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Blood 142 (2023) 28–30

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

Hereditary Hemorrhagic Telangiectasia May be the Most Clinically Significant and Morbid Inherited Bleeding Disorder of Women

Ellen Zhang, MD[1], *Zain Virk, MD*[2], *Josanna Rodriguez-Lopez, MD*[3], *Hanny Al-Samkari, MD*[4]

[1]Department of Medicine, Stanford University Medical Center, Palo Alto, CA
[2]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[3]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, MA
[4]Division of Hematology Oncology, Massachusetts General Hospital, Boston, MA

Background

Hereditary hemorrhagic telangiectasia (HHT) is the second most common inherited bleeding disorder (1 in 5000 people) behind von Willebrand disease (VWD) and has no FDA- or EMA-approved therapies. HHT causes serious bleeding resulting in severe iron deficiency anemia, major psychosocial complications, and visceral arteriovenous malformations in brain, lung, and liver that can cause life-threatening hemorrhage, stroke, and other morbid complications. While HHT prevalence is equal in men and women, manifestations may be worse in women (as evidenced by a female predominance in HHT clinical trials). Due to the focus on hemophilia (an X-linked disease nearly exclusive to men) in the hemostasis research community, no study has examined the relative morbidity of the most common inherited bleeding disorders in women: HHT and VWD.

Methods

We performed an observational cohort study of women with HHT or VWD cared for at our institutional Comprehensive Hemophilia and Von Willebrand Disease Treatment Center or HHT Center of Excellence. Using an electronic patient data registry, a representative sample of 100 randomly selected women with HHT were age-matched to 100 randomly selected women with VWD for analysis. All data was extracted and confirmed using manual chart review; we quantified and compared bleeding and healthcare utilization outcomes.

Results

Patient Population. The mean (range) age in both groups was 49 (14-87) years. Mean BMI was 27 in both groups, and racial/ethnic breakdown was similar in both groups. Mean follow-up durations were 9.07 years (HHT) and 14.83 years (VWD) per patient. The VWD group included 86 patients with type 1 VWD and 14 with type 2 VWD.

Bleeding Outcomes. Bleeding outcomes are detailed in **TABLE 1**. In women with HHT compared with VWD, recurrent epistaxis and GI bleeding were more likely (odds ratio [OR] [95% CI] = 32.73 [13.81-71.80], $P<0.0001$ and 5.69 [2.59-12.89], $P<0.0001$, respectively), and heavy menstrual bleeding was less likely (OR 0.32 [0.18-0.57], $P<0.0001$). Iron deficiency anemia was significantly more likely, and lowest hemoglobin significantly lower, in HHT versus VWD. Requirements for IV iron and RBC transfusion were significantly more likely in HHT versus VWD. Women with HHT had 17-fold higher odds of iron infusion dependence and 8-fold higher odds of requiring hemostatic surgical procedures than women with VWD.

Healthcare Utilization for HHT or VWD Management. Healthcare utilization is detailed in **TABLE 2**. In women with HHT compared with VWD, emergency department (ED) visits and hospital admissions specifically to manage disease complications were significantly more likely (OR [95% CI] = 3.83 [1.67-8.48], $P=0.001$ and 7.33 [3.57-14.73], $P<0.0001$, respectively). Rates of ED visitation, admission, and outpatient encounters specifically for HHT or VWD management were significantly higher in women with HHT vs. women with VWD: ED visits, 10.3 per 100 patient-years (pt-yrs) vs. 0.74 per 100 pt-yrs, $P=0.001$; admissions, 14.4 per 100 pt-yrs vs. 1.0 per 100 pt-yrs, $P<0.0001$; outpatient encounters, 386.5 per 100 pt-yrs vs. 43.7 per 100 pt-yrs, $P<0.0001$. Adjusting these rates for the prevalence of HHT (1 in 5000) and VWD (1 in 1000) at the population level, all rates were still higher in the HHT group. Infusion visits, radiology encounters, and nearly all subspecialty provider visit types were much higher in women with HHT (**TABLE 2**).

Conclusions

Analyzing matched populations of women at a health system that serves as a tertiary referral center for both diseases, HHT, a historically neglected bleeding disorder, was responsible for much higher morbidity and healthcare utilization in women than VWD, certainly at the individual patient level and possibly at the population level (prevalence-adjusted). Overall incidence

of disease complications in each group was consistent with the published literature for both HHT and VWD, supporting the generalizability of our findings. These findings are critically important in achieving gender equity in the hemostasis field, given that both government and industry funding for VWD research is many times greater than for HHT research and such funding for hemophilia research, a disease of men, is at least 10-fold greater than for HHT research. Continued neglect of funding for clinical care and research of HHT within the hemostasis academic community and industry will only sustain and exacerbate gender inequities in hematology.

Disclosures Al-Samkari: *Agios:* Consultancy, Research Funding; *Sobi:* Consultancy, Research Funding; *Novartis:* Consultancy; *Amgen:* Research Funding; *argenx:* Consultancy; *Pharmacosmos:* Consultancy; *Moderna:* Consultancy.

Table 1. Table 1. Bleeding outcomes of women with HHT versus VWD. IQR, interquartile range. 95% CI, 95% confidence interval.

	Hereditary hemorrhagic telangiectasia N = 100	Von Willebrand disease N = 100	Odds ratio (95% CI) for incidence in HHT group relative to VWD group	*P* value
Incidence of Bleeding by Site				
Recurrent epistaxis, n (%)	92 (92)	26 (26)	32.73 (13.81-71.80)	<0.0001†
Gastrointestinal bleeding, n (%)	36 (36)	9 (9)	5.69 (2.59-12.89)	<0.0001†
Heavy menstrual bleeding, n (%)	35 (35)	63 (63)	0.32 (0.18-0.57)	<0.0001†
Other bleeding, n (%)	12 (12)	16 (16)	0.72 (0.31-1.57)	0.42†
Hemoglobin, Hematologic Support Requirements, and Interventions				
Lowest measured hemoglobin, median (IQR)	10.7 (7.9-12.6)	11.4 (9.9-12.5)	n/a	0.02^
Iron deficiency anemia, n (%)	66 (66)	50 (50)	1.94 (1.09-3.41)	0.02†
Requirement for intravenous iron, n (%)	41 (41)	10 (10)	6.25 (2.99-12.78)	<0.0001†
Intravenous iron dependence*, n (%)	26 (26)	2 (2)	17.22 (4.49-74.77)	<0.0001‡
Requirement for red cell transfusion, n (%)	42 (42)	21 (21)	2.72 (1.45-4.99)	0.001†
Requirement for hemostatic procedure**, n (%)	78 (78)	31 (31)	7.89 (4.16-14.60)	<0.0001†
Hemostatic procedures, per 100 patient-years	27.2	3.0	n/a	<0.0001ᵛ
Death due to bleeding complications, n (%)	3 (3)	0 (0)	n/a	0.25‡

*Defined as a requirement for ≥2000 mg elemental iron infused over any contiguous 12-month period.
**Included surgical or other interventional procedures in the uterus to manage heavy menstrual bleeding (e.g., hysterectomy), nasal cavity to manage epistaxis (e.g., nasal cautery), GI tract to manage GI bleeding (e.g., endoscopy), or other interventional procedures done to manage bleeding at any site.
†Per Chi-square test.
‡Per Fisher's exact test.
^Per two-tailed *t*-test (parametric data).
ᵛPer Wilcoxon rank sum test (non-parametric data).

Table 2. Healthcare utilization specifically for HHT or VWD management in women with HHT versus VWD. ED, emergency department.

	Hereditary hemorrhagic telangiectasia N = 100	Von Willebrand disease N = 100	*P* value‡
Emergency Department (ED) Visits and Hospital Admissions Specifically for HHT or VWD Management			
Requirement for ED visit*, n (%)	25 (25)	8 (8)	0.001†
ED visits, per 100 patient-years	10.3	0.74	0.001
Requirement for hospital admission, n (%)	50 (50)	12 (12)	<0.0001†
Hospital admissions, per 100 patient-years	14.4	1.0	<0.0001
Length of hospital stay, mean (range)	5.5	4.3	0.47
*Outpatient Encounters** Specifically for HHT or VWD Management*			
Any outpatient encounter, per 100 patient-years	386.5	43.7	<0.0001
Primary care provider, per 100 patient-years	37.9	19.1	0.28
Hematology, per 100 patient-years	62.3	11.3	0.005
Pulmonology, per 100 patient-years	36.5	0.1	<0.0001
Cardiology, per 100 patient-years	4.3	0.9	0.005
Gastroenterology, per 100 patient-years	14.7	0.9	<0.0001
Otolaryngology, per 100 patient-years	18.3	0.7	<0.0001
Obstetrics & Gynecology, per 100 patient-years	4.4	5.9	0.003
Medical Genetics, per 100 patient-years	7.7	0.0	<0.0001
Dermatology, per 100 patient-years	5.1	0.0	0.003
Outpatient infusion, per 100 patient-years	97.6	5.3	<0.0001
Radiology/imaging, per 100 patient-years	74.0	0.3	<0.0001
Other, per 100 patient-years	23.3	1.3	<0.0001

*Includes only ED visits in which the patient was discharged from the ED without hospital admission. ED visits ending in hospital admission were counted only once, as hospital admissions.
**All outpatient encounters except for outpatient infusion and radiology/imaging were face-to-face visits with a clinician (physician, nurse practitioner or physician assistant).
‡*P* values marked with a dagger (†) symbol are per Chi-square test. All other *P* values in this table are per Wilcoxon rank sum test.

Figure 1

https://doi.org/10.1182/blood-2023-187772