Hemorrhage Rates From Brain Arteriovenous Malformation in Patients With Hereditary Hemorrhagic Telangiectasia

Helen Kim, PhD; Jeffrey Nelson, MS; Timo Krings, MD, PhD; Karel G. terBrugge, MD; Charles E. McCulloch, PhD; Michael T. Lawton, MD; William L. Young, MD†; Marie E. Faughnan, MD, MSc; the Brain Vascular Malformation Consortium HHT Investigator Group

Background and Purpose—Hereditary hemorrhagic telangiectasia (HHT) is a systemic disease characterized by mucocutaneous telangiectasias, epistaxis, and arteriovenous malformations (AVMs). Intracranial hemorrhage (ICH) rates in this population are not well described. We report ICH rates and characteristics in HHT patients with brain AVMs (HHT-BAVMs).

Methods—We studied the first 153 HHT-BAVM patients with follow-up data enrolled in the Brain Vascular Malformation Consortium HHT Project. We estimated ICH rates after BAVM diagnosis.

Results—The majority of patients were women (58%) and white (98%). The mean age at BAVM diagnosis was 31±19 years (range, 0–70), with 61% of cases diagnosed on asymptomatic screening. Overall, 14% presented with ICH; among symptomatic cases, 37% presented ruptured. During 493 patient-years of follow-up, 5 ICH events occurred yielding a rate of 1.02% per year (95% confidence interval, 0.42–2.44%). ICH-free survival differed significantly by ICH presentation (P=0.003); ruptured cases had a higher ICH rate (10.07%; 95% confidence interval, 3.25–31.21%) than unruptured cases (0.43%; 95% confidence interval, 0.11–1.73%).

Conclusions—Patients with HHT-BAVM who present with hemorrhage are at a higher risk for rehemorrhage compared with patients with BAVM detected presymptomatically. **(*Stroke*. 2015;46:1362-1364. DOI: 10.1161/STROKEAHA.114.007367.)**

Key Words: arteriovenous malformations ■ cerebral hemorrhage ■ natural history ■ telangiectasia, hereditary hemorrhagic

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease caused by mutations in transforming growth factor-β signaling genes (*ENG*, *ALK1*, or *SMAD4*). HHT is characterized by mucocutaneous telangiectasia, frequent epistaxis, and organ arteriovenous malformations (AVMs). Patients with HHT often have multiple brain AVMs (BAVMs), which is highly predictive of HHT diagnosis.[1] Previous series have suggested that patients with HHT-BAVM may have a lower risk of intracranial hemorrhage (ICH) than patients with sporadic BAVM.[2] We describe hemorrhage rates and characteristics in patients with HHT-BAVM enrolled in a multicenter study.

Methods

Study Population

Patients with HHT (n=932) were enrolled in the Brain Vascular Malformation Consortium (BVMC) HHT Project between April 2010 and June 2014 from 14 HHT centers of excellence (Table I in the online-only Data Supplement).[3] Eligible patients with HHT either had a genetic diagnosis (*ENG*, *ALK1*, or *SMAD4* mutation) or a definite clinical diagnosis (≥3 following Curaçao criteria)[4]: (1) spontaneous recurrent nosebleeds; (2) mucocutaneous telangiectasia (lips, oral cavity, fingers, or nose); (3) visceral AVM involvement (pulmonary, hepatic, or brain); or (4) affected first-degree relative by the same criteria. All patients with HHT were screened for BAVM regardless of symptoms; BAVM was diagnosed by angiography, magnetic resonance imaging, or surgical resection.

Data Collection

Data were collected retrospectively at study enrollment using AVM-reporting guidelines,[5] including age, sex, race, HHT gene mutation, presentation symptoms, hemorrhage at BAVM diagnosis or during follow-up (assessed retrospectively and prospectively from the time of enrollment), and BAVM treatment type and date (Table). All patients were also prospectively followed annually for ICH events, new symptoms, and any new treatments up to 4 years after enrollment. ICH events are determined from clinicians during medical history, chart review, and imaging where available.

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From the Departments of Anesthesia and Perioperative Care (H.K., J.N., W.L.Y.), Epidemiology and Biostatistics (H.K., C.E.M.), and Neurological Surgery (M.T.L., W.L.Y.), University of California, San Francisco; Division of Neuroradiology, Department of Medical Imaging (T.K., K.G.T.), Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada; and Division of Respirology, Keenan Research Centre, and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (M.E.F.).

†Deceased.

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Correspondence to Helen Kim, PhD, Department of Anesthesia and Perioperative Care, University of California, San Francisco, 1001 Potrero Ave, Box 1363, San Francisco, CA 94110. E-mail kimhel@anesthesia.ucsf.edu

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Statistical Analysis

A total of 194 enrolled patients with HHT had BAVM and 153 had follow-up data. Follow-up time started after the date of BAVM diagnosis until the date of hemorrhage, censoring at the date of first treatment, death, or last follow-up, and truncated at 15 years from diagnosis. ICH rates (number of first ICH events/patient-years at risk×100) and 95% confidence intervals (CIs) were calculated using Stata (StataCorp version 13.1; College Station, TX). Kaplan–Meier survival curves are presented by ICH presentation, and log-rank test exact *P* values were calculated using StatXact.[6] To assess the effect of missing data on ICH rates, we performed multiple imputation using chained equations in Stata,[7] allowing us to include all 194 patients with HHT-BAVM (Figure I in the online-only Data Supplement).

Results

Characteristics of our HHT-BAVM cohort are shown in Table and are similar to other HHT populations.[8,9] The mean follow-up time was 3.2±4.3 years after BAVM diagnosis, and mean age at BAVM diagnosis was 31±19 years (range, 0–70), with 61% of cases diagnosed from asymptomatic screening. Overall, 14% presented with ICH; among symptomatic cases, 37% presented initially with ICH.

A total of 5 ICH events occurred over 493 patient-years, yielding an overall ICH rate of 1.02% (95% CI, 0.42–2.44%) per year. The ICH rate was significantly higher (*P*=0.003) for ruptured than unruptured cases at presentation (Figure). In ruptured cases, the annual ICH rate was 10.07% (95% CI, 3.25%–31.21%), whereas the rate in unruptured cases was 0.43% (95% CI, 0.11–1.73%). Four of 5 ICH events occurred in women, but this was not statistically significant (*P*=0.556). Sensitivity analysis of imputed datasets resulted in similar ICH rates and 95% CIs (Figure I in the online-only Data Supplement).

Table. Characteristics of 153 Hereditary Hemorrhagic Telangiectasia-BAVM Patients With Follow-Up

Characteristics	Summary*
Demographics	
Age at enrollment, y	40.0±19.0
Female sex	88/153 (58%)
White	146/149 (98%)
Clinical	
Age at BAVM diagnosis, y	30.7±19.1
Initial hemorrhagic presentation	22/153 (14%)
Anemia	53/145 (37%)
Epistaxis	136/147 (93%)
GI bleeding	14/139 (10%)
Symptomatic liver VM(s)	15/139 (11%)
Pulmonary AVM(s)	83/141 (59%)
Gene mutation	
ALK1	21/93 (23%)
ENG	65/93 (70%)
SMAD4	2/93 (2%)
All tests negative	5/93 (5%)
Survival	
Survival time, y	3.21±4.32
Event/censor cause	
Hemorrhage (event)	5/153 (3%)
Death	4/153 (3%)
Last follow-up	56/153 (37%)
Treatment	88/153 (58%)

*Mean±SD or number with specified characteristic over number with nonmissing information (percent). BAVM indicates brain arteriovenous malformation; and GI gastrointestinal.

Discussion

This is the largest study to date examining hemorrhage risk in HHT patients with BAVM. Despite the small number of hemorrhages, the upper bound of our 95% CI limits the overall annual ICH rate in patients with HHT-BAVM to <2.5% per year, which is consistent with ICH rates from 4 large sporadic BAVM populations of 2.3% (95% CI, 2.0%–2.7%).[10] A similar pattern is also observed in patients with sporadic BAVM with an almost 4-fold higher ICH rate in ruptured (4.8%; 95% CI, 3.9%–5.9%) than unruptured (1.3%; 95% CI, 1.0%–1.7%) BAVMs at presentation.[10]

Only one previous study has directly quantified ICH risk in patients with HHT-BAVM; Willemse et al[2] identified 22 Dutch HHT patients with BAVMs (of 196 screened) and reported an overall ICH rate of 0.41% to 0.72% per year. The apparently lower ICH rate in HHT-BAVM has led some to speculate that the risk may be lower than for patients with sporadic BAVM and more similar to that of unruptured sporadic BAVMs (1.3%[10] to 2.2% per year[8]). However, the HHT-BAVM and sporadic BAVM populations are markedly different with respect to how BAVMs are ascertained. In reported HHT populations, BAVMs are frequently identified on asymptomatic screening after HHT diagnosis, contributing to the lower ICH rates. This study is the first to demonstrate a significant association with specific features of BAVM, specifically that patients with HHT-BAVM presenting ruptured have higher rerupture rates, similar to that seen for patients with sporadic BAVM. Thus, depending on additional BAVM features, there may be subgroups of patients with HHT-BAVM at higher or lower risk for hemorrhage. For example, patients with HHT-BAVM often display multiple lesions as well as a range of other neurovascular phenotypes.[1,9]

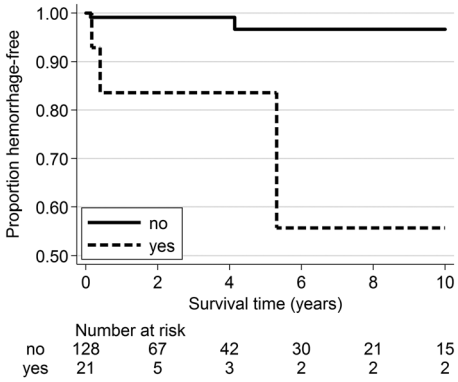

Figure. Kaplan–Meier survival curves of time-to-intracranial hemorrhage (ICH) in the natural history course of hereditary hemorrhagic telangiectasia-brain arteriovenous malformation patients, by ICH presentation.

Our study had several limitations. The small number of ICH events precluded us from evaluating additional ICH risk factors, for example, angiographic characteristics. Second, our results may be subject to selection bias, which may affect ICH rates. However, our calculations based on patient-years of risk reflect current treatment practices for HHT-BAVM, and we observed similar patterns of ICH risk as for patients with sporadic BAVM. In addition, imputation analysis of missing data yielded strikingly similar ICH rates as those observed. Finally, our analysis did not consider per-lesion risk of hemorrhage at this time, which may also alter risk.

In summary, we found that patients with ruptured HHT-BAVM have a higher risk of subsequent hemorrhage compared with those who present unruptured, similar to patients with sporadic BAVM.

Appendix

BVMC HHT Investigator Group

Murali Chakinala, Marie E. Faughnan, James R. Gossage, Katharine Henderson, Vivek Iyer, Raj Kasthuri, Helen Kim, Timo Krings, Michael T. Lawton, Doris Lin, Johannes Jurgen Mager, Justin McWilliams, Jamie McDonald, Ludmila Pawlikowska, Jeffrey Pollak, Felix Ratjen, Karen Swanson, Karel terBrugge, Dilini Vethanayagam, Andrew White, Robert I. White Jr, Pearce Wilcox, William L. Young

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Disclosures

None.

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ONLINE SUPPLEMENT

Hemorrhage Rates From Brain Arteriovenous Malformation in Hereditary Hemorrhagic Telangiectasia Patients

Study Population

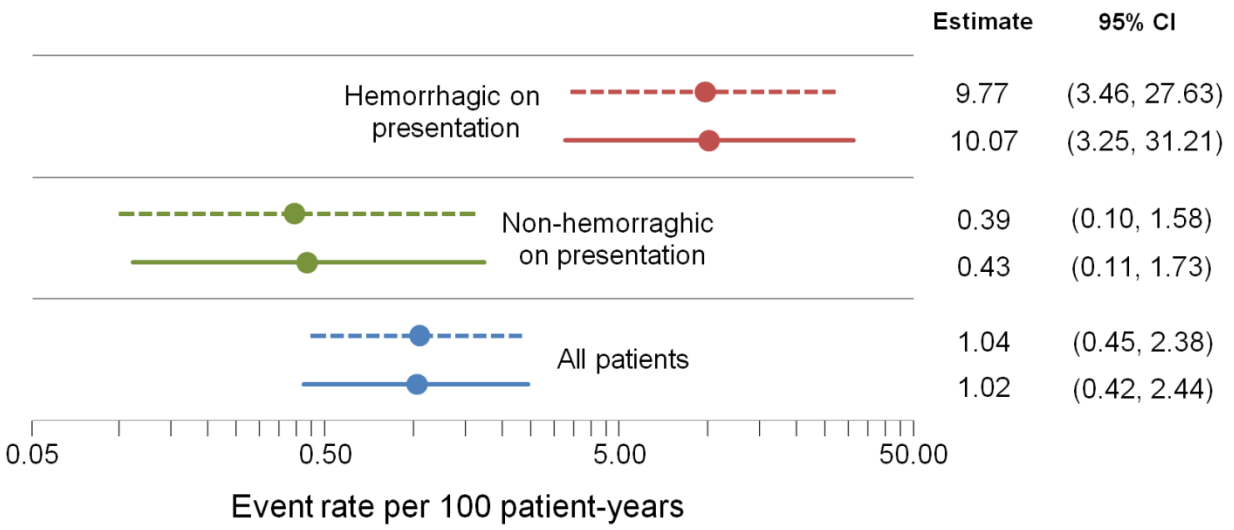
There were 932 HHT patients enrolled in the Brain Vascular Malformation Consortium (BVMC) HHT Project between April 2010 and June 2014 from 14 HHT Centers of Excellence. Participating Centers and site investigators are listed in **Supplementary Table I**. Among 932 enrolled HHT cases, there were 194 with BAVM and 153 with follow-up data for survival analysis. Among those included in the survival analysis, 56 (37%) were censored at their most recent follow-up visit, i.e., cases without ICH or other censoring cause (treatment or death). Of the 41 (21%) HHT-BAVM patients not included in the survival analysis, the primary reasons for exclusion were: a) incomplete or same dates for both diagnosis and treatment (n=26), b) marked unknown for hemorrhage event during follow-up (n=8), c) marked unknown for treatment during follow-up (n=5), and d) newly enrolled case with no follow-up time accrued yet (n=4).

Participating Center	**Principal Investigator**
Georgia Regents University	James R. Gossage, MD
Johns Hopkins University School of Medicine	Doris Lin, MD, PhD
Mayo Clinic	Karen L. Swanson, DO
University of California-Los Angeles	Justin McWilliams, MD
University of California-San Francisco	William L. Young, MD; Michael T. Lawton, MD
University of North Carolina at Chapel Hill	Raj Kasthuri, MD
University of Utah	Jamie McDonald, MS
Washington University School of Medicine	Murali Chakinala, MD; Andrew J. White, MD
Yale University School of Medicine	Robert White, Jr., MD
University of Alberta	Dilini Vethanayagam, MD
St. Paul's Hospital (University of British Columbia)	Pearce Wilcox, MD
Hospital for Sick Children (University of Toronto)	Felix Ratjen, MD
St. Michael's Hospital (University of Toronto)	Marie Faughnan, MD
St Antonius Hospital Netherlands	Johannes J. Mager, MD, PhD

Supplementary Table I. HHT Centers of Excellence participating in the Brain Vascular Malformation Consortium HHT Project between June 2010 and June 2014

Imputation Methods

To assess the effect of missing data on our observed ICH rates, we performed multiple imputation allowing us to include all 194 HHT-BAVM patients in a sensitivity analysis. We generated 10 imputed data sets using chained equations in Stata. Missing values of censor cause, length of follow-up time, and presentation reason (hemorrhagic versus non-hemorrhagic) were imputed; conditional models used to generate these values also factored in age at BAVM diagnosis and sex. As can be seen in **Supplementary Figure I**, the ICH rates overall and by hemorrhagic presentation derived from imputation (dashed lines) is very similar to observed ICH rates (solid lines). Thus, we feel that our observed hemorrhage rates are not unduly influenced by missing data.



Supplementary Figure I. Hemorrhage rates and 95% CI for observed (solid) and imputed (dashed) data of HHT BAVM patients.

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