Bleeding risk of cerebrovascular malformations in hereditary hemorrhagic telangiectasia

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Object. Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal-dominant vascular dysplasia with a high prevalence of cerebrovascular malformations (CVMs), mostly manifested as arteriovenous malformations (AVMs). The natural history and bleeding risk of these CVMs is unknown. The authors investigated the risk of bleeding in conjunction with clinical and radiological features in patients with HHT and proven CVMs.

Methods. Intravenous digital subtraction (DS) angiography was used to screen 196 patients with HHT for the presence of CVMs. Patients with abnormal results on DS angiography were asked to undergo a conventional cerebral angiographic study. All patients with a proven CVM were assessed by a neurologist. The bleeding risk was retrospectively and prospectively calculated for patients with AVMs only, as well as for the whole cohort of patients with CVMs.

Twenty-four patients (12.2%; 16 female and eight male), aged 14 to 66 years (mean 35.4 years) with one or more CVMs were identified. Fifteen patients (62.5%) had a CVM and a pulmonary AVM. Eleven patients (45.8%) exhibited no neurological signs of their CVM; six (25%) had headache or migraine; four (16.7%) had seizures; and three (12.5%) had an intracranial hemorrhage. Twenty-two patients had at least one AVM (with a total of 28 AVMs), whereas as two patients only had telangiectases. Twenty-seven AVMs were small (96%), 36% were located in eloquent areas of the brain, and 82% had superficial venous drainage. One third of the patients had multiple CVMs. The bleeding risk for patients with at least one AVM ranged from 0.41 to 0.72% per year, and for the whole cohort the range was 0.38 to 0.69% per year. Calculation of the bleeding risk as determined by lesion-years ranged from 0.36 to 0.56% per year for patients with AVMs and from 0.27 to 0.46% per year for all patients with CVMs.

Conclusions. Patients with HHT have a high risk of harboring a CVM, especially in the presence of a pulmonary AVM. These CVMs are mostly low-grade AVMs (Spetzler–Martin Grade I or II), are frequently multiple, and have a lower risk of bleeding than that associated with sporadic AVMs. Female patients are more often affected than male patients. The inherent low sensitivity of DS angiography screening for CVMs may yield false negative results.

Key Words • hereditary hemorrhagic telangiectasia • telangiectasis • cerebral vascular malformation • arteriovenous malformation • bleeding risk

Hereditary hemorrhagic telangiectasia or Rendu-Osler-Weber disease is a rare autosomal-dominant disorder characterized by multiple mucocutaneous telangiectases and associated vascular malformations, which can give rise to hemorrhagic complications in multiple organ systems.10,12 An epistaxis caused by bleeding from telangiectases of the nasal mucosa is the most common manifestation of HHT. Pulmonary AVMs and CVMs, with an estimated prevalence of 14 to 33% and 5 to 13%, respectively,10,13,41 constitute a potential risk for morbidity or mortality.

Genetic studies have shown that HHT is associated with gene defects in the transforming growth factor–β binding protein endoglin, which is located on chromosome 9q33-q34,12 and also to nonendoglin-linked genes on chromosome 12q.13,18 The question of whether there are phenotype–genotype interactions regarding visceral localization has not yet been resolved.14

In two thirds of the cases neurological involvement in HHT is considered secondary to a pulmonary AVM,29,41 which can cause ischemic cerebral events by paradoxical emboli or brain abscesses due to septic emboli. Cerebrovascular malformations in patients presenting with headache, seizures, intracerebral hemorrhage, and subarachnoid hemorrhage11,28,29 are another substantial cause of neurological symptoms.

The presence of CVMs in HHT, notably telangiectases, AVMs, venous angiomas, and aneurysms, have scarcely been documented in the literature, and their clinical implications are not fully understood. Approximately 5 to 13%
of patients with HHT have cerebral AVMs, whereas the prevalence of cerebral AVMs in the general population is reportedly only 0.6%. Generally, it has been assumed that the bleeding risk of cerebral AVMs in patients with HHT is similar to that of sporadic cerebral AVMs in the general population, which has been well documented. However, the natural course of AVMs associated with HHT is not known. The frequency of multiple AVMs and the presence of other CVMs make it difficult to assess the natural course of this heterogeneous disorder. In this report we describe our experience in 24 patients with HHT associated with vascular malformations of the brain, with special reference to the clinical profile, radiological aspects, and bleeding risk associated with these lesions.

Clinical Material and Methods

Patient Population

Since 1982 all patients with HHT have been advised to undergo screening for pulmonary AVMs and CVMs. In addition, between 1990 and 1998 all family members of these patients were asked to undergo screening for HHT because of the hereditary nature of this disease. The diagnosis of HHT was made by one author (C.J.J.W.) based on typical lesions observed on skin and mucosa that were present in conjunction with familial occurrence. One hundred ninety-six patients with HHT (114 women and 82 men) of a total of 204 patients agreed to the screening for CVM. These patients came from 48 different families with no known relationship to each other.

Screening for CVM was performed using intravenous DS angiography, and all patients with abnormal DS angiography results were offered conventional cerebral angiography. All patients with a proven CVM were screened for neurological signs and symptoms by the same neurologist (H.M.). The cerebral angiograms obtained in each patient were reviewed by a radiologist (T.T.C.O.) and a neurosurgeon (J.G.W.). For each vascular lesion, the type of vascular malformation, its location, the number of lesions, and the presence of other CVMs were recorded. The natural course of AVMs associated with HHT is not known. The frequency of multiple AVMs and the presence of other CVMs make it difficult to assess the natural course of this heterogeneous disorder. In this report we describe our experience in 24 patients with HHT associated with vascular malformations of the brain, with special reference to the clinical profile, radiological aspects, and bleeding risk associated with these lesions.

Clinical Material and Methods

Patient Population

Since 1982 all patients with HHT have been advised to


TABLE 1
Clinical and neuroradiological features in 24 patients with HHT*

<table>
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* El = eloquence; PAVM = pulmonary AVM; TL = telangiectasis; + = present; – = absent.
† Grade of AVM according to the Spetzler–Martin classification, or other type of CVM.
Bleeding risk of CVMs in HHT

sions, venous drainage, size, and the presence of associated aneurysms were described.

The AVMs in this study were described according to a system proposed by Spetzler and Martin, in which three variables are used: size (1, < 3 cm; 2, 3–6 cm; 3, > 6 cm), pattern of venous drainage (0, superficial; 1, deep), and neurological eloquence of the adjacent brain region (0, none; 1, eloquent). The AVM grade, which is correlated with postoperative neurological complications, can be determined by adding the three scores. Grade IV applies to inoperable AVMs in the brainstem and hypothalamus.

The annual bleeding risk for the CVMs was calculated in several ways. First, we calculated the time from each patient’s date of birth to the time of hemorrhage or treatment, with either surgery or stereotactically guided radiosurgery. If patients had neither hemorrhage nor treatment, August 1998 was specified as the end of the analysis. None of the patients underwent endovascular embolization. We defined this period as $T_{\text{max}}$. The $T_{\min}$ was defined as the time elapsed between diagnosis of the CVM and the time of hemorrhage, treatment, or end of the analysis. To calculate the annual bleeding risk per patient independent of the number of lesions, the number of hemorrhages observed was divided by the total number of patient-years ($\sum T_{\text{min}}$ and $\sum T_{\text{max}}$) that the study population was at risk for a hemorrhage. This method has been used previously by Pollock et al. Independent of the number of patients, we also calculated the bleeding risk in terms of lesion-years, which were determined by multiplying the total number of lesions by $T_{\text{min}}$ and $T_{\text{max}}$ in years for each patient. These methods yielded an annual bleeding risk range, determined by $T_{\text{min}}$ and $T_{\text{max}}$. We then calculated the bleeding risk range for the whole cohort of 24 patients and for the AVM subgroup, which consisted of 22 patients with at least one AVM. Finally, we made the same calculation, based on lesion-years, for all 38 CVMs and 28 AVMs.

Results

The CVMs were suspected on the basis of DS angiography results in 29 patients and were subsequently proven on conventional cerebral angiographic studies in 24 patients aged 14 to 66 years (mean 35.4 years). In two patients, results of the conventional cerebral angiographic study were normal, one refused to undergo the study, and in one patient it was not performed because of a severe allergy to the contrast material. In one patient the conventional cerebral angiographic study was not diagnostic after a demonstrated hemorrhage, and this case was excluded from further analysis. Twenty-four (12.2%) of the 196 patients screened had a CVM; eight (9.8%) of the 82 men screened and 16 (14%) of the 114 women. Fifteen patients (62.5%; 12 women and three men) also had a pulmonary AVM. Eleven patients were asymptomatic (45.8%); six had atypical headache or migraine (25%); four had epilepsy (16.7%); three had an intracranial hemorrhage (12.5%); and one had an infantile encephalopathy (Case 4). One patient had both migraine and epilepsy (Case 18).

Twenty-two patients had at least one AVM, and two only had telangiectases. All but one AVM was small (that is, < 3 cm), and only one was medium sized (3–6 cm). Five (17.9%) of the 28 AVMs had deep venous drainage, and 10 (35.7%) of the 28 were located in eloquent areas of the brain. Sixteen AVMs (57.1%) were Grade I, eight (28.6%) were Grade II, and three (10.7%) were Grade III, and one was Grade IV (3.6%). Thirty-four CVMs (89%) were located supratentorially, two were located in the cerebellum, one was in the pons, and there was one CCF.

In 24 patients 38 vascular malformations were identified: 28 AVMs, nine telangiectases, and one CCF. Multiple lesions were present in eight patients (33.3%). One patient had an AVM and a CCF, two patients had two AVMs; one patient had two AVMs and two telangiectases; two patients had one AVM and one telangiectasia; one patient had four AVMs and two telangiectases, and one patient had two telangiectases. In one patient (Case 5) the CVM had disappeared spontaneously on the most recent conventional angiographic study. Clinical and radiological features of the patient group are summarized in Table 1.

In none of the patients was an associated aneurysm or venous angioma found. The range of bleeding risks for all CVMs and the AVM subgroup are shown in Table 2. The total number of patient-years ($\sum T_{\text{min}}$) in the AVM group was 740 (mean 33.6 years); the three hemorrhages reflect an annual hemorrhage rate of 0.41%. In the CVM group this total was 793 patient-years (mean 33 years) and corresponds to a bleeding risk of 0.38% per year. There were 840 lesion-years in the AVM group, with a 0.36% bleeding risk per year, and 1096 lesion-years for all CVMs, with a 0.27% risk per year.

From the moment of diagnosis of a CVM in HHT the $T_{\text{min}}$ was 144 years (mean 6 years), which is a conservative approach because we defined the moment of stereotactically guided radiosurgery as the end point, although patients actually still have a chance of bleeding until complete obliteration is achieved, within approximately 24 months after treatment. However, no hemorrhages occurred in the follow-up period. Hemorrhages were the presenting symptom in three individuals in our patient group; in one of these the AVM was considered not treatable. Therefore it is not possible to calculate the risk of hemorrhage in the follow-up period. Theoretically, however, the upper limit of the bleeding risk can be calculated by adding one hypothetical hemorrhage in the follow-up period. Thus, in the AVM subgroup 139 patient-years of follow up would lead to an annual risk of 0.72% and 177 lesion-years to a risk of 0.56%. For the whole CVM group this would correspond to 144 patient-years of follow up in 24 patients and 218 lesion-years for 38 CVMs, with a risk of 0.69% and 0.46%, respectively.

| TABLE 2 | Annual bleeding risks in CVMs and the AVM subgroup in HHT* |
|---------|---------------------|---------------------|---------------------|---------------------|
| Factor  | CVM (24 patients) | AVM (22 patients) | CVM (38 lesions) | AVM (28 lesions) |
| $\Sigma T_{\text{min}}$ (yrs) | 793 | 740 | 1096 | 840 |
| $\Sigma T_{\text{max}}$ (yrs) | 144 | 139 | 218 | 177 |
| bleeding risk (%) | 0.38–0.69 | 0.41–0.72 | 0.27–0.46 | 0.36–0.56 |

* Range of bleeding risk based on one theoretical hemorrhage for the $T_{\text{min}}$ and three actual hemorrhages for the $T_{\text{max}}$. |
Discussion

To our knowledge, this is the largest screening study for CVMs associated with HHT. Vascular malformations of the brain in HHT constitute a heterogeneous group with respect to clinical presentation, radiological aspects, natural history, and management strategies.

Clinical Presentation

Neurological symptoms in HHT have been related to complications of pulmonary AVMs in two thirds of the cases due to paradoxical cerebral embolism with brain abscess and ischemic stroke. In addition, cerebral injury related to pulmonary AVMs could be caused by systemic hypoxia due to right-to-left arteriovenous shunting, air embolism, and secondary polycythemia. The prevalence of migraine is not well understood. The remainder of the neurological symptoms are caused by cerebral or spinal vascular malformations. In an extensive literature review, Román, et al., found CVMs in 28% of 215 patients with HHT and neurological involvement.

It is as yet unclear how many patients with CVMs associated with HHT have neurological manifestations. In the general population with AVMs, intracranial hemorrhage occurs as the initial symptom in approximately 50 to 70% of cases, seizures in 18 to 33%, and headaches in approximately 5%. The prevalence of epilepsy in our population is comparable with data on AVMs in the general population.

Natural History

Capillary telangiectases are mostly clinically silent, although they can cause subarachnoid, intracerebral, or intraventricular hemorrhage in HHT. The number of telangiectases and the corresponding follow-up period in our group was insufficient to estimate the bleeding risk. The natural course of sporadic, untreated, cerebral AVMs has been well documented, with an annual hemorrhage rate of 2 to 4%. In cases of HHT, the natural history of the associated AVMs is unknown. The annual hemorrhage rate of 0.41 to 0.72% in our group reflects a significantly lower bleeding risk than in the group with sporadic AVMs. It is unclear what causes this difference. Due to its genetic nature, AVMs found in HHT may constitute a different AVM population with intrinsic characteristics different from sporadic lesions. Another possible explanation is that the population is relatively young, and most AVMs become symptomatic in patients by the time they are 40 years of age. However, it is more likely that the difference can be explained by the screening procedure, in which symptomatic and asymptomatic patients were included. Studies performed in nonfamilial AVMs have always consisted of selected patients. It is assumed that AVMs are congenital and have the
same risk of hemorrhage throughout a patient’s lifetime, which is a reasonable assumption based on large series of surgically treated patients, medically treated symptomatic patients, and autopsy results.\(^1\)\(^{-}\)\(^3\)\(^{-}\)\(^4\) Therefore, we used a calculation method based on an observation period extending from the time of birth to the time of hemorrhage or treatment, which is a retrospective method. The prospective method, in which follow up is a mean of 6 years, is generally more reliable. However, we had to add a hypothetical hemorrhage because otherwise the bleeding risk would be nil. Altogether, we think that our data indicate quite reliably the prevalence and the lower bleeding risk of cerebral AVMs in patients with HHT.

**Multiple AVMs**

Multiple CVMs are exceptional: they are found in approximately 1% of patients with AVMs, if there is no underlying systemic disorder such as HHT.\(^8\) In our group, one third of the patients had multiple CVMs. These findings support those in previous studies, which indicate a significantly higher prevalence of multiple CVMs, particularly AVMs, associated with HHT.\(^26\)\(^{,}27\)\(^{,}43\) Therefore, if one encounters a patient with multiple AVMs, HHT should be strongly suspected.

**Prevalence and Screening**

With a CVM prevalence of approximately 12%, patients with HHT have a significantly higher risk of harboring an intracranial vascular malformation compared with the general population. However, bias may be present in our study: one patient (Case 13) was referred because of hemorrhage and eight patients were primarily referred because of pulmonary AVM, both conditions that may be associated with CVMs. The true prevalence can only be found by using the gold standard, conventional cerebral angiography, to screen family members. In our study intravenous DS angiography has been used as the screening tool, because it is a minimally invasive and low-risk procedure providing information on both CVMs and pulmonary AVMs. Clearly, intravenous DS angiography screening is prone to false negative results due to low spatial resolution, motion artifacts, and the partial superposition of cerebral vessels.\(^5\)\(^6\) Small aneurysms, capillary telangiectases, and venous angioma especially may be missed. In this study there were two false positive findings (1%). The number of false negative findings is not known, but one patient with a nondiagnostic DS angiogram died 1 year later of a cerebral hemorrhage, although autopsy disclosed no abnormal vascular structures. Fulbright, et al.,\(^8\) showed that MR imaging in a large cohort of 184 patients with HHT revealed a CVM prevalence of 23%, which is substantially higher than that in our group. Apart from population bias (for example, a genetically different subgroup), this difference in prevalence might be explained by the lower sensitivity of DS angiography. However, additional conventional cerebral angiography performed in a subgroup of patients with abnormal MR findings in the study published by Fulbright, et al., demonstrated that MR imaging also misses a substantial number of CVMs. Because of false negative findings, DS angiography and MR imaging as screening methods both carry the risk of underestimating the actual number of CVMs. Thus, with respect to our calculations, the yearly bleeding risk might be even lower. Nevertheless, screening for CVMs in patients with HHT seems indicated because of the relatively high prevalence of these lesions and the availability of low-risk screening and treatment modalities.

**Treatment Protocols**

The treatment modalities for cerebral AVMs are as follows: observation, surgical excision, endovascular embolization, radiosurgery, and a combination of these. Treatment protocols are difficult because of the heterogeneity of AVMs with regard to clinical and radiological presentation. The most important determinants of surgical management are the size, location, and venous drainage of the malformation,\(^3\)\(^3\) but the frequent multiplicity of AVMs in HHT poses additional problems. A lesion size exceeding 3 cm is a limiting factor for radiosurgery. In our experience, endovascular embolization is of limited value because of the generally low-flow appearance of the AVMs without enlarged feeding arteries. The question of whether asymptomatic AVMs should be treated is still being debated. Treatment policies vary according to the assumptions made about the risk of bleeding, risk of lethal bleeding, and treatment risks.\(^2\)\(^{,}3\)\(^{-}\)\(^7\)\(^{-}\)\(^8\)

**Conclusions**

Clearly, our data indicate a lower bleeding risk for AVMs in HHT than that for sporadic AVMs, which has implications for screening and treatment policies. For the moment, it appears that the treatment of AVMs in HHT is advisable only in patients with a negligible therapeutic risk profile. However, accurate advice can only be given after further studies in a larger cohort with a longer follow-up period after diagnosis.

**References**


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