Brain Arteriovenous Malformation Multiplicity Predicts the Diagnosis of Hereditary Hemorrhagic Telangiectasia
Quantitative Assessment

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Background and Purpose—The purpose of this study was to quantitatively estimate the relationship between multiplicity of brain arteriovenous malformations (bAVMs) and the diagnosis of hereditary hemorrhagic telangiectasia (HHT).

Methods—We combined databases from 2 large North American bAVM referral centers, including demographics, clinical presentation, and angiographic characteristics, and compared patients with HHT with non-HHT patients. Logistic regression analysis was performed to quantify the association between bAVM multiplicity and odds of HHT diagnosis. Sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios were calculated to determine accuracy of bAVM multiplicity for screening HHT.

Results—Prevalence of HHT was 2.8% in the combined group. bAVM multiplicity was present in 39% of patients with HHT and was highly associated with diagnosis of HHT in univariate (OR, 83; 95% CI, 40–173; P<0.001) and multivariable (OR, 86; 95% CI, 38–195; P<0.001) models adjusting for age at presentation (P=0.013), symptomatic presentation (P=0.029), and cohort site (P=0.021). bAVM multiplicity alone was associated with high specificity (99.2%; 95% CI, 98.7%–99.6%) and negative predictive value (98.3%; 95% CI, 97.6%–98.8%) and low sensitivity (39.3%; 95% CI, 26.5%–53.2%) and positive predictive value (59.5%; 95% CI, 42.1%–75.2%). Positive and negative likelihood ratio was 51 and 0.61, respectively, for diagnosis of HHT. HHT bAVMs were also more often smaller in size (<3 cm), noneloquent in location, and associated with superficial venous drainage compared with non-HHT bAVMs.

Conclusions—Multiplicity of bAVMs is highly predictive of the diagnosis of HHT. The presence of multiple bAVMs should alert the clinician to the high probability of HHT and lead to comprehensive investigation for this diagnosis. (Stroke. 2012;43:72-78.)

Key Words: arteriovenous malformation ■ brain ■ hereditary hemorrhagic telangiectasia

Brain arteriovenous malformations (bAVMs) are abnormal tangles of blood vessels that shunt blood directly from the arterial to venous circulation. Although bAVMs are an important cause of hemorrhagic stroke, especially in children and young adults, little is known about how bAVMs develop and progress.\(^4\) Surgical, endovascular, and radiotherapy-induced obliteration are available for treatment, but each is associated with risk of neurological injury. There are no specific medical therapies to treat bAVMs. bAVMs have a population prevalence of 10 to 18 per 100,000 adults\(^2\) and a new detection rate of 1.2 to 1.3 per 100,000 person-years.\(^3,4\) Most bAVMs are sporadic, but a small percent are associated with hereditary disorders, the most important of which is hereditary hemorrhagic telangiectasia (HHT), which accounts for approximately 2% of cases\(^5,6\) as estimated in nonpopulation-based case series.

HHT, also known as Osler-Weber-Rendu disease, is a rare autosomal-dominant multisystem disorder characterized by the presence of vascular malformations. Arteriovenous malformations (AVMs) are found in various organs in HHT, including the brain, lungs, liver, and spinal cord. Smaller malformations in HHT, telangiectasia, typically occur on the
skin and mucosal surfaces, but also the gastrointestinal tract and liver. The prevalence of HHT is estimated at approximately 1 per 5000 to 1 per 10 000.7–9 However, HHT is felt to be underdiagnosed, at least in part due to its variable and age-related clinical expression. For example, the typical clinical diagnostic features of HHT, recurrent epistaxis and mucocutaneous telangiectasia, are often not present until adult life,10 whereas children can present with complications of bAVMs.11 When HHT is diagnosed in a patient, screening and preventive treatment should then be recommended to that patient and also their affected family members as detailed in the recent International HHT Guidelines.12 As such, the diagnosis of bAVMs may be an opportunity for prevention in an entire HHT family. This would be particularly feasible if an “HHT phenotype” for bAVMs such as multiplicity can be defined.

bAVMs are present in 5% to 23% of patients with HHT13–15 with intracranial hemorrhage rates estimated at 0.41% to 2% per year,16,17 although data are limited. One of the most striking features of HHT-related bAVMs noted to date is that there is a greater tendency for bAVMs to be multiple in patients with HHT with bAVM multiplicity reported in as many as 50% of cases in a series of 14 patients with HHT with bAVMs reported by our group 10 years ago and in approximately 25% of 50 patients with HHT with central nervous system AVMs as reported by the Bicetre group.18 In addition, the same authors noted that approximately 20% to 43% of HHT bAVMs were micro-AVMs, 29% to 50% were arteriovenous fistulas, and 81% to 100% were cortical in location.5,18 The arteriovenous fistulas reported by the Bicetre group were almost all diagnosed in children.18 The high prevalence of micro-AVMs (nidus <1 cm) among HHT bAVMs has also been noted in other series.19,20 Cases of extreme multiplicity have also been reported.19 There have been no large studies to date, however, comparing bAVMs in patients with HHT and non-HHT patients or any studies quantifying the predictive accuracy of these associations.

The purpose of this study was to quantitatively estimate the relationship between bAVM multiplicity in patients with HHT compared with those with non-HHT bAVMs by analyzing a large population of consecutive patients with bAVM from 2 large North American bAVM referral centers. We found a strong association, which has the clinical implication that the presence of bAVM multiplicity should trigger a thorough search for an underlying diagnosis of HHT. We also reviewed other aspects of the neurovascular phenotype and clinical features of HHT-associated bAVMs compared with non-HHT bAVMs.

**Methods**

**Study Population**

We combined data from 2 large bAVM referral centers in North America. Each center maintains a prospective registry and database of all bAVM cases referred for evaluation and management.

The UHN Toronto Brain Vascular Malformation Study Group is based at a tertiary academic referral center (University Health Network [UHN]) of the University of Toronto. The UHN group receives referrals of patients with bAVM from clinical centers across Ontario (90%), other Canadian provinces (8%), and non-Canadian centers (2%). The UHN Toronto Brain Vascular Malformation Study Group is also a referral center for patients with bAVM from 2 HHT Centers of Excellence, the Toronto HHT Centre and the Yale University HHT Center. The Toronto database includes all patients with a confirmed bAVM diagnosis referred to the UHN Toronto Brain Vascular Malformation Study Group from 1984 to 2009.

Because the University of Toronto is also home to an HHT Center of Excellence, based at St Michael’s Hospital, patients in the UHN series with any clinical suspicion of HHT were routinely referred to the Toronto HHT Centre and underwent full clinical assessment for HHT as well as screening for pulmonary AVMs as per International HHT Guidelines.12

The University of California at San Francisco (UCSF) is a tertiary academic referral center and receives referrals of patients with bAVM from the San Francisco Bay Area and Northern California as well as some out-of-state referrals. The UCSF database includes all patients with a confirmed bAVM diagnosis who were referred to UCSF for evaluation and management from March 2000 to June 2010.

**Definitions**

Data fields from both databases were harmonized and combined into a single data set that included demographics, clinical presentation, type of imaging available, and morphological features of bAVMs.

We used definitions whenever possible as described in the Joint Writing Group document21 such as the definition of “symptomatic presentation” of bAVM, which includes hemorrhage, seizure, neurological deficit, and “other” related symptoms. The diagnosis of bAVM required neuroradiological confirmation of intracranial AVM with imaging (CT/CT angiography, MR/MR angiography, or angiography [digital subtraction angiography]) or surgical pathology. Multiplicity was defined as the presence of ≥2 discrete intracranial bAVMs.

The diagnosis of HHT was based on clinical diagnostic criteria and/or genetic mutation results, when available.12,22 The HHT clinical diagnostic criteria, also known as the Curaçao Criteria, are consensus criteria first published in 2000 and widely used for HHT diagnosis. The Curaçao Criteria were also upheld in the recent International HHT Guidelines. The criteria are: (1) spontaneous recurrent nosebleeds; (2) mucocutaneous telangiectasia at characteristic sites (lips, oral cavity, nose, or fingers); (3) visceral involvement such as pulmonary, hepatic, or central nervous system AVMs; and (4) an affected first-degree relative according to these criteria.

Patients were classified22 as “definite HHT” when at least 3 criteria were present, “possible HHT” when 2 criteria, or “unlikely HHT” when 1 or no criteria. We included “possible HHT” in the HHT group given the age-related expression of HHT and the younger age of our study population and therefore the expected absence of full clinical criteria in many patients. Data for the clinical diagnosis of HHT were obtained from routine clinical assessment. All patients assessed for bAVM at the UHN Center were asked about family history of cerebrovascular disease as well as assessed for the possibility of HHT with routine questions about personal epistaxis history as well as family history of HHT. At the UCSF Center, all patients assessed for bAVM were asked about familial cerebrovascular disease, but not routinely asked about personal epistaxis history or a family history of HHT.

**Imaging Data Collection**

The majority of cases underwent complete (3- or 4-vessel) catheter angiography and a subset underwent superselective angiography. The number of bAVMs was determined using digital subtraction angiography data where available. If digital subtraction angiography was not available, then the number of bAVMs was determined using other available information (ie, results of cross-sectional imaging studies and surgical records). Angiographic data including morphology, size, location, arterial supply, and venous drainage of the AVM(s) were recorded where available.
Analysis
HHT and non-HHT patients and site differences were evaluated using descriptive statistics, including t-tests for continuous variables and \( \chi^2 \) tests for categorical variables. Logistic regression analysis was performed to determine the relationship between HHT status (outcome) and bAVM multiplicity (predictor). Variables associated with HHT status at \( P<0.05 \) in univariate logistic regression models were included as covariates in multivariable logistic models. Because UHN is also a HHT referral center, we evaluated the possible interaction effect of site (UHN versus UCSF) with predictors in our models by including interaction terms. However, no significant interactions (\( P>0.10 \)) were observed between site and bAVM multiplicity or any other predictors. Thus, the data were combined and all regression models were adjusted for site.

We calculated the specificity, sensitivity, positive and negative predictive values (PPV and NPV, respectively), and positive and negative likelihood ratios (LRs) to characterize how well multiple bAVM predicted HHT diagnosis. These measures can be defined by the number of true-positives, true-negatives, false-positives, and false-negatives. Specificity is calculated as true-negative/(true-positive+false-negative); sensitivity is calculated as true-positive/(true-positive+false-positive); PPV is calculated as true-positive/(true-positive+false-positive) and depends on the prevalence of the outcome. Likewise, NPV is calculated as true-negative/(false-negative); sensitivity is calculated as true-negative/(false-positive). For dichotomous tests, the LR for a positive test is sensitivity/(1-specificity) and for a negative test is (1-sensitivity)/specificity. Exact binomial 95% CIs were calculated for sensitivity, specificity, PPV, and NPV; 95% CIs for positive and negative LR were calculated using the \( \delta \) method. Generalized estimating equations were used to check for differences in the univariate and multivariable ORs between the full data set and specific subsets of the data. Data were analyzed using Intercooled Stata, Version 11 (Stata Corp, College Station, TX).

Results
A total of 1989 patients with bAVM were included in the analysis (723 from UCSF and 1266 from UHN). Demographic and clinical characteristics are shown in Table 1 for the combined population and stratified by HHT status. Overall, the prevalence of HHT was 2.8% and multiplicity was present in 1.9% of the combined population. Ethnicity data were not available for the UHN subgroup.

Gender distribution was similar, but age at presentation was younger in the HHT group compared with the non-HHT group (\( P=0.002 \)). bAVM multiplicity was more frequent in the HHT group (39%) compared with the non-HHT group (1%; \( P<0.0001 \)). There was a greater prevalence of symptomatic clinical presentation (\( P=0.032 \)) in the non-HHT group with a trend (\( P=0.065 \)) toward increased presentation with hemorrhage in the same group.

Univariate logistic regression results are detailed in Table 2 assessing the association of demographic and clinical characteristics with HHT. These univariate models identified age at presentation (\( P=0.002; \) OR, 0.77; 95% CI, 0.65–0.91), symptomatic presentation (\( P=0.035; \) OR, 0.54; 95% CI, 0.30–0.96), bAVM multiplicity (<0.001; OR, 83; 95% CI, 40–173), and cohort site (\( P=0.005; \) OR, 2.69; 95% CI, 1.35–5.36) as predictors of HHT with the UHN site having a greater prevalence of HHT patients (3.6% versus 1.4%) as expected. Multivariable logistic regression analysis using all significant univariate predictors is shown in Table 3. bAVM multiplicity was found to be the strongest predictor of HHT (<0.001; OR, 86; 95% CI, 38–195) after adjusting for age at presentation, symptomatic presentation, and cohort site.
Having multiple bAVMs results in high specificity (>99%) but low sensitivity (<40.0%) for predicting HHT status. Among those who test positive (multiple bAVMs), the probability of having HHT was 60% to 81% (PPV) depending on the model used. Among those who test negative (single bAVM), the probability of not having HHT is 98% (NPV). PPV and NPV are well-known to be sensitive to prevalence. Even at a low prevalence site like UCSF, the PPV using the multivariate model was estimated to be 0.69 (compared with 0.81 overall). Using the multivariate model, the NPVs for UCSF and UHN (a high prevalence site) were 0.99 and 0.98, respectively. The positive LR was 51 (univariate) and 160 (multivariable), indicating that when a patient presents with multiple bAVMs, there is a very high likelihood of having HHT. In contrast, having only a single bAVM does not clearly rule out the diagnosis of HHT, as indicated by a negative LR of 0.61 to 0.66.

In secondary analysis, we compared angiographic characteristics of HHT with non-HHT bAVMs (Table 5). Patients with HHT had a total of 89 bAVMs with a mean of 1.7±1.4, ranging from 1 to >4 lesions. Size of bAVMs was significantly different (P<0.001) between groups with a greater proportion of small bAVMs (<3 cm) in the HHT group. Eloquence was significantly greater with non-HHT bAVMs (P=0.020). Venous drainage was significantly different (P<0.001) with a predominance of superficial drainage in HHT bAVMs. There were no other significant differences in regard to location (rates of lobar, deep, and posterior fossa bAVMs). Angiography is an important mechanism in diagnosing HHT, and because roughly one fifth of the patients did not undergo angiography, we checked for differences between the OR based on the subset of patients that underwent angiography compared with the full data set. Neither the OR for bAVM multiplicity from the univariate model nor the OR for bAVM multiplicity from the multivariable model was.

### Table 2. Univariate Analysis of Risk Factors for Predicting HHT in Patients With bAVM

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, decade</td>
<td>1937</td>
<td>0.77</td>
<td>0.65–0.91</td>
<td>0.002</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1989</td>
<td>0.65</td>
<td>0.38–1.12</td>
<td>0.122</td>
</tr>
<tr>
<td>Hemorrhagic presentation</td>
<td>1989</td>
<td>0.58</td>
<td>0.32–1.04</td>
<td>0.068</td>
</tr>
<tr>
<td>Symptomatic Presentation</td>
<td>1985</td>
<td>0.54</td>
<td>0.30–0.96</td>
<td>0.035</td>
</tr>
<tr>
<td>Multiple bAVM</td>
<td>1983</td>
<td>1.37</td>
<td>0.66–2.83</td>
<td>0.380</td>
</tr>
<tr>
<td>Site (UHN)</td>
<td>1989</td>
<td>2.69</td>
<td>1.35–5.36</td>
<td>0.005</td>
</tr>
</tbody>
</table>

### Table 3. Multivariate Logistic Regression Analysis in 1937 Patients in UCSF and UHN Cohorts Combined

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, decade</td>
<td>0.79</td>
<td>0.66–0.95</td>
<td>0.013</td>
</tr>
<tr>
<td>Symptomatic presentation</td>
<td>0.46</td>
<td>0.23–0.92</td>
<td>0.029</td>
</tr>
<tr>
<td>Multiple bAVM</td>
<td>86.35</td>
<td>38.20–195.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Site (UHN)</td>
<td>2.52</td>
<td>1.15–5.54</td>
<td>0.021</td>
</tr>
</tbody>
</table>

### Table 4. Results of Using bAVM Multiplicity for the Diagnosis of HHT

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Univariate Model 95% CI</th>
<th>Multivariable Model* 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.393</td>
<td>0.265–0.532</td>
<td>0.340</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.992</td>
<td>0.987–0.996</td>
<td>0.998</td>
</tr>
<tr>
<td>PPV</td>
<td>0.595</td>
<td>0.421–0.752</td>
<td>0.810</td>
</tr>
<tr>
<td>NPV</td>
<td>0.983</td>
<td>0.976–0.988</td>
<td>0.983</td>
</tr>
<tr>
<td>Positive LR</td>
<td>50.63</td>
<td>20.25–81.01</td>
<td>160.40</td>
</tr>
<tr>
<td>Negative LR</td>
<td>0.61</td>
<td>0.48–0.74</td>
<td>0.66</td>
</tr>
</tbody>
</table>

bAVM indicates brain arteriovenous malformation; HHT, hereditary hemorrhagic telangiectasia; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; CI, confidence interval. *Includes age in decades, symptomatic presentation, bAVM multiplicity, and cohort site.

### Table 5. Angiographic Characteristics of HHT bAVMs Compared With Non-HHT bAVMs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HHT (n=56)</th>
<th>Non-HHT (n=1933)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bAVMs</td>
<td>89</td>
<td>1954</td>
<td>0.465</td>
</tr>
<tr>
<td>Lobar</td>
<td>No</td>
<td>21 (27)</td>
<td>594 (31)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>58 (73)</td>
<td>1352 (69)</td>
</tr>
<tr>
<td>Deep</td>
<td>No</td>
<td>53 (90)</td>
<td>1667 (86)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>6 (10)</td>
<td>274 (14)</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>No</td>
<td>52 (93)</td>
<td>1823 (94)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4 (7)</td>
<td>111 (6)</td>
</tr>
<tr>
<td>Eloquent</td>
<td>No</td>
<td>37 (55)</td>
<td>684 (39)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>30 (45)</td>
<td>1090 (61)</td>
</tr>
<tr>
<td>Venous drainage</td>
<td>No</td>
<td>11 (18)</td>
<td>748 (45)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>46 (75)</td>
<td>794 (47)</td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td>4 (7)</td>
<td>132 (8)</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;3 cm</td>
<td>37 (88)</td>
<td>993 (60)</td>
</tr>
<tr>
<td></td>
<td>≥3 cm</td>
<td>5 (12)</td>
<td>662 (40)</td>
</tr>
</tbody>
</table>

*Includes age in decades, symptomatic presentation, bAVM multiplicity, and cohort site.

Numbers are presented as no. (%). HHT indicates hereditary hemorrhagic telangiectasia; bAVMs, brain arteriovenous malformations.
Table 6. Detailed Information Regarding Clinical Characteristics in Patients With HHT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HHT (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of HHT</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Yes</td>
<td>45 (88)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Yes</td>
<td>34 (81)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (85)</td>
</tr>
<tr>
<td>Pulmonary AVM</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (57)</td>
</tr>
<tr>
<td>Yes</td>
<td>18 (43)</td>
</tr>
<tr>
<td>GI bleed</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35 (83)</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Clinical criteria for diagnosis of HHT</td>
<td></td>
</tr>
<tr>
<td>At least 3</td>
<td>36 (82)</td>
</tr>
<tr>
<td>2</td>
<td>7 (16)</td>
</tr>
<tr>
<td>1</td>
<td>1 (2)</td>
</tr>
<tr>
<td>HHT genetic testing results</td>
<td></td>
</tr>
<tr>
<td>ACVRL1 mutation</td>
<td>5 (9)</td>
</tr>
<tr>
<td>ACVRL1 VUS</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Endoglin mutation</td>
<td>25 (44)</td>
</tr>
<tr>
<td>Endoglin VUS</td>
<td>1 (2)</td>
</tr>
<tr>
<td>SMAD4 mutation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SMAD4 VUS</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No mutation detected</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Not done or not available</td>
<td>21 (38)</td>
</tr>
</tbody>
</table>

Numbers are presented as no. (%).

HHT indicates hereditary hemorrhagic telangiectasia; AVM, arteriovenous malformation; GI, gastrointestinal; VUS, variant of unknown significance.

Discussion

We have quantified the association of bAVM multiplicity with HHT diagnosis in a large referral series of patients with bAVM. The odds of HHT was 86-fold higher in those with multiple bAVMs compared with those with high specificity, NPV, and positive LR. The clinical implication is that HHT should be strongly suspected in any patient with bAVM with multiple lesions. Multiplicity of bAVMs has been reported in case series and small case series to date of patients with HHT and estimated to be present in up to 50% of patients with HHT with bAVMs. In our study, we report bAVM multiplicity in 39% of patients with HHT and have compared this with a large database of non-HHT patients from 2 bAVM referral centers to quantify the association. The OR is highly significant with excellent specificity and positive LR for the diagnosis of HHT. In other words, if a clinician detects multiple lesions in a patient with bAVM, there is a very high likelihood that the patient has HHT and further diagnostic assessment should be pursued. However, given the low sensitivity and negative LR of bAVM multiplicity for HHT diagnosis, it cannot be concluded that the presence of only a single bAVM rules out the diagnosis of HHT. The clinician should therefore always consider the diagnosis of HHT in patients with bAVM, but suspicion should be much greater in patients with multiple bAVMs and comprehensive assessment should be undertaken in these cases to rule out the diagnosis of HHT.

The clinical relevance of diagnosing HHT in this context is severalfold. First, it allows for appropriate screening for pulmonary AVMs in the newly diagnosed patient, because approximately 30% of patients with HHT have pulmonary AVMs and preventive treatment is recommended. Second, the diagnosis of HHT in 1 patient can lead to the diagnosis of other family members, because HHT is an autosomal-dominant disorder. HHT is an undiagnosed disorder with estimates of undiagnosed cases in the range of 70% in North America and therefore it is entirely plausible that, for example, a child presenting with bAVMs may be the index case for an undiagnosed HHT family, although many adult family members actually have epistaxis. Because HHT genetic testing is now available, identifying the index case can lead to identification of the causative familial mutation and subsequent genetic diagnosis of asymptomatic family members.

The prevalence of HHT in our combined bAVM population was 2.8%, but as high as 3.6% in the UHN series, similar to rates reported in other series, including our group. However, given that HHT is frequently undiagnosed, disease expression is age-related (and therefore children and young adults often do not have the typical symptoms) and that we have not performed HHT genetic testing routinely in all bAVM cases, there may be unrecognized cases in our series and even the 3.6% may be an underestimate.

The analysis revealed other factors associated with HHT among patients with bAVM, including earlier age at presen-
tation and being asymptomatic at diagnosis, but for obvious reasons, these are less clinically useful than bAVM multiplicity for predicting HHT. In secondary analyses, bAVMs in patients with HHT also tended to be smaller in size than those not associated with HHT. This is in keeping with previous reports of a high prevalence of micro-AVMs in HHT, although in our data set, we did not have morphological subclassification (arteriovenous fistulas, nidus-type, micro-AVMs, etc) data in a sufficient number of patients to analyze. In addition, HHT bAVMs generally had superficial venous drainage, in keeping with previous reports.5,18

The clinical features of our identified HHT group are similar to those in HHT series in the literature.24–28 The prevalence of epistaxis and telangiectasia is lower than reported for older adult HHT populations but as expected for a younger population such as ours given that the expression of these clinical features is known to be age-related in HHT. The prevalence of pulmonary AVMs in the HHT group is in the same range as that described for patients with HHT of all ages in published series. In other words, it is reasonable to conclude that the bAVM characteristics of the patients with HHT identified in this series are generalizable to those of patients with HHT in general.

Despite increasing literature about the genetics and mechanisms of disease in HHT, the clinical heterogeneity, as evidenced by variability in organ involvement, remains poorly understood. The 2 main subtypes of HHT (HHT1 and 2) are caused by loss-of-function mutations in 2 genes29 originally implicated in transforming growth factor-β signaling pathways. The first is endoglin (ENG), which encodes an accessory protein of transforming growth factor-β receptor complexes. The second is activin receptor-like kinase 1 (ALK-1 or ACVRL1), which codes for a transmembrane kinase also thought to participate in transforming growth factor-β signaling. A third candidate gene for HHT is SMAD4, encoding a downstream mediator for both transforming growth factor-β and BMP signaling. SMAD4 is mutated in a combined syndrome of juvenile polyposis and HHT.30 Two additional independent loci, termed HHT3 and HHT4, have been reported31,32 but the genes underlying these less common forms of HHT have yet to be identified. ENG mutations are associated with bAVMs25,27 and pulmonary AVMs,25–27 but the role of ENG mutation in the mechanism of AVM development remains to be elucidated and it remains unclear why not all affected patients in ENG families have AVMs in these organs. The distribution of genetic mutation results in our series, with 5× greater prevalence of ENG compared with ACVRL1 mutations, reflects the association between ENG and bAVMs, as expected.

The role of these HHT-related genes in sporadic bAVM cases is not clear. However, a common intronic variant of ACVRL-I, IVS3–35A>G, has been found to be associated with bAVMs33 and independently replicated by another group.34,35 This single nucleotide polymorphism may be associated with alternative splicing. Thus, common variation in a gene that, when mutated, causes HHT, may also contribute to the sporadic AVM phenotype. Recently a concept has emerged that a response to a perturbation or injury appears to be a necessary component to initiate vascular dysplasia,36–38 which is hypothesized to be an early stage of bAVM development. This might suggest that even in sporadic cases, there is some kind of underlying genetic variation that, when exposed to an altered environment, can produce the sequence of events that results in the human sporadic phenotype.

There are some potential limitations to the study that warrant discussion. The most significant is that of referral bias on 2 separate levels. First, because Toronto is also an HHT referral center, bAVM cases seen at the UHN site may have been more likely to receive a clinical diagnosis of HHT and get referred for follow-up tests leading to confirmation of the diagnosis. This is likely part of the explanation for the higher prevalence of HHT in the UHN cohort compared with the UCSF cohort. However, there was no significant interaction between bAVM multiplicity and site, and the association between bAVM multiplicity and HHT diagnosis remained significant after adjustment for site. Second, because the UHN site receives referrals from HHT Centers of Excellence, who routinely screen asymptomatic patients with HHT for bAVMs, it is not surprising that more of the patients with HHT would be asymptomatic and younger at presentation compared with the non-HHT patients. Despite these biases, the strong association described here between bAVM multiplicity and HHT diagnosis should be generalizable to other referral centers that evaluate bAVMs. Finally, we do not have detailed morphological classification data of HHT and non-HHT bAVMs and therefore this aspect of HHT bAVMs remains to be systematically compared with non-HHT bAVMs.

In conclusion, multiplicity of bAVMs is highly predictive of the diagnosis of HHT and patients with multiple bAVMs should undergo comprehensive assessment to rule out the diagnosis. Future research is needed to guide therapeutic decisions in patients with bAVM and particularly in HHT cases with bAVMs, in whom the risk of hemorrhage remains insufficiently evaluated.

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Disclosures
None.

References


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