local modification of the Curacao criteria. A probable HHT was diagnosed when 2 formal Curacao criteria were met but when the patient was otherwise felt to have a clinical presentation highly suspicious for HHT (for example, a patient with mucocutaneous telangiectasias and multiple pulmonary AVMs; or a patient with nosebleeds, mucocutaneous telangiectasias, and a highly suspicious family history).

Two hundred eighty referred patients had been screened for brain vascular malformations with either contrast-enhanced MRI of the brain or CT angiography (CTA) of the head. Based on modified Curacao criteria, 209 patients had a diagnosis of definite HHT, 29 probable HHT, and 42 possible HHT. Two hundred two of these patients underwent MRI examinations at our institution (with images reviewed by 2 physicians in a blinded fashion), 73 patients underwent MRI examinations performed at an outside institution, and 5 patients were screened with CTA. In the cases in which CTA was conducted, the patients had either a contraindication to MRI or claustrophobia.

Two hundred thirty patients had definite HHT in this population, 209 of whom had screening examinations of the brain. Of these patients, 95% had 4 or more cutaneous telangiectasias, 96% had nosebleeds, and 50% had pulmonary AVMs. There was documented involvement of the gastrointestinal tract in 26.5% of the patients with definite HHT, and liver AVMs in 19.1%. Patients tended to be Caucasian (96.5%), female (61%), and most were adults (88%), with an average age of 44 years.

Forty-five CVMs were identified in 39 patients (19 AVMs, 5 saccular aneurysms, 8 capillary telangiectasias, 3 cavernous malformations, 9 DVAs, and 1 AVF). Six patients harbored multiple lesions. There were 2 patients with 2 AVMs (Fig. 1), 3 patients with multiple capillary telangiectasias, and 1 patient who had both an AVM and an aneurysm. Table 1 provides a summary of these data.

Six of the 19 AVMs identified had been treated prior to the acquisition of images at our institution. Of the remaining 13 AVMs, 85% were supratentorial (n = 11), 100% were less than 3 cm in size (n = 13), 54% were in eloquent cortex (n = 7), and 85% were cortical (n = 11). These data are summarized in Table 2. Three of these AVMs were symptomatic (2 presented with intracerebral hemorrhage and 1 with seizure). Thirteen of the HHT AVMs had been treated at the time of data collection: 5 with open resection only, 6 with stereotactic radiosurgery (SRS) only, 1 with SRS plus open surgery, and 1 with glue embolization plus SRS. In all but one case in which there was MRI/MRA suspicion of an aneurysm, AVM, or AVF, the diagnosis was confirmed by catheter angiography.
Cerebral vascular malformations in HHT

Of the 280 HHT patients with MRI or CTA examinations, 19 had a history of seizures, 5 had a history of intracerebral hemorrhage, 5 had findings consistent with cerebral abscess, and 11 had experienced an ischemic stroke. The most common neurological complaint in these patients was headache—118 of 280 patients complained of headache on their review of systems.

Discussion

Arteriovenous Malformations

Arteriovenous malformations were identified in 7.7% of the HHT patients in the present study. Bharatha et al. recently demonstrated that brain AVM multiplicity predicts the diagnosis of HHT. They also showed a trend toward small size, cortical location, and superficial venous drainage in the HHT population.5 The HHT AVMs in our series tended to be supratentorial (85%, n = 11), less than 3 cm in size (100%, n = 13), and cortical (85%, n = 11). Slightly more than half (54%, n = 7) were located in eloquent cortex. We found no statistically significant difference (p < 0.05) between our HHT population and the Bharatha et al. population with regard to location, size, and eloquence of cortex.5

The incidence of cerebral AVMs has been estimated at 0.01% in the general population.3 The prevalence of AVMs is estimated at 1.1 per 100,000 with autopsy cases excluded or 2.1 per 100,000 for all cases. The Cooperative Study of Intracranial Aneurysms and SAH reported a prevalence of 140–500 per 100,000. The most recent literature suggests a rate of 10.3 per 100,000.40 The rate of AVMs in our control group exceeds that of historical controls and may reflect a selection bias in our MRI population.

At the time of data collection, 13 of the HHT AVMs had been treated. The vast majority of these lesions (85%, n = 11) were treated with single-modality therapy, 5 with resection and 6 with SRS. Multimodality therapy was used in the other 15% of cases (n = 2) and consisted of either resection plus SRS or glue embolization plus SRS. The choice of single-modality therapy is likely influenced by the small size and superficial location of the majority of HHT AVMs.

Cerebral Aneurysms and Other CVMs

The rate of cerebral aneurysms was 2.4% in this population of HHT patients. Large meta-analyses, such as that published by Rinkel et al., have estimated the prevalence of cerebral aneurysms at 1.7%–3.1% in “adults without specific risk factors [for aneurysm formation].”31

The 5 cerebral aneurysms found in the HHT patient group were all associated with the anterior circulation, were all associated with the carotid wall, and only one aneurysm’s parent vessel fed a vascular bed containing an AVM. Two of the aneurysms were at the medial wall of the cavernous segment of the carotid artery (Kobayashi’s cave), 1 was at the ophthalmic segment, and 2 were at the posterior communicating segment. Three of the aneurysms were small (≤3 mm), and 2 had previously been treated by clip ligation prior to referral to our HHT center. The patient harboring both a cerebral aneurysm and an AVM had a posterior carotid wall aneurysm at the posterior communicating artery segment that had been previously treated with clip ligation. A small, left, frontoparietal Spetzler-Martin Grade II AVM was also present in the territory of the left middle cerebral artery. This lesion was ultimately treated with SRS.

The rate of DVA was 4.3% in the HHT group. Developmental venous anomalies occur in 2.5%–3% of the general population based on autopsy studies.9,32 The prevalence of DVA has been estimated by other authors at 0.6%.2

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<th>TABLE 1: Number and type of CVMs</th>
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<td>HHT referrals</td>
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Comparison With Unmatched Controls

Magnetic resonance images of HHT were reviewed in a blinded fashion alongside 413 unmatched MRI/MRA studies that included gradient echo sequences that are sensitive for blood products. The presence of CVMs was tabulated and compared with the HHT group. There was a significant difference in the number of AVMs (7.7%, p < 0.001), DVAs (4.3%, p < 0.025), and cerebral aneurysms (2.4%, p < 0.05) in the HHT group compared with the control group (0.5%, 1.2%, and 0.5%, respectively). To our knowledge, this is the first report of an increased prevalence of cerebral aneurysms in the HHT population. The prevalence of multiple arteriovenous shunting lesions, including AVMs and AVFs, was also increased in the HHT group (p < 0.05). For a summary of these data, please refer to Table 3.

Clinical Implications

Debate is ongoing regarding the role for routine screening for brain vascular malformations in patients with HHT. Critics argue that cerebral AVMs in HHT patients have a different natural history than cerebral AVMs in the general population—with lower rupture rates and better prognosis at the time of rupture.24,41 These studies have been criticized for selection bias and survivor bias leading to better AVM rupture rates and better outcomes for intracerebral hemorrhage in HHT.25 The present data tend to support the increased incidence of cerebral AVMs in the HHT population. Given the potential for catastrophic outcomes associated with the rupture of brain AVMs, we routinely screen for CVMs in patients with definite or probable HHT at our center.

Study Limitations

The present study is limited by several factors. While the vast majority of our HHT patients were screened with MRI or CTA, a number of these studies were done off-site at outside hospitals as a matter of convenience for our patients. Additionally, some patients were referred for HHT evaluation after their cerebral vascular lesion had already been treated. Ideally, all patients (both HHT and controls) would have undergone imaging at our institution on a 3-T magnet. We may have underestimated the incidence of capillary telangiectasia, DVAs, and other subtle findings in the HHT patients who did not undergo imaging at our institution. This study may also be limited by a survivor bias. Previous reports in the literature have expounded upon the devastating outcomes associated with HHT-related AVM rupture in the pediatric population.28 This may cause us to further underestimate the incidence of CVM in the HHT group. Furthermore, our control population does not represent a cross-section of the “normal” population; it represents a population of patients with suspected neurological disease and may overestimate the incidence of some vascular lesions. Finally, because the gold standard for the diagnosis of arteriovenous shunting lesions is catheter angiography, this study may have underestimated the incidence of AVFs and micro-AVMs.

Conclusions

Arteriovenous malformations were identified in 7.7%, DVAs in 4.3%, and cerebral aneurysms in 2.4% of the HHT patients. Arteriovenous fistula, cavernous malformation, and capillary telangiectasia were identified in 0.5%, 1%, and 1.9% of HHT patients, respectively. Arteriovenous malformations in the HHT population have a tendency to be supratentorial, small in size, and cortical in location. As such, single-modality treatment is often pursued in these patients. In light of the devastating consequences that can be associated with AVM hemorrhage, routine screening of patients with definite or probable HHT is recommended to evaluate for brain vascular malformations. Further study is needed regarding the incidence and natural history of brain vascular malformations in HHT patients to better care for this unique patient population.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation

* Overall there were 209 HHTs and 413 controls.
include the following. Conception and design: Gossage, Alleyne. Acquisition of data: Woodall, McGettigan, Figueroa, Alleyne. Analysis and interpretation of data: Woodall, Gossage, Alleyne. Drafting the article: Woodall. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Woodall. Statistical analysis: Woodall, Gossage. Study supervision: Gossage, Alleyne.

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