Title

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Journal

Stroke, 46(5)

ISSN

0039-2499

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Publication Date

2015-05-01

DOI

10.1161/strokeaha.114.007367

Peer reviewed

HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Stroke. 2015 May ; 46(5): 1362–1364. doi:10.1161/STROKEAHA.114.007367.

Hemorrhage Rates From Brain Arteriovenous Malformation in Hereditary Hemorrhagic Telangiectasia Patients

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Abstract

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

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 female (58%) and Caucasian (98%). The mean age at BAVM diagnosis was 31±19 years (range: 0–70), with 61% of cases diagnosed upon 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% CI: 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% CI: 3.25–31.21%) than unruptured cases (0.43%, 95% CI: 0.11–1.73%).

Conclusions—HHT-BAVM patients who present with hemorrhage are at a higher risk for re-hemorrhage compared to BAVMs detected pre-symptomatically.

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Disclosures

None

Keywords

arteriovenous malformation; hereditary hemorrhagic telangiectasia; intracerebral hemorrhage; natural history; osler-weber rendu

Introduction

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

Methods

Study Population

HHT patients (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 (Supplementary Table I).[3] Eligible HHT patients either had a genetic diagnosis (*ENG*, *ALK1*, or *SMAD4* mutation) or a definite clinical diagnosis (≥3 following Curaçao criteria):[4] (a) spontaneous recurrent nosebleeds; (b) mucocutaneous telangiectasia (lips, oral cavity, fingers or nose); (c) visceral AVM involvement (pulmonary, hepatic or brain); or (d) affected first-degree relative by same criteria. All HHT patients were screened for BAVM regardless of symptoms; BAVM was diagnosed by angiography, MRI, 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 time of enrollment), and BAVM treatment type and date (Table 1). 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.

Statistical Analysis

A total of 194 enrolled HHT patients had BAVM, and 153 had follow-up data. Follow-up time started after date of BAVM diagnosis until date of hemorrhage, censoring at date of first treatment, death, or last follow-up, and truncated at 15 years from diagnosis. ICH rates (# first ICH events/patient-years at risk × 100) and 95% confidence intervals (CI) were calculated using Stata (StataCorp v13.1; College Station, TX). Kaplan-Meier survival curves are presented by ICH presentation and log-rank test exact p-values were calculated in StatXact.[6] To assess impact of missing data on ICH rates, we performed multiple imputation

using chained equations in Stata,[7] allowing us to include all 194 HHT-BAVM patients (Supplementary Figure I).

Results

Characteristics of our HHT-BAVM cohort are shown in Table 1 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 1). 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 five ICH events occurred in females, but this was not statistically significant (P=0.556). Sensitivity analysis of imputed datasets resulted in similar ICH rates and 95% CIs (Supplementary Figure I).

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 HHT-BAVM patients to <2.5% per-year, which is consistent with ICH rates from four large sporadic BAVM populations of 2.3% (95% CI: 2.0%–2.7%).[10] A similar pattern is also observed in sporadic BAVM patients 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 prior study has directly quantified ICH risk in HHT-BAVM patients; Willemse et al[2] identified 22 Dutch HHT patients with BAVMs (out of 196 screened) and reported an overall ICH rate of 0.41–0.72% per-year. The apparently lower ICH rate in HHT-BAVM has led some to speculate that the risk may be lower than for sporadic BAVM patients 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 upon 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 HHT-BAVM patients presenting ruptured have higher re-rupture rates, similar to that seen for sporadic BAVM patients. Thus, depending on additional BAVM features, there may be subgroups of HHT-BAVM patients at higher or lower risk for hemorrhage. For example, HHT-BAVM patients often display multiple lesions as well as a range of other neurovascular phenotypes.[1, 9]

Our study had several limitations. The small number of ICH events precluded us from evaluating additional ICH risk factors, e.g., angiographic characteristics. Second, our results may be subject to selection bias, which may affect ICH rates. However, our calculations

based on person-years of risk reflect current treatment practices for HHT-BAVM, and we observed similar patterns of ICH risk as for sporadic BAVM patients. Additionally, 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 ruptured HHT-BAVM patients have a higher risk of subsequent hemorrhage compared to those who present unruptured, similar to sporadic BAVM patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding

BVMC/U54 NS065705 (part of the Rare Diseases Clinical Research Network, and supported through collaboration between NIH Office of Rare Diseases Research at the National Center for Advancing Translational Science, and the National Institute of Neurological Disorders and Stroke); Nelson Arthur Hyland Foundation, and Li Ka Shing Knowledge Institute (M.E.F.).

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Appendix

BVMC HHT Investigator Group

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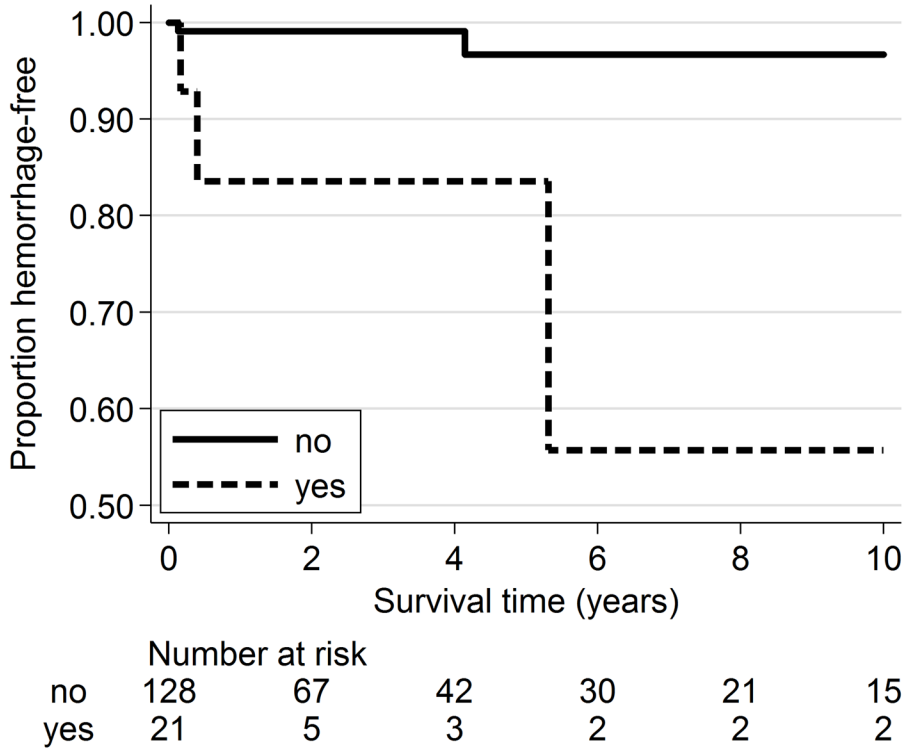

Figure 1.
Kaplan-Meier survival curves of time-to-ICH in the natural history course of HHT-BAVM patients, by ICH presentation.

Table 1

Characteristics of 153 HHT-BAVM patients with follow-up.

Characteristic	Summary*
Demographic	
Age at enrollment (years)	40.0±19.0
Female sex	88/153 (58%)
Caucasian	146/149 (98%)
Clinical	
Age at BAVM diagnosis (years)	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 (years)	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±standard deviation or number with specified characteristic over number with non-missing information (percent)