Cerebrovascular Manifestations in 321 Cases of Hereditary Hemorrhagic Telangiectasia

Cormac O. Maher, MD; David G. Piepgras, MD; Robert D. Brown, Jr, MD; Jonathan A. Friedman, MD; Bruce E. Pollock, MD

Background and Purpose—Patients with hereditary hemorrhagic telangiectasia (HHT) are at risk for developing cerebral vascular malformations and pulmonary arteriovenous fistulae. We assessed the risk of neurological dysfunction from these malformations and fistulae.

Methods—Three hundred twenty-one consecutive patients with HHT seen at a single institution over a 20-year period were studied. Any evidence of prior neurological symptoms or presence of an intracranial vascular malformation was recorded. All cases of possible cerebral arteriovenous malformation were confirmed by conventional arteriography.

Results—Twelve patients (3.7%) had a history of cerebral vascular malformations. Ten patients had arteriovenous malformations, 1 had a dural arteriovenous fistula, and 1 had a cavernous malformation. Seven patients (2.1%) presented with intracranial hemorrhage, 2 presented with seizures alone, and 3 were discovered incidentally. The average age at the time of symptomatic intracranial hemorrhage was 25.4 years. All patients with a history of intracranial hemorrhage were classified as Rankin grade I or II at a mean follow-up interval of 6.0 years. A history of cerebral infarction or transient ischemic attack was found in 29.6% of patients with HHT and a pulmonary arteriovenous fistula.

Conclusions—The risk of intracranial hemorrhage is low among people with HHT. Furthermore, a majority of these patients have a good functional outcome after hemorrhage. The data do not suggest a compelling indication for routine screening of patients with HHT for asymptomatic cerebral vascular malformations. By comparison, pulmonary arteriovenous fistulae are a much more frequent cause of neurological symptoms in this population. (Stroke. 2001;32: 877-882.)

Key Words: cerebral arteriovenous malformations ▪ hereditary disease ▪ intracerebral hemorrhage ▪ stroke

Hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber disease, is an inherited vascular dysplasia that is transmitted as an autosomal dominant trait with high penetrance and variable expressivity.1 The estimated prevalence is 1 or 2 cases per 100 000.1,2 Chromosomes 9q and 12q have been implicated in the inheritance of this disease.3–7 A family history of HHT, although not required to make the diagnosis, is almost universally present. The vascular malformations of HHT may occur in multiple organs, including the lung, liver, kidney, and brain.8,9 Epistaxis is the most common presentation, followed by gastrointestinal bleeding.10,11 Pulmonary arteriovenous fistulae (AVFs) are often accompanied by dyspnea or hemoptysis and, less frequently, ischemic neurological symptoms.12–14 Telangiectasias are frequently noted on the skin and mucous membranes, often not appearing until the second or third decade.8,9

Brown et al15,16 have reported that the detection rate of intracranial vascular malformations in a population-based study in the most recent time period was 2.75 per 100 000 person-years. The prevalence of intracranial hemorrhage from a vascular malformation was 7.50 per 100 000 people in the population at large.15,16 Patients with HHT are thought to be at increased risk for harboring cerebral vascular malformations compared with the entire population. Arteriovenous malformations (AVMs), cavernous malformations, dural arteriovenous fistulae, and aneurysms have all been reported in these patients (Figure 1).14,17–24 Vascular malformations are found throughout the central nervous system, including the spinal cord.25 Several reports have analyzed the frequency of radiological detection of cerebral AVMs in this population.26–28 The risk of hemorrhage from these lesions, however, is an ongoing subject of debate. Because the risk of intracranial hemorrhage is low, it is necessary to evaluate a large number of patients to determine the clinical significance of cerebral AVMs. Furthermore, analysis of a consecutive series of patients from a single institution will minimize the reporting bias. We report our experience with a large consecutive series of HHT patients evaluated at a single institution between 1980 and 1999 to determine the occurrence of cerebral vascular malformations, associated neurological symptoms, and intracranial hemorrhage.
Subjects and Methods

The medical records of 321 consecutive patients with HHT seen at the Mayo Clinic over a 20-year period were reviewed. There were 132 men and 189 women. The mean age at the time of the most recent evaluation was 50.3 years (range 6 to 85). In every case, the diagnosis of HHT was made or confirmed by a primary care physician at our institution. All patients underwent a complete general medical evaluation. All patients were asked to complete an inventory of current symptoms, past medical history, and family medical history at the time of their evaluation. The inventory of current symptoms included visual symptoms, hearing loss, slurred speech, seizures, or focal weakness. The inventory of past medical history included stroke or transient ischemic attack (TIA), as well as any intracranial procedures.

Although patients were not routinely radiologically screened for the presence of a cerebral vascular malformation, 70 patients underwent at least 1 head CT. Forty-six patients underwent a head MRI and 24 underwent a 4-vessel cerebral angiogram. CT or MRI confirmation was obtained for all cases of intracranial hemorrhage that were evaluated at our institution. All cases of cerebral AVM discovered on MRI or CT underwent catheter angiography. Patients were considered to have a cerebral AVM if the angiographic appearance was consistent with this diagnosis or, in operated cases, if pathological investigation confirmed the diagnosis. Angiographic criteria for AVM were the presence of a pial feeding vessel, a draining vein, and a nidus.

Patients were included without regard to the treatment for the malformations. Data collected included age at initial hemorrhage or ischemic event, presence of a family history of cerebral hemorrhage, location and number of malformations, type of intervention(s), and patient’s neurological condition at the time of the most recent evaluation. Functional status was assessed with the Rankin scale.29 Those patients with a known pulmonary AVF were screened for a history of cerebral abscess, infarction, TIAs, and migraine headache. Age at the time of initial neurological symptoms, family history information, and therapeutic interventions were recorded.

Results

Twelve (3.7%) of 321 patients were found to have cerebral vascular malformations. There were 10 AVMs, 1 dural AVF, and 1 cavernous malformation (Table). Multiple vascular malformations were seen in 3 cases. The malformations were located supratentorially in 7 cases, infratentorially in 2 cases, and both supratentorially and infratentorially in 3 cases. Seven patients (2.1%) presented with symptoms of intracranial hemorrhage, 2 (0.6%) presented with seizures alone, and 3 cerebrovascular malformations (0.9%) were discovered incidentally. Neither of the 2 patients who presented with seizures had evidence of prior hemorrhage on MRI. Mean age at the time of hemorrhage was 25.4 years (range 8 to 50, SD 16.8). Three patients were sibling members of a single family.

Cerebral vascular malformations were treated by excision in 8 patients and by radiosurgery in 2. In 2 cases, the vascular malformations were managed conservatively. After a mean follow-up interval of 6.0 years (SD 10.7), 10 patients were classified as a grade I on the Rankin disability scale, and 2 were grade II.27 Six patients were neurologically intact, and 6 had a mild focal deficit, including hemiparesis in 5 patients and homonymous hemianopsia in 1. Two patients were unable to return to their prior level of functioning but were independent in all activities of daily living. Although both of these patients had undergone craniotomy for excision of their AVMs, the persistent hemiparesis was thought to be a result of the hemorrhage and not the surgical treatment.

Three patients were found to have multiple low-flow cerebral telangiectasias. None of the telangiectasias were known to have hemorrhaged, and none of the cerebral hemorrhages in this series were thought to be related to these lesions. In a single patient, cerebral telangiectasias were noted to develop over serial imaging.

Neurological symptoms were more likely to be secondary to pulmonary AVF than to cerebral vascular malformations. Seventy-one patients (22.1%) had a known pulmonary AVF. Of these, 21 (29.6%) had a history of cerebral infarction or TIA, and 5 (7.0%) had a history of 1 or more cerebral abscesses. Four of the 5 cases of cerebral abscesses were multiple or recurrent. A history of cerebrovascular embolic complications (TIA, cerebral infarction, or intracranial ab-

Figure 1. Case 2. Lateral (A) and anteroposterior (B) views of a left internal carotid injection angiogram demonstrating a single AVM with a compact nidus in a patient with HHT.
scess) in patients with known pulmonary AVFs was present in 1 (10%) of 10 patients younger than 30 years, 11 (44%) of 25 patients between 31 and 50 years of age, and 14 (47%) of 30 patients older than 50 years. A history of migraine headaches was found in 18 (25.4%) of those with pulmonary AVF.

Discussion

Patients with HHT are at increased risk for developing cerebral AVMs. Roman et al.,14 in reviewing collected cases in the literature, reported that cerebral vascular malformations were found in 36% of 215 cases of HHT with neurological manifestations. The majority of these were cavernous malformations and venous angiomas; AVMs were noted in only 7.9% of reported cases. It is difficult to derive AVM occurrence data, however, from a synthesis of case reports as a result of reporting bias. Fulbright et al.26 reported on MRI findings in a series of 184 patients with HHT. They found cerebral vascular malformations in 22.8% and true AVMs in 4.9% of these patients. Willemse et al.27 screened 196 patients with HHT for the presence of cerebral AVMs using digital subtraction angiography. Using this technique, they found cerebral AVMs in 11%. In the present series, the occurrence of cerebral AVM was lower (3.7%), most likely because of the absence of radiological screening in asymptomatic patients.

The risk of hemorrhage for unruptured nonsyndromic intracranial AVMs is ≈2% to 4% per year.30–33 For several reasons, it has been suggested that this rate may not be applicable to AVMs in the HHT population.26 First, cerebral vascular malformations may be dynamic in HHT, like the pulmonary and gastrointestinal malformations that are known to enlarge over time.34–37 This dynamic tendency may not be relevant, however, to cerebral AVMs that are congenital in origin. Second, the majority of AVMs in HHT that have been described in the literature are smaller than 25 mm in maximum diameter.22,23,26 Some studies have suggested a correlation between small AVM size and an increased risk of hemorrhage,32,38,39 although this has not been a consistent finding.30,33 Finally, multiple AVMs and low-flow telangiectasias are thought to occur with greater frequency in this population (Figures 2 and 3).19,20,23,24,26,28,40–43

In the present series, the risk of presenting with an intracerebral hemorrhage from a cerebral AVM in patients with HHT was very low, occurring in 7 (2.1%) of 321 patients. This is supported by Fulbright et al.,26 who found no history of intracranial hemorrhage in a series of 184 patients with HHT. Willemse et al.27 encountered 3 cases of intracranial hemorrhage in their series of 196 patients (1.5%). Taken together, these data suggest that the overall long-term risk of intracranial hemorrhage among all people with HHT is likely low. Furthermore, our data suggest that many patients who do present with intracranial hemorrhage may have a good functional outcome.

We believe that all patients with a history of symptomatic intracranial hemorrhage in this study population were identified. Nevertheless, as with any retrospective analysis, the results of this study should be interpreted with caution. It is not possible, based on these data, to determine lifetime risk or annual risk of hemorrhage. We were unable to determine whether there was referral bias at our institution for HHT patients with cerebrovascular manifestations versus those patients with HHT in the absence of these symptoms. The rarity of intracranial hemorrhage in the HHT population seen at other centers would argue against such bias.27

The average age of hemorrhage in this series was in the third decade. Young age at the time of hemorrhage has been observed in multiple case reports and case series.14,20,22,41–44 There are 5 prior reports of familial AVMs in HHT.20,45–48 Our series includes 3 patients harboring an AVM who were sibling members of a single family. It is possible that a family history of a first-degree relative with a cerebral AVM or intracranial hemorrhage may be a risk factor for AVM in the HHT population, but more data are needed to clarify this relationship.

Pulmonary AVFs are frequently encountered in patients with HHT and are known to predispose patients to paradoxical emboli and neurological complications. Pulmonary AVFs are the most frequent cause of neurological symptoms in this population.14 Approximately 20% of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type</th>
<th>Location</th>
<th>Multiple</th>
<th>Presentation</th>
<th>Intervention</th>
<th>Outcome/Rankin Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AVM</td>
<td>Infratentorial</td>
<td>No</td>
<td>Hemorrhage</td>
<td>Excision</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>AVM</td>
<td>Supratentorial</td>
<td>No</td>
<td>Incidental</td>
<td>Excision</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>Cavernous malformation</td>
<td>Both</td>
<td>Yes</td>
<td>Hemorrhage</td>
<td>Excision</td>
<td>II</td>
</tr>
<tr>
<td>4</td>
<td>AVM</td>
<td>Supratentorial</td>
<td>No</td>
<td>Seizures</td>
<td>Excision</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>AVM</td>
<td>Both</td>
<td>Yes</td>
<td>Incidental</td>
<td>Radiosurgery</td>
<td>I</td>
</tr>
<tr>
<td>6</td>
<td>AVM</td>
<td>Supratentorial</td>
<td>No</td>
<td>Hemorrhage</td>
<td>Excision</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>AVM</td>
<td>Both</td>
<td>Yes</td>
<td>Incidental</td>
<td>Radiosurgery</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>AVM</td>
<td>Supratentorial</td>
<td>No</td>
<td>Hemorrhage</td>
<td>Excision</td>
<td>I</td>
</tr>
<tr>
<td>9</td>
<td>DAVF</td>
<td>Supratentorial</td>
<td>No</td>
<td>Hemorrhage</td>
<td>No treatment</td>
<td>I</td>
</tr>
<tr>
<td>10</td>
<td>AVM</td>
<td>Infratentorial</td>
<td>No</td>
<td>Hemorrhage</td>
<td>Excision</td>
<td>I</td>
</tr>
<tr>
<td>11</td>
<td>AVM</td>
<td>Supratentorial</td>
<td>No</td>
<td>Seizures</td>
<td>Excision</td>
<td>II</td>
</tr>
<tr>
<td>12</td>
<td>AVM</td>
<td>Supratentorial</td>
<td>No</td>
<td>Seizures</td>
<td>Excision</td>
<td>I</td>
</tr>
</tbody>
</table>
with HHT will develop a pulmonary AVF, and between one fourth and one third of HHT patients with pulmonary AVFs will develop cerebral ischemic symptoms. Brain abscesses from septic emboli occur in 5% to 9% of HHT patients with pulmonary AVFs. Others have noted a high occurrence of cases of migraine headaches in patients with HHT and pulmonary AVFs. It remains unsettled whether this frequent finding represents an increase over the normal incidence of migraine headaches in the population.

Our data confirm the high risk of cerebral ischemic complications and abscesses in patients with HHT that is related to pulmonary AVFs. A history of cerebral embolic complications referable to a pulmonary AVF was rare in young patients but became much more common in the fourth through sixth decades. Given the frequent occurrence of neurological complications of pulmonary AVFs, strong consideration should be given both to screening patients with HHT for asymptomatic fistulae and to treating these fistulae once they are discovered. The most frequent means of screening for pulmonary AVF at our institution is arterial blood gas analysis, chest radiography, and physical examination. When clinically indicated, based on clinical suspicion alone or a positive result on one of the screening tests, a pulmonary angiogram, the most sensitive test for pulmonary AVF, is obtained.

Figure 2. Case 8. Cerebral angiogram demonstrating 3 small AVMs in a patient with HHT. Lateral (A) and anteroposterior (B) views of the posterior circulation demonstrate small AVMs in the medial left temporal lobe and the left cerebellum. There were additional AVMs noted in the right frontal lobe and left parietal lobe (not shown). A nidus of abnormal vessels is seen in each case.

Figure 3. Case 5. Lateral views of the left carotid (A) and vertebral (B) angiograms 4 years after radiosurgery for a right occipital AVM. The AVM is no longer seen. Multiple small telangiectasias that lack a nidus are demonstrated in both anterior and posterior circulations. We advised against treatment for these telangiectasias.
Conclusions
Regarding cerebral vascular malformations, the risk of having a symptomatic intracranial vascular malformation or intracranial hemorrhage in this population appears to be low. With the information that is currently available, we do not see a compelling indication for routine screening of all patients with HHT for asymptomatic cerebral vascular malformations. If cerebral AVMs are discovered that have not hemorrhaged, treatment of the AVM should be performed in accordance with standard neurosurgical principles for the management of AVMs in the general population. There are no data to support the neurosurgical treatment of asymptomatic cerebral telangiectasias in patients with HHT.

Acknowledgment
The authors wish to express their appreciation to Mary Soper for assistance with the preparation of this manuscript.

References
Cerebrovascular Manifestations in 321 Cases of Hereditary Hemorrhagic Telangiectasia
Cormac O. Maher, David G. Piepgras, Robert D. Brown, Jr, Jonathan A. Friedman and Bruce E. Pollock

Stroke. 2001;32:877-882
doi: 10.1161/01.STR.32.4.877

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/4/877

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/