Published in final edited form as:
Stroke. 2012 January ; 43(1): 72–78. doi:10.1161/STROKEAHA.111.629865.

Brain arteriovenous malformation multiplicity predicts diagnosis of Hereditary Hemorrhagic Telangiectasia: Quantitative assessment

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Abstract

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Conflict of Interest Disclosures: None

Purpose—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 two large North American bAVM referral centers, including demographics, clinical presentation and angiographic characteristics, and compared HHT patients 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 (PPV, NPV), and positive and negative likelihood ratios (LR) 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 HHT patients and was highly associated with diagnosis of HHT in univariate (OR=83, 95% CI:40–173, P<0.0001) and multivariable (OR=87, 95% CI: 38–195, P<0.001) models, adjusting for age at presentation (P=0.013), non-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 NPV (98.3%, 95% CI: 97.6–98.8%), and low sensitivity (39.3%, 95% CI: 26.5–53.2%) and PPV (59.5%, 95% CI: 42.1–75.2%). Positive and negative LR was 51 and 0.61, respectively, for diagnosis of HHT. HHT bAVMs were also more often smaller in size (<3 cm), non-eloquent in location and associated with superficial venous drainage, compared to non-HHT bAVMs.

Conclusion—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.

Keywords

arteriovenous malformation; hereditary hemorrhagic telangiectasia; brain

INTRODUCTION

Brain arteriovenous malformations (bAVMs) are abnormal tangles of blood vessels that shunt blood directly from the arterial to venous circulation. Though bAVMs are an important cause of hemorrhagic stroke, especially in children and young adults, little is known about how bAVMs develop and progress [1]. 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 10–18 per 100,000 adults [2] and a new detection rate of 1.2–1.3 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 non-population 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 1/5,000 – 1/10,000 [7–9]. However, HHT is felt to be under diagnosed, 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 one patient, screening and preventative 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 5–23% of patients with HHT [13–15], with intracranial hemorrhage rates estimated at 0.41%–2% per year[16, 17], though data is 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 HHT patients, with bAVM multiplicity reported in as many as 50% of cases in the one series of 14 HHT patients with bAVMs [5] reported by our group ten years ago, and in approximately 25% of 50 HHT patients with central nervous system AVMs, as reported by the Bicetre group [18]. In addition, the same authors noted that approximately 20–43% of HHT bAVMs were micro-AVMs, 29–50% were arteriovenous fistulas (AVFs) and 81–100% were cortical in location [5, 18]. The AVFs reported by the Bicetre group were almost all diagnosed in children [18]. The high prevalence of microAVMs (nidus<1cm) amongst 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 HHT patients 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 HHT patients compared to those with non-HHT bAVMs, by analyzing a large population of consecutive bAVM patients from two 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 to non-HHT bAVMs.

METHODS

Study Population

We combined data from two 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 bAVM patients 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 bAVM patients from two HHT Centers of Excellence, the Toronto HHT Centre and the Yale University HHT Center. The Toronto database includes all patients, with confirmed bAVM diagnosis, referred to the UHN Toronto Brain Vascular Malformation Study Group from 1984–2009.

As 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 bAVM patients from the San Francisco Bay Area and Northern California, as well as some out of state referrals. The UCSF database includes all patients

with confirmed bAVM diagnosis who were referred to UCSF for evaluation and management from March 2000–June 2010.

Definitions

Data fields from both databases were harmonized and combined into a single dataset 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 document [21], 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/CTA, MR/MRA or Angiography [DSA]) or surgical pathology. Multiplicity was defined as the presence of two or more 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 Curacao 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 CNS arteriovenous malformations (AVMs);
4. An affected first degree relative according to these criteria.

Patients were classified [22] as "definite HHT" when at least three criteria were present, "possible HHT" when two criteria or "unlikely HHT" when one 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 was 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 family history of HHT.

Imaging Data Collection

The majority of cases underwent complete (3 or 4-vessel) catheter angiography and a subset underwent super-selective angiography. The number of bAVMs was determined using Digital Subtraction Angiography (DSA) data where available. If DSA was not available, then the number of bAVMs was determined using other available information (i.e. results of cross sectional imaging studies, and surgical records). Angioarchitectural data including morphology, size, location, arterial supply and venous drainage of the AVM(s) was recorded where available.

Analysis

HHT and non-HHT patients and site differences were evaluated using descriptive statistics, including t tests for continous variables and chi-square 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 vs. 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 (LR) to characterize how well multiple bAVM predicted HHT diagnosis. These measures can be defined by the number of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN). Specificity is calculated as TP/(TP+FN); sensitivity is calculated as TN/(FP+TN). PPV is calculated as TP/(TP+FP) and depends on the prevalence of the outcome. Likewise, NPV is calculated as TN/(FN+TN). 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% confidence intervals (CI) 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 odds ratios 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 and non-HHT status. Overall, the prevalence of HHT was 2.8% and multiplicity was present in 1.9% of the combined population. Ethnicity data was not available for the UHN subgroup.

Gender distribution was similar, but age at presentation was younger in the HHT group, compared to the non-HHT group ($P=0.002$). bAVM multiplicity was more frequent in the HHT group (39%) compared to 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 ($P=0.065$) towards 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 ($P<0.001$, OR=82, 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% vs 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 ($P<0.001$, OR=86, 95% CI=38–195) after adjusting for age at presentation, symptomatic presentation, and cohort site. We checked the robustness of our odds ratio estimates for bAVM multiplicity by intentionally misclassifying some patient outcomes and re-estimating these odds ratios. We falsely increased the number of cases by 50% and found bAVM multiplicity was still a very strong predictor of HHT ($P<0.001$, OR=53, 95% CI=26–108), which was consistent with our original results.

Table 4 summarizes the results of using bAVM multiplicity as a "diagnostic test" for HHT, either alone (univariate) or in conjunction with other significant predictors (multivariable). 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 to 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 to non-HHT bAVMs (Table 5). HHT patients had a total of 89 bAVMs with a mean of 1.7 ± 1.4, ranging from 1 to greater than 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 regards to location (rates of lobar, deep and posterior fossa bAVMs). Angiography is an important mechanism in diagnosing HHT, and since roughly 1/5 of the patients did not undergo angiography, we checked for differences between the odds ratio based on the subset of patients that underwent angiography compared to the full data set. Neither the odds ratio for bAVM multiplicity from the univariate model, nor the odds ratio for bAVM multiplicity from the multivariable model, were significantly different from the estimates found using the full data set (OR_{full} =83, OR_{subset}=71, P=0.219; and OR_{full}=86, OR_{subset}=71, P=0.274, respectively). We had data regarding bAVM morphology subclassification (AVF vs. nidus vs. microAVM, etc.) in only 7% of patients; thus, were not able to analyze this variable. Detailed information regarding clinical features and genetic testing results in the HHT patients is presented in Table 6. Telangiectasias were present in 85%, epistaxis in 81%, pulmonary AVMs in 43% and GI bleeding in 17% of HHT patients. Genetic testing results were available in 35/56 (63%), with *ENG* mutation in 25/35 (71%), *ACVRL1* mutation in 5/35 (14%), variants of unknown significance (VUS) in 1/35 (2%) and no evidence of mutation in 4/35 (11%). Further sensitivity analysis was conducted to check for potential differences in estimated odds ratios between the full data set and those patients that did not receive genotyping. There was no difference for the univariate odds ratio for bAVM multiplicity (OR_{full} =86, OR_{subset} =58, P=0.219), as well no difference for the multivariable odds ratio for bAVM multiplicity (OR_{full} =83, OR_{subset} =53, P=0.274), between the full data set and the subset of patients that did not undergo genotyping.

DISCUSSION

We have quantified the association of bAVM multiplicity with HHT diagnosis in a large referral series of bAVM patients. The odds of HHT was 86-fold higher in those with multiple bAVMs, with high specificity, negative predictive value, and positive likelihood ratio. The clinical implication is that HHT should be strongly suspected in any bAVM patient with multiple lesions. Multiplicity of bAVMs has been reported in case reports and small case series to date, of HHT patients [5, 18] and estimated to be present in up to 50% of HHT patients with bAVMs. In our study, we report bAVM multiplicity in 39% of HHT patients and have compared this to a large database of non-HHT patients from two bAVM referral centers, to quantify the association. The OR is highly significant with excellent

specificity and positive likelihood ratio for the diagnosis of HHT. In other words, if a clinician detects multiple lesions in a bAVM patient, 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 bAVM patients 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 several-fold. First, it allows for appropriate screening for pulmonary AVMs in the newly diagnosed patient, since approximately 30% of HHT patients have pulmonary AVMs and preventative treatment is recommended [12]. Second, the diagnosis of HHT in one patient can lead to the diagnosis of other family members, as HHT is an autosomal dominant disorder. HHT is an underdiagnosed disorder, with estimates of undiagnosed cases in the range of 70% in North America [23], and therefore it is entirely plausible that, for example, a child presenting with bAVMs may be the index case for an undiagnosed HHT family, even though many adult family members actually have epistaxis. Since 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[6]. 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 bAVM patients, including earlier age at presentation 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 HHT patients 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, though in our dataset we did not have morphologic subclassification (AVFs, nidus-type, microAVMs, 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 are 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 HHT patients of all ages in published series. In other words, it is reasonable to conclude that the bAVM characteristics of the HHT patients identified in this series are generalizable to those of HHT patients 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 two main subtypes of HHT (HHT1 and 2) are caused by loss-of-function mutations in two genes [29] originally implicated in TGF-β signaling pathways. The first is endoglin (*ENG*), which encodes an accessory protein of TGF-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 TGF-β signaling. A third candidate gene

for HHT is *SMAD4*, encoding a downstream mediator for both TGF-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 reported [31, 32] but the genes underlying these less common forms of HHT have yet to be identified. *ENG* mutations are associated with bAVMs [25, 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 five times greater prevalence of *ENG* compared to *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-1*, IVS3-35A>G, has been found to be associated with bAVMs [33] and independently replicated by another group [34, 35]. This single nucleotide polymorphism (SNP) 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 two 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 to 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. Secondly, since the UHN site receives referrals from HHT Centers of Excellence, who routinely screen asymptomatic HHT patients for bAVMs, it is not surprising that more of the HHT patients would be asymptomatic and younger at presentation, compared to the non-HHT patients. Despite these biases, the strong association described here between bAVM multiplicity and HHT diagnosis should be generalizeable to other referral centers that evaluate bAVMs. Finally, we do not have detailed morphologic classification data of HHT and non-HHT bAVMs and therefore this aspect of HHT bAVMs remains to be systematically compared to 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 bAVM patients and particularly in HHT cases with bAVMs, in whom the risk of hemorrhage remains insufficiently evaluated.

Acknowledgments

Funding: This project was supported in part by grants from the National Institutes of Health: U54 NS065705 (Brain Vascular Malformation Consortium) and R01 NS034949; other financial support for MEF: Keenan Research Centre and Li Ka Shing Knowledge Institute of St. Michael's Hospital; Nelson Arthur Hyland Foundation.

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Table 1

Demographic and Clinical Characteristics of bAVM Cases for Combined Cohort Stratified by HHT Status

Characteristics	Total (n = 1989)	HHT (n= 56)	Non-HHT (n = 1933)	P Value
Demographic				
Gender				
Male (#, %)	1021 (51)	23 (41)	998 (52)	0.119
Female (#, %)	968 (49)	33 (59)	935 (48)	
Age at presentation (decades, SD)	3.65 ± 1.8	2.87 ± 1.6	3.67 ± 1.8	0.002
Ethnicity				0.334
Caucasian (#, %)	374 (19)	7 (13)	367 (19)	
Black (#, %)	51 (3)	0 (0)	51 (3)	
Hispanic (#, %)	184 (9)	2 (4)	182 (9)	
Asian (#, %)	97 (5)	1 (2)	96 (5)	
American Indian (#, %)	9 (0.5)	0 (0)	9 (1)	
Unknown * (#, %)	1267 (64)	41 (81)	1226 (63)	
Clinical				
HHT diagnosis				
No (#, %)	1933 (97)			
Yes (#, %)	56 (2.8)			
Multiple bAVMs				< 0.001
No (#, %)	1952 (98)	34 (61)	1918 (99)	
Yes (#, %)	37 (1.9)	22 (39)	15 (1)	
Number of bAVMs				< 0.001
1 (#, %)	1952 (98)	34 (61)	1918 (99)	
2 (#, %)	25 (1)	14 (25)	11 (< 1)	
3 (#, %)	7 (<1)	5 (8)	2 (< 1)	
4 (#, %)	4 (<1)	2 (4)	2 (< 1)	
≥ 4 (#, %)	1 (<1)	1 (2)	0 (0)	
Angiography				0.395
No (#, %)	439 (22)	9 (17)	430 (22)	
Yes (#, %)	1544 (78)	43 (83)	1501 (78)	
Symptomatic Presentation				0.032
No (#, %)	436 (22)	18 (34)	418 (22)	
Yes (#, %)	1549 (78)	35 (66)	1514 (78)	
Hemorrhagic Presentation				0.065
No (#, %)	1183 (60)	40 (71)	1143 (59)	
Yes (#, %)	806 (40)	16 (29)	790 (41)	

* No available information existed about the ethnicities of patients from the UHN cohort

Table 2

Univariate Analysis of Risk Factors for Predicting HHT in Patients with bAVM

Variable	N	OR	95% CI	P Value
Age, decade	1937	0.77	0.65–0.91	0.002
Gender, male	1989	0.65	0.38–1.12	0.122
Hemorrhagic presentation	1989	0.58	0.32–1.04	0.068
Symptomatic Presentation	1985	0.54	0.30–0.96	0.035
Multiple bAVM	1989	82.74	39.53–173.19	< 0.001
Angiography	1983	1.37	0.66–2.83	0.380
Site (UHN)	1989	2.69	1.35–5.36	0.005

Table 3

Multivariate Logistic Regression Analysis in 1937 Patients in UCSF and UHN Cohorts Combined

Variable	OR	95% CI	P Value
Age, decade	0.79	0.66–0.95	0.013
Symptomatic Presentation	0.46	0.23–0.92	0.029
Multiple BAVM	86.35	38.20–195.15	< 0.001
Site (UHN)	2.52	1.15–5.54	0.021

Table 4

Results of using bAVM Multiplicity for the Diagnosis of HHT.

Diagnostic	Univariate Model	95% CI	Multivariable Model*	95% CI
Sensitivity	0.393	0.265–0.532	0.340	0.212–0.488
Specificity	0.992	0.987–0.996	0.998	0.995–0.999
PPV	0.595	0.421–0.752	0.810	0.581–0.946
NPV	0.983	0.976–0.988	0.983	0.976–0.988
Positive LR	50.63	20.25–81.01	160.40	−8.40–329.19
Negative LR	0.61	0.48–0.74	0.66	0.53–0.79

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

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Table 5

Angiographic Characteristics of HHT bAVMs compared to non-HHT bAVMs.

Characteristics	HHT (n= 56)	Non HHT (n = 1933)	P Value
Number bAVMs	89	1954	
Lobar			0.465
No (%)	21 (27)	594 (31)	
Yes (%)	58 (73)	1352 (69)	
Deep			0.358
No (%)	53 (90)	1667 (86)	
Yes (%)	6 (10)	274 (14)	
Posterior Fossa			0.713
No (%)	52 (93)	1823 (94)	
Yes (%)	4 (7)	111 (6)	
Eloquent			0.020
No (%)	37 (55)	684 (39)	
Yes (%)	30 (45)	1090 (61)	
Venous Drainage			< 0.001
Deep Venous (%)	11 (18)	748 (45)	
Superficial (%)	46 (75)	794 (47)	
Both (%)	4 (7)	132 (8)	
Size			< 0.001
< 3cm (%)	37 (88)	993 (60)	
>3 cm (%)	5 (12)	662 (40)	
Spetzler-Martin Score			< 0.001
1 (%)	28 (44)	255 (15)	
2 (%)	24 (37)	481 (30)	
3 (%)	8 (12)	538 (33)	
4 (%)	1 (2)	294 (18)	
5 (%)	3 (5)	57 (4)	

Table 6

Detailed information regarding clinical characteristics in HHT patients.

Characteristics	HHT (n=56)
Family history of HHT	
No	6 (12)
Yes	45 (88)
Epistaxis	
No	8 (19)
Yes	34 (81)
Telangiectasia	
No	6 (14)
Yes	36 (85)
Pulmonary AVM	
No	24 (57)
Yes	18 (43)
GI Bleed	
No	35 (83)
Yes	7 (17)
Clinical Criteria for Diagnosis of HHT	
At least 3	36 (82)
Two	7 (16)
One	1 (2)
HHT genetic testing results	
ACVRL1 mutation	5 (9)
ACVRL1 VUS	0 (0)
Endoglin mutation	25 (44)
Ebdoglin VUS	1 (2)
SMAD4 mutation	0 (0)
SMAD4 VUS	0 (0)
No mutation detected	4 (7)
Not done or not available	21 (38)