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Authors

Saparia, Tina
Faughnan, Marie E
Schneider, Jennifer L
et al.

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Assessing the Hereditary Hemorrhagic Telangiectasia Algorithms in a Community-Based Patient Population

Tina Saparia, MD[1]; Marie E Faughnan, MD[2]; Jennifer L Schneider, MPH[3]; Lucy M Almers, MPH[3]; Norma Chow, MS LCGC[4]; Scott D Grosse, PhD[5]; Helen Kim, PhD[6]; Jonathan G Zaroff, MD[3]

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ABSTRACT

Introduction: Hereditary hemorrhagic telangiectasia (HHT) is a rare, genetic, and underdiagnosed disease that causes vascular malformations throughout the body. Two specific combinations of International Classification of Diseases, Ninth Revision-Clinical Modification diagnosis codes, the "HHT Algorithms" (HHTAs), were developed previously from a derivation cohort to help identify undiagnosed HHT cases.

Objectives: To test these 2 algorithms, and a third, newly designed HHTA, in an independent population with available clinical records and thus identify people who might have undiagnosed HHT.

Methods: The HHTAs were applied to the patient population of Kaiser Permanente Northern California. The HHTAs produced 3 groups (A, B, and C) using different combinations of diagnosis codes reflecting clinical manifestations of HHT. First, the number of Kaiser Permanente Northern California patients with each code was determined by database programming. Next, detailed chart review was performed, and patients with a Curaçao score of 2 or higher were considered to have possible HHT.

Results: Of 3,065,210 records queried, 163 patients met HHTA criteria. After chart review, the study identified 113 patients with possible undiagnosed HHT (Group A: n = 3, Group B: n = 3, Group C: n = 107).

Conclusion: Employing the HHTAs in this community-based population resulted in a modest yield of patients with possible HHT. Further research is required to assess the utility of the HHTAs in identifying patients with actual HHT.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an inherited disorder of blood vasculature, with an estimated prevalence of 1 in 5000 to 1 in 10,000 people worldwide. It is a highly penetrant disorder that causes diverse manifestations, including epistaxis (most commonly)[1]; telangiectasias caused by dilation of superficial capillaries usually in the nasal, oral, or gastric mucosa or the dermis of the hands or face; and arteriovenous malformations (AVMs) found in the lungs, brain, or liver, whose rupture can cause life-threatening complications, such as stroke and brain abscess.[2] Chronic gastrointestinal bleeding may result in the development of iron-deficiency anemia with advancing age. HHT may go unrecognized and untreated for decades and can cause premature death.[3-5] Among patients presenting before age 60 years, mortality is twice that expected in the general population and is directly attributed to severe manifestations of HHT such as gastrointestinal bleeding, cerebral hemorrhage, and pulmonary hemorrhage and/or hypoxemic respiratory failure caused by pulmonary AVMs.[6] HHT is underdiagnosed because physicians can fail to connect HHT's diverse manifestations as part of an underlying syndrome.

Previously, 2 specific combinations of International Classification of Diseases, Ninth Revision-Clinical Modification (ICD-9-CM) codes, the "HHT Algorithms" (HHTA Group A and Group B), were developed from an administrative database derivation cohort to help identify potential undiagnosed HHT cases.[7] The purpose of the present study was to test those 2 HHTAs in an independent population with available clinical records and thus identify people who might have undiagnosed HHT. In addition, a third HHTA (Group C) was designed for this study in an attempt to increase the sensitivity for detecting HHT. If data-mining using the HHTA in a clinical population could be established to be effective in identifying patients with undiagnosed HHT, it would likely represent a cost-effective strategy to prevent premature morbidity and mortality.

METHODS

We conducted a cross-sectional study of the Kaiser Permanente (KP) Northern California (KPNC) population, an integrated health services delivery organization. Containing approximately 4 million persons, KPNC's membership has demographics that closely approximate those of the underlying census population of Northern California.[8] Eligible subjects were all living adult (aged 21 years or older) members who were continuously enrolled in KPNC between January 2010 and May 2012 (allowing gaps of 6 months or less). In addition, the electronic medical record had to include the presence of at least 1 of the combinations of ICD-9-CM codes in the HHTAs listed in Table 1. Members with an ICD-9-CM diagnosis code for HHT (448.0) present in administrative data from January 2008 onward were excluded from this study.

In the first phase of this study, a KPNC database programmer/analyst queried the KPNC research databases to determine how

Author Affiliations

[1] Redwood City Medical Center, CA
[2] University of Toronto, Ontario, Canada
[3] Division of Research, Oakland, CA
[4] San Francisco Medical Center, CA
[5] US Centers for Disease Control and Prevention, Atlanta, GA
[6] University of California, San Francisco Center for Cerebrovascular Research

Corresponding Author

Jonathan G Zaroff, MD (jonathan.g.zaroff@kp.org)

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Table 1. Hereditary hemorrhagic telangiectasia algorithm definitions

HHTA Group	Clinical findings	ICD-9-CM coding
A	Pulmonary AVM *and* at least 1 of the following: Epistaxis, brain AVM, peripheral AVM, or gastrointestinal angiodysplasia	[747.3 or 417.0] *and* [784.7, 747.81, 747.6, 537.82, 537.83, 569.84, or 569.85]
B	Brain AVM *and* gastrointestinal angiodysplasia	747.81 *and* [537.82, 537.83, 569.84, or 569.85]
C	Epistaxis (≥ 2 encounters) *and* at least 1 of the following: Gastrointestinal angiodysplasia, peripheral AVM, or other unspecified capillary diseases	784.7 *and* [537.82, 537.83, 569.84, 569.85, 747.6, or 448.9]

AVM = arteriovenous malformation; HHTA = hereditary hemorrhagic telangiectasia algorithm; ICD-9-CM = International Classification of Diseases, Ninth Revision-Clinical Modification.

many KPNC members met the study inclusion criteria, according to the different HHTA groups.

In the second phase of the study, we performed a detailed review of all members' charts identified in Phase 1. During this process, the investigators (TS, JGZ) reviewed electronic medical records to verify each individual ICD-9-CM code in the HHTA identified for each member. Physician review (TS, JGZ) of clinical notes, encounters, imaging, and laboratory results was completed for subjects with verified codes. Data were collected from the medical records using an electronic case report form that included demographic data and the presence or absence of the following diagnostic Curaçao criteria for HHT: Epistaxis (at least 2 encounters < 7 days apart), telangiectasias (multiple, mucocutaneous), visceral AVM or gastrointestinal telangiectasias, and family history of HHT.[2,9] The Curaçao score was calculated, and the clinical diagnosis of HHT was considered possible when 2 or more of the criteria were present. A lack of information (eg, detailed family history) resulted in that criterion being considered absent. To ensure quality of chart review, all charts were reviewed by 2 physicians (TS, JGZ). When questions arose, those physicians consulted with another group of physician specialists with expertise in the diagnosis and management of HHT.

The statistical analysis for this study was descriptive. We reported the prevalence of each of the 3 HHTA (and each component ICD-9-CM code) in the KPNC population (per 10,000 people), stratified according to the age of the members at the time of our analysis. Finally, we reported the proportions of chart-reviewed cases with possible HHT for each HHTA category.

The Kaiser Foundation Research Institute's institutional review board (IRB) approved this study with a waiver of consent. When joining KP, most members give permission for database research to be done using their health information. The IRB thus approved the data-mining aims but would not approve patient contact with prospective testing for manifestations of HHT without research funding available to pay for the testing, which was beyond the budgetary scope of the present study. For patient safety, the IRB did approve communication from the study investigators to each subject's primary care practitioner about the data-mining results so that they could order HHT testing if clinically appropriate, but the results of clinically indicated testing could not be reviewed for research purposes as part of this research study. The study investigators and the IRB agreed that the potential benefit of preventing rare but dangerous complications in subjects with previously undiagnosed HHT outweighed any discomfort or anxiety the patients might experience by knowing the information was obtained from a data-mining study.

Table 2. Prevalence of hereditary hemorrhagic telangiectasia algorithm groups by age distribution

		Prevalence per 10,000			
Group	N	Total	Age ≤ 35 y	Age 36-50 y	Age > 50 y
Known HHT	129	0.421	0.246	0.414	0.792
Algorithm A	11	0.039	0.095	0	0.053
Algorithm B	9	0.029	0.000	0.015	0.071
Algorithm C	143	0.467	0.057	0.153	1.156

HHT = hereditary hemorrhagic telangiectasia.

RESULTS

The database program queried the charts of 3,065,210 adult KPNC members and identified 129 persons with an existing diagnosis (ICD-9-CM Code 448.0) of HHT (prevalence = 0.42/10,000), all of whom were excluded from the HHTA analysis.

The number of KPNC members meeting criteria for each of the HHTA is shown in Table 2 for the total and age-stratified populations. For HHTA Group C, there was a notable rise in population prevalence associated with increasing age. The mean age (standard deviation) for Group A was 61 (25) years, for Group B it was 65 (17) years, and for Group C it was 72 (15) years.

The distribution of the specific ICD-9-CM code combinations leading to inclusion into the 3 different HHTA groups is shown in Table 3. Using the HHTAs, we identified 11 KPNC members who met Group A criteria, 9 members who met Group B criteria, and 143 members who met Group C criteria (1 of whom was also identified by the Group B program). Most Group C cases (n = 99) had ICD-9-CM codes for epistaxis and "Other capillary diseases (unspecified)."

For the second (chart review) phase of the study, all patients meeting programmatic criteria for HHTA Groups A through C were chart reviewed. Chart review discovered 1 member, identified by both HHTA Group B and Group C, with known HHT that did not have ICD-9-CM code 448.0 in the patient's record, and that patient was excluded from the analysis. One individual met criteria for both Groups B and C, so the total chart review sample size was 162 members. These members had a mean age of 68 years (median = 71 years, range = 28-93 years). The distribution of self-identified race/ethnicity was as follows (> 1 response allowed): 48%, white; 22%, Latino; 13%, Asian; 13%, multiracial; 7%, African American; and 19%, unknown. A family history of HHT, brain AVM, or pulmonary AVM was not identified in any of the records that were reviewed.

The chart review results according to HHTA group are shown in Table 4. Programmatic false-positives were common. For example, it was discovered that the HHTA Group A program, which was previously published, had erroneously included ICD-9-CM code 747.3X (allowing both 747.31 and 747.32) instead of just 747.32.[7] Thus, 4 cases with code 747.31 (pulmonary artery coarctation and atresia) were accidentally included in HHTA Group A. The chart review evaluation of Group B revealed a high programmatic false-positive rate, generally because of cerebral aneurysms or other types of cerebral vascular abnormalities being miscoded (hospital coder error) as brain AVM. Programmatic false-positives owing to other confounding disease processes causing the finding of interest were also common. For example, the program identified several people who had hepatic cirrhosis as the cause of pulmonary AVMs, skin abnormalities, and vascular abnormalities of the gastrointestinal tract. After exclusion of these patients, a total of 113 patients met our definition of possible HHT with a Curaçao score of 2 or greater. The primary care practitioners for these members were notified so that the patients could be referred for appropriate clinical evaluation.

Table 3. Distribution of ICD-9-CM code combinations in each hereditary hemorrhagic telangiectasia algorithm group

Group	ICD-9-CM codes	Diagnoses	N
A (n = 11)	(747.3 or 417.0) + 784.7	Pulm AVM + epistaxis	8
	(747.3 or 417.0) + 747.81	Pulm AVM + brain AVM	2
	(747.3 or 417.0) + 537.82	Pulm AVM + GIAng	1
B (n = 9)	747.81 + 537.82	Brain AVM + upper GIAng	4
	747.81 + 569.84	Brain AVM + GIAng	5
C (n = 143)	784.7 + 53782	Epistaxis + upper GIAng	17
	784.7 + 53783	Epistaxis + upper GIAng w/ hemorrhage	3
	784.7 + 56984	Epistaxis + GIAng	17
	784.7 + 56985	Epistaxis + GIAng w/ hemorrhage	7
	784.7 + 4489	Epistaxis + other capillary diseases	99

AVM = arteriovenous malformation; GIAng = gastrointestinal angiodysplasia; ICD-9-CM = International Classification of Diseases, Ninth Revision-Clinical Modification; Pulm = pulmonary; w/ = with.

Table 4. Chart review outcomes according to hereditary hemorrhagic telangiectasia algorithm group

	HHTA Group		
Outcome	A	B	C
Total charts reviewed	11	9	143
False-positives	8	6	36
Possible HHT (Curaçao score ≤ 2)	3	3	107
Pulmonary AVM	3	0	0
Brain AVM	0	3	3
Spinal AVM	0	0	4
Hepatic AVM	0	0	4

AVM = arteriovenous malformation; HHT = hereditary hemorrhagic telangiectasia; HHTA = hereditary hemorrhagic telangiectasia algorithm.

DISCUSSION

This study's database program found a diagnosed HHT prevalence of 0.42 per 10,000, or approximately 1 per 24,000, in the adult KPNC population who satisfied the study's membership criterion. This result is substantially lower than the likely true prevalence of HHT (1 in 5000 to 1 in 8000).[6,10-13] It is virtually identical, though, to that found among adults in the published analysis of nationwide IBM MarketScan claims data (IBM Corp, Armonk, NY).[7] Thus, it is very likely that there are numerous KPNC members with undiagnosed HHT, just as in the general US population with health insurance. The objective of this study was to attempt to close that gap by identifying KPNC members likely to have HHT on the basis of signs and symptoms of HHT recorded in medical records.

The chart review evaluation unearthed a variety of issues leading to false-positive programmatic designation into the HHTA groups, including an erroneous ICD-9-CM code in the program, hospital miscodes, and the confounding presence of hepatic cirrhosis, which may result in pulmonary AVM formation and gastrointestinal bleeding. Future studies of the HHTAs might thus consider adding an ICD-9-CM code for hepatic cirrhosis as a programmatic exclusion criterion.

The chart review evaluation of Group C patients revealed a lower (25%) false-positive programming rate than for Groups A and B patients, although the majority (69%) of cases without miscodes had abnormalities limited to less-specific HHT findings, such as skin telangiectasias, epistaxis, and/or gastrointestinal angiodysplasia. Thus, it is unlikely that a large proportion of the Group C cases actually have undiagnosed HHT, despite having a Curaçao score of 2 (in most cases) or greater by chart review.

This study has several important limitations, mostly related to its retrospective design. First, not all patients with known HHT or the component findings of the HHTAs have the appropriate ICD-9-CM code linked into their medical records, because of coding errors. Second, family history is generally underdocumented in KPNC medical records, limiting the chance of finding a family history of HHT, brain AVM, or pulmonary AVM by retrospective chart review. Third, epistaxis and gastrointestinal angiodysplasia are not specific to HHT and likely become more commonly coded in the charts of older patients who have accrued many office visits during their years of KPNC membership. Thus, HHTA Group C may be more likely to identify elderly patients without HHT than patients who truly have HHT.

Finally, the clinical evaluations to determine whether the patients identified in this research study actually have HHT are ongoing, and the findings of those evaluations are beyond the scope and IRB approval of this retrospective research study. As stated earlier, there was no IRB approval for direct patient contact by the study investigators to encourage patients to get further testing or to complete surveys. In other words, the present study was designed to test the HHTAs to the level of retrospective chart review without patient contact. A future study will be required to describe the results of clinical testing and outcomes in this population.

CONCLUSION

The HHTAs identified a modest number of patients with possible HHT in this community-based retrospective cohort study. The HHTAs also identified patients who clearly did not have HHT but did have hospital coding errors leading to cohort inclusion or confounding conditions mimicking the effects of HHT, such as hepatic cirrhosis. Further examination of the HHT algorithms using a prospective study design allowing for patient contact, a detailed family history, and HHT-specific testing would likely be informative. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Compliance with Ethics Guidelines

No human subjects research was involved in this study by any of the authors. The Kaiser Foundation Research Institute's institutional review board approved this study with a waiver of consent.

How to Cite this Article

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References

1. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: An overview of diagnosis, management, and pathogenesis. Genet Med 2011 Jul;13(7):607-16. DOI: https://doi.org/10.1097/gim.0b013e3182136d32.
2. Faughnan ME, Palda VA, Garcia-Tsao G, et al; HHT Foundation International-Guidelines Working Group. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. J Med Genet 2011 Feb;48(2):73-87. DOI: https://doi.org/10.1136/jmg.2009.069013.
3. Pierucci P, Lenato GM, Suppressa P, et al. A long diagnostic delay in patients with hereditary haemorrhagic telangiectasia: A questionnaire-based retrospective study. Orphanet J Rare Dis 2012 Jun 7;7:33. DOI: https://doi.org/10.1186/1750-1172-7-33.
4. Latino GA, Brown D, Glazier RH, Weyman JT, Faughnan ME. Targeting underdiagnosis in hereditary hemorrhagic telangiectasia: A model approach for rare diseases? Orphanet J Rare Dis 2014 Jul 25;9:115. DOI: https://doi.org/10.1186/s13023-014-0115-7.
5. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. Complications and mortality in hereditary hemorrhagic telangiectasia: A population-based study. Neurology 2015 May 5;84(18):1886-93. DOI: https://doi.org/10.1212/wnl.0000000000001538.
6. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: A population-based study of prevalence and mortality in Danish patients. J Intern Med 1999 Jan;245(1):31-9. DOI: https://doi.org/10.1046/j.1365-2796.1999.00398.x.
7. Grosse SD, Boulet SL, Grant AM, Hulihan MM, Faughnan ME. The use of US health insurance data for surveillance of rare disorders: Hereditary hemorrhagic telangiectasia. Genet Med 2014 Jan;16(1):33-9. DOI: https://doi.org/10.1038/gim.2013.66.
8. Krieger N. Overcoming the absence of socioeconomic data in medical records: Validation and application of a census-based methodology. Am J Public Health 1992 May;82(5):703-10. DOI: https://doi.org/10.2105/ajph.82.5.703.
9. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000 Mar 6;91(1):66-7. DOI: https://doi.org/10.1002/(sici)1096-8628(20000306)91:1<66::aid-ajmg12>3.0.co;2-p.
10. Bideau A, Plauchu H, Brunet G, Robert J. Epidemiological investigation of Rendu-Osler disease in France: Its geographical distribution and prevalence. Popul 1989 Sep;44:3-22.
11. Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. Hum Mutat 2002 Feb;19(2):140-8. DOI: https://doi.org/10.1002/humu.10026.
12. Guttmacher AE, Marchuk DA, White RI Jr. Hereditary hemorrhagic telangiectasia. N Engl J Med 1995 Oct 5;333(14):918-24. DOI: https://doi.org/10.1056/nejm199510053331407.
13. Westermann CJ, Rosina AF, De Vries V, de Coteau PA. The prevalence and manifestations of hereditary hemorrhagic telangiectasia in the Afro-Caribbean population of the Netherlands Antilles: A family screening. Am J Med Genet A 2003 Feb 1;116A(4):324-8. DOI: https://doi.org/10.1002/ajmg.a.10002.