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CORRESPONDENCE

Prevalence and predictors of anemia in hereditary hemorrhagic telangiectasia

To the Editor:

Hereditary hemorrhagic telangiectasia (HHT, or Osler Weber Rendu syndrome) is an inherited disorder characterized by the development of arteriovenous malformations (AVMs) in visceral organs (brain, lungs, spinal cord, and liver) and on mucocutaneous surfaces (skin, lips, nasal and buccal mucosa, gastrointestinal mucosa) where they are called telangiectasias.[1] HHT is caused by mutations in endoglin (*ENG*) and activin A receptor-like kinase 1 (*ACVRL-1*), which account for over 80% of cases.[1] A small number (~3%-5%) result from mutations in the *SMAD4* gene and present with features of both HHT and juvenile polyposis.[1] HHT has a prevalence of 1 in 5000,[2] and the most common clinical features are recurrent epistaxis and mucocutaneous telangiectasias, both occurring in over 90% of affected individuals by age 40.[1] HHT can be diagnosed clinically using the Curaçao clinical diagnostic criteria[3] or by genetic testing.

Anemia secondary to iron deficiency from recurrent epistaxis and/or gastrointestinal (GI) bleeding is common in HHT, although the burden of anemia in HHT is not known. Affected individuals require chronic oral and/or intravenous iron replacement therapy and, in severe cases, blood transfusions. Anemia is commonly associated with weakness, fatigue, decreased exercise tolerance, headache, irritability, and poor quality of life (QOL).[4,5] The goal of this study was to define the prevalence of anemia in HHT, and to identify predictors of anemia. We used data from the HHT project (Cerebral Hemorrhage Risk in HHT) of the Brain Vascular Malformation Consortium, which represents the first large-scale collaboration in HHT research. Patients were recruited from 14 HHT Centers of Excellence in Canada, the United States, and Europe.

We performed a cross-sectional analysis of baseline data from the first 763 patients with HHT recruited to the HHT project between January 2010 and August 2013. Data collected included age, sex, HHT gene mutation type, HHT clinical presentations and symptoms, and presence of AVMs on imaging. Our primary outcome was prevalence of anemia defined as positive response on any of the following self-reported variables (verified by study site): history of anemia, age at initial presentation with anemia, history of requiring blood transfusions, and number of blood transfusions (lifetime total). Those with unknown anemia status were excluded. Of the 763 patients, 83 did not have information on anemia status, leaving 680 patients for analysis. All patients provided informed consent and the study was approved by each Institutional Review Board.

We tested for differences in clinical characteristics between anemic and nonanemic patients using Fisher's exact test for categorical variables and two-sample *t*-tests (allowing for unequal variances) for continuous variables. Characteristics significantly associated with anemia were used as predictors in multivariable logistic regression models and odds ratios (OR) and corresponding 95% confidence intervals were estimated. We tested for the effect of each possible pairwise interaction of significant predictors and included significant interactions in the multivariable models. Two separate multivariable analyses were performed: (1) analysis including all individuals; and (2) restricted analysis including only individuals with mutation information and with additional predictors to test the effect of mutation (indicator variables with *ENG* set as the reference group). We considered two-tailed *P*-values $< .05$ to be statistically significant. Statistical analyses were performed using Stata/SE 13.1.

A summary of patient characteristics and mutation status is presented in the Table 1. Majority of subjects were women (59%) and average age at recruitment was 46. Genetic testing results were available in 60% (410/680) of participants. No mutation was found in 20 subjects who underwent genetic testing. Epistaxis was reported in 96% of subjects and the average age at presentation was 14.2. GI bleeding was reported in 17% of subjects and the average age at onset was 47.2. Both epistaxis and GI bleeding were more common in the anemia group (99% vs. 93% and 32% vs. 3%, respectively; $P < .001$).

The prevalence of anemia was 50% (339/680). The average age at diagnosis of anemia was 38. Anemic subjects were older at enrollment ($P < .001$) and females were more likely to report anemia ($P = .008$). In the anemia group, 52% reported receiving a blood transfusion compared to <1% in the nonanemic group ($P < .001$). Mutation status was significantly associated with anemia ($P = .004$). Anemia was more frequent among subjects with *ACVRL-1* mutations (54%) or *SMAD4* mutations (60%) than with *ENG* mutations (36%).

In the multivariate Table 2 model that included all subjects, epistaxis (OR = 3.79, $P = .036$) and GI bleeding (OR = 13.65, $P < .001$) were independent predictors of anemia. We identified a significant interaction between age and gender in our model ($P = .007$). The risk for anemia at birth is higher for females than males (OR = 6.65, $P = .002$) and females remain at higher risk until age 57. In both males and females, the odds of anemia with each decade increase in age is significant (OR = 1.98, $P < .001$ and OR = 1.41, $P < .001$, respectively). In the multivariable model that included only gene mutation status, epistaxis (OR = 2.80, $P = .165$) was no longer a significant predictor of anemia.

This is the first study to evaluate the prevalence and risk factors for anemia in HHT. We found the prevalence of a history of anemia to be 50%. This is much greater than the estimated global prevalence of

TABLE 1 Demographic and clinical characteristics

Characteristic	Nonanemic ($n = 341$)	Anemic ($n = 339$)	Overall ($n = 680$)	P-value
Age at anemia diagnosis (y)	N/A	38.4 ± 16.1	N/A	N/A
Age at recruitment (y)	38.5 ± 19.0	53.5 ± 14.1	46.0 ± 18.3	<.001
Female sex	185 (54)	218 (64)	403 (59)	.008
Gene status[a]				.004
ENG	132	75	207 (50)	
ACVRL-1	78	90	168 (41)	
SMAD4	6	9	15 (4)	
Testing uninformative	12	8	20 (5)	
Missing	*113*	*157*	*270 (40)*	
Epistaxis	318 (93)	335 (99)	653 (96)	<.001
Age at epistaxis presentation (y)	11.9 ± 9.9	16.2 ± 12.5	14.2 ± 11.6	<.001
GI bleeding	10 (3)	108 (32)	118 (17)	<.001
Age at GI bleeding diagnosis (y)	29.0 ± 30.7	48.8 ± 13.6	47.2 ± 15.8	.229
Transfusions	1/266 (<1)	170/325 (52)	171/591 (29)	<.001

Values are mean ± standard deviation or *n* (%). *P*-values compare anemic and nonanemic groups with Fisher's exact test or *t*-test (allowing for unequal variances).

[a]For gene status, % values in parenthesis for overall numbers reflect the subset of subjects in whom gene status was tested.

anemia of 32% in 2010.[6] Epistaxis and GI bleeding were independently associated with anemia. In multivariable models that included mutation status, the *ACVRL-1* mutation and GI bleeding were independent predictors of anemia whereas the association with epistaxis was no longer significant, possibly due to the high prevalence of epistaxis in all patients (96% in this study). The association of age and gender with anemia is interesting. Young and middle-aged females with HHT were more likely to be anemic. This is similar to the trend of anemia in the general population and likely reflects causes of anemia that are independent of HHT, such as menstrual blood loss and pregnancy. The odds of developing anemia increased with age in both males and females, suggesting that disease related factors affect risk for anemia in an age-dependent manner. This is also the likely explanation for the interaction between age and anemia observed in our study. Our finding that anemic patients tended to be older further supports this inference. Our study has a few limitations. This is a secondary analysis of the BVMC HHT project. The data on anemia are self-reported even though the history was confirmed by the interviewing physician. Finally, this was a cross-sectional study and we can only infer association and not causation.

In conclusion, this study highlights the significant burden of anemia in HHT and underscores the importance of ongoing surveillance for anemia in this population. Iron deficiency related to chronic blood loss is the likely cause of anemia in patients with HHT. Aggressive screening for and management of iron deficiency and anemia could have a significant impact on disease related morbidity, productivity, and health related QOL in patients with HHT.

TABLE 2 Multivariable logistic regression analysis

	All subjects ($n = 680$)			Subjects with mutation ($n = 410$)		
Characteristic	OR	95% CI	P-value	OR	95% CI	P-value
Age at registration (per decade)	1.98	(1.63, 2.40)	<.001	2.10	(1.61, 2.72)	<.001
Female sex	6.65	(2.02, 21.94)	.002	7.32	(1.58, 33.80)	.011
Female sex × Age at registration (per decade)[a]	0.72	(0.56, 0.91)	.007	0.71	(0.52, 0.98)	.036
Epistaxis	3.79	(1.09, 13.17)	.036	2.80	(0.65, 12.00)	.165
GI bleeding	13.65	(6.85, 27.20)	<.001	10.38	(3.99, 26.97)	<.001
Mutation status[b]						
ACVRL-1	—	—	—	2.80	(1.66, 4.73)	<.001
SMAD4	—	—	—	3.55	(0.92, 13.70)	.066
No mutation identified	—	—	—	0.98	(0.35, 2.74)	.971

[a]Interaction term of age and gender.

[b]*ENG* considered the reference group.

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CONFLICTS OF INTEREST

The authors do not have any relevant conflicts of interest to report.

AUTHOR CONTRIBUTIONS

R.S.K., M.M., M.T.L., and M.E.F. developed the study concept, analyzed the data and prepared the manuscript. H.K. and J.N. performed the statistical analysis. Members of the BVMC HHT Investigator Group recruited all study subjects, collected data, and reviewed/edited the manuscript.

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Elevated soluble α-hemoglobin pool in sickle cell anemia

To the Editor:

Sickle cell anemia (SCA) exhibits broad inter-individual variability as well as intra-individual variability during the patient's lifetime, ranging from mild phenotype to severe disease. The gravity of SCA is modulated by the remaining fetal hemoglobin (HbF $\alpha_2\gamma_2$) synthesis or/and the coinheritance of α-thalassemia (α-thal) which lead to decreased abnormal sickle hemoglobin (HbS $\alpha_2\beta^S{}_2$) amount and concentration in red blood cells (RBCs) and thus reducing its polymerization tendency.[1–3] A distinguishing characteristic of the abnormal β^S is its lower affinity, relative to normal β^A, for α-chain during Hb assembly thus modulating the HbS concentration.[4] Hence, there is a problem of a relative inefficiency of $\alpha_2\beta_2$ tetramer formation with β^S chains, that could lead to a relative and/or a dynamic excess of free α-Hb. In sickle cell disease, some cytosolic RBC proteins are upregulated such Alpha-Hemoglobin Stabilizing Protein (AHSP)[5] which not only specifically interacts with free α-Hb but also in the assembly of normal Hb tetramers.[6] Thus, the α-Hb pool could be a resultant of various genetic factors (HbF, α-thal, AHSP, HS-40…) modulating the SCA phenotype.

We postulated that the free soluble α-Hb (α-Hb pool) is increased in SCA patients (SS patients) and that the coinheritance of α-thal could significantly modulate this α-Hb pool.