Complications and mortality in hereditary hemorrhagic telangiectasia

A population-based study

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ABSTRACT

Objectives: Studies report that the risks of significant neurologic complications (including stroke, cerebral abscess, and migraine) and hemorrhagic sequelae are high in patients with hereditary hemorrhagic telangiectasia (HHT), and that life expectancy in this cohort is reduced. However, most published cohorts derive from specialist centers, which may be susceptible to bias.

Methods: We used a population-based approach to estimate the risks of developing neurologic and hemorrhagic complications of HHT, the association of a diagnosis of HHT with common cardiovascular and malignant comorbidities, and also long-term survival of those with the disease.

Results: From a UK primary care database of 3.5 million patients (The Health Improvement Network), we identified 675 cases with a diagnosis of HHT and compared them with 6,696 controls matched by age, sex, and primary care practice. Risks of stroke (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.2–2.6), cerebral abscess (OR 30.0, CI 3.1–288), and migraine (OR 1.7, CI 1.3–2.2) were elevated over controls. Bleeding complications including epistaxis (OR 11.6, CI 9.1–14.7) and gastrointestinal hemorrhage (OR 6.1, CI 2.8–13.4) were more common in cases with HHT. Survival of cases with HHT was poorer than controls with a hazard ratio for death of 2.0 (CI 1.6–2.6) and a median age at death 3 years younger.

Conclusions: Patients with HHT are at substantially increased risk of serious neurologic and hemorrhagic complications of the disease. Because a diagnosis of HHT is associated with a significantly poorer survival compared with those who have no disease, evaluation of new strategies to improve clinical management is required. *Neurology*® 2015;84:1886–1893

GLOSSARY

AVM = arteriovenous malformation; **CI** = confidence interval; **HHT** = hereditary hemorrhagic telangiectasia; **HR** = hazard ratio; **OR** = odds ratio; **THIN** = The Heath Improvement Network.

Hereditary hemorrhagic telangiectasia (HHT) is a dominantly inherited genetic disorder of blood vessel development characterized by epistaxis, mucocutaneous telangiectasia, and visceral arteriovenous malformations (AVMs). It is estimated that between 1% and 10% of patients with HHT have cerebral AVMs,[1–3] and between 15% and 45% develop pulmonary AVMs.[4,5] Neurologic complications of HHT attributed to these AVMs include embolic stroke,[6] cerebral abscess,[7,8] migraine,[9,10] hemorrhagic stroke,[2] and seizures.[3] Although relatively rare compared with other causes of stroke, AVMs are causally important because they have the potential to be identified and treated in high-risk patients before complications develop. While embolization of pulmonary AVMs may be associated with a reduced risk of neurologic sequelae,[6] no consensus exists as to the optimal management of cerebral AVMs.[11,12]

Many of the observational studies of the natural history of HHT are published from specialist centers and are potentially susceptible to selection bias if the more severe cases are referred for specialist care, possibly leading to an overestimate of the frequency and severity of complications identified. While HHT undoubtedly causes significant morbidity in some, there are relatively few published studies that have looked at survival in patients with the disease,[13–16] the largest of which included 113 individuals, limiting the provision of reliable estimates.[16] Using a

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

population-based UK primary care database (The Heath Improvement Network [THIN]), we undertook a matched case-control analysis to investigate the association of various complications and comorbidities with a diagnosis of HHT, and to provide a population-based estimate of survival in 675 individuals with HHT compared with age- and sex-matched controls.

METHODS THIN is a computerized primary care database collecting information on patient demographics, diagnoses, consultations (both in primary and secondary care), and prescriptions. Data are entered prospectively by family physicians at the point of care or, if derived from secondary care correspondence, are entered retrospectively by administrative staff. The THIN database has been validated for use in epidemiologic research using associations observed in external primary care datasets replicated in THIN[17] and by auditing patients' medical records and comparing them with THIN data.[18] Although the THIN database was officially launched in 2003, many practices in the United Kingdom were already using computerized software to collect clinical information with some providing data to THIN dating back as far as 1985. At the time of data extraction (September 2011), THIN covered 5% of the UK population with 3.5 million people contributing data across 550 primary care practices,[19] and is representative of the UK population.[20,21] We have recently used THIN to estimate the prevalence of HHT in the United Kingdom.[22]

Case-control set. Cases were defined as those with a diagnosis of HHT or Rendu-Osler-Weber disease coded in their THIN computerized records between January 1, 1985, and September 1, 2011. THIN collects most data contemporaneously, although in some cases historical data (from consultations before the start of a practice contributing to THIN) are available because they have been retrospectively added to the database. For the majority of patients, an index date was set as the first recorded diagnosis of HHT appearing in their existing records and they were categorized as "contemporaneous" cases. If a diagnosis of HHT was made before a patient's practice began contributing to THIN, then the date the practice joined THIN and started to provide longitudinal data was set as the index date (these individuals were categorized as "historical" cases). Each case had a stop date defined as either the last date of data collection within THIN or the date of death. Up to 10 control subjects who did not have a coded diagnosis of either HHT or pulmonary AVMs and who were alive and contributing data on each case's index date were matched to cases by age, sex, and primary care practice.

Data extraction and processing. We extracted data on age (grouped in 3 categories: younger than 15 years, 15–49 years, and 50 years and older), sex, socioeconomic status (as defined by Townsend score in quintiles,[23] including a category for missing data), geographical location (defined by UK Health Authority), smoking status (never smoker, ex-smoker, current smoker, or unknown status), any complications potentially related to HHT (anemia, cerebral abscess, dyspnea, epistaxis, gastrointestinal bleeding, hemoptysis, intracerebral hemorrhage, migraine, seizure, stroke, and TIA), common cardiovascular comorbidities (ischemic heart disease, myocardial infarction, cardiac failure, and venous thromboembolism), and solid organ cancers (breast, lung, prostate, and bowel). The occurrence of any complication was counted only once for each HHT case or control. Date of death was extracted for any case or control that died while contributing data to THIN.

Data analysis. Conditional logistic regression was used to quantify the association between a diagnosis of HHT and the occurrence of the differing complications potentially associated with the disease when compared with control subjects. THIN provided information on smoking status, diabetes, and hypertension, which were considered as possible a priori confounding variables for some complications. Only smoking status differed significantly between the cases and control groups and as such we adjusted all crude odds ratios (ORs) solely for smoking status. Survival analysis was performed using Kaplan–Meier methods, comparing individuals who had HHT with controls. Start date was set as the index date (defined above) and end date was date of death or loss to follow-up. Cox regression analysis was used to compare mortality rates between the 2 groups adjusting for smoking status. We looked at survival differences stratified by sex and socioeconomic group among the cases with HHT and also explored survival of cases younger than 60 years vs those 60 years and older at the time of inclusion to the database, as a previous study had reported a survival paradox with a subset of younger patients with HHT having a higher mortality.[14] The Cox proportional hazards assumption was tested using log-minus-log plots of survival and Schoenfeld residuals. A sensitivity analysis was undertaken to look at complication rates and survival outcomes in the contemporaneous cases with HHT and the historical cases with HHT. No interactions were considered in the statistical analysis plan. Data analysis was performed using Stata statistical software version 12.0 (StataCorp, College Station, TX). The study was covered by appropriate ethical approval.

RESULTS Six hundred seventy-five individuals with a diagnosis of HHT or Rendu-Osler-Weber disease were identified, together with a total of 6,696 controls. The mean age of individuals with HHT was 53.8 years (SD 23.0 years) and 63% were female. Cases had a similar socioeconomic distribution and a lower proportion of never smokers (38.5% vs 42.4%) compared with controls (table 1).

Complications. Univariate analysis determined that ORs for several complications were significantly higher in cases with HHT than in matched controls, including neurologic sequelae (cerebral abscess, migraine, and ischemic/embolic stroke) and bleeding complications (anemia, epistaxis, hemoptysis, and gastrointestinal hemorrhage) (table 2). We did not detect significantly increased odds of seizures, intracerebral hemorrhage, TIA, or venous thromboembolism in individuals with HHT. After adjustment for smoking as a confounder, most ORs did not change appreciably. The adjusted OR for cardiac failure was higher in those with HHT, although not that of ischemic heart disease or myocardial infarction. The odds of colon cancer in individuals with HHT were higher than those in controls, but there was no detectable difference in rates of other solid organ tumors.

Table 1 Characteristics of cases and controls

	Cases (n = 675)	Controls (n = 6,696)	OR (95% CI)
Mean age, y	53.8 (SD 23.0)	53.9 (SD 22.8)	
Age group, y			
<15	29 (4.3)	269 (4.0)	Matching variable
15-49	256 (38.0)	2,547 (38.0)	
50+	390 (58.0)	3,880 (58.0)	
Sex			
Male	249 (36.9)	2,469 (36.9)	Matching variable
Female	426 (63.1)	4,227 (63.1)	
Socioeconomic status			
1 (least deprived)	182 (27.0)	1,899 (28.4)	Reference
2	134 (19.9)	1,423 (21.3)	1.00 (0.79-1.28)
3	133 (19.7)	1,250 (18.7)	1.14 (0.89-1.46)
4	111 (16.4)	1,068 (16.0)	1.13 (0.86-1.48)
5 (most deprived)	67 (9.9)	671 (10.0)	1.10 (0.79-1.53)
Missing	48 (7.1)	385 (5.75)	1.62 (1.03-2.55)
Smoking status			
Never smoker	260 (38.5)	2,841 (42.4)	Reference
Ex-smoker	161 (23.9)	1,231 (18.4)	1.47 (1.19-1.83)
Current smoker	114 (16.9)	1,078 (16.1)	1.17 (0.92-1.48)
Unknown/missing	140 (20.7)	1,546 (23.1)	0.93 (0.72-1.19)
Diabetes			
Never coded as diabetic	619 (91.7)	6,233 (93.1)	Reference
Ever coded as diabetic	56 (8.3)	463 (6.9)	1.24 (0.92-1.67)
Hypertension			
Never coded as hypertensive	531 (78.7)	5,258 (78.5)	Reference
Ever coded as hypertensive	144 (21.3)	1,438 (21.5)	0.98 (0.78-1.23)

Abbreviations: CI = confidence interval; OR = odds ratio.
Data are n (%) unless otherwise indicated.

Survival analysis. The median follow-up time was 6.9 years for cases, 10.1 years for controls, 6.5 years for historical cases, and 8.2 years for contemporaneous cases. A total of 75 cases with HHT (11.1%) and 488 controls (7.3%) died. The overall crude mortality rate in cases with HHT was 11.0 per 1,000 patient-years (95% confidence interval [CI] 8.8–13.9), and in their matched controls the comparable figure was 6.1 per 1,000 patient-years (CI 5.5–6.6). We found a worse survival in patients with HHT compared with their age-, sex-, and practice-matched controls with a hazard ratio (HR) for death of 2.03 (CI 1.59–2.60, $p < 0.0001$) (figure). The proportional hazards assumption did not hold true for these data and thus the adjusted HRs were split into 3 time periods of follow-up demonstrating a higher mortality in the time period closest to a recorded diagnosis of HHT: 0–3 years (HR 4.57, CI 2.56–8.18, $p < 0.001$), 3–10 years (HR 2.07, CI 1.42–2.99, $p < 0.001$), and 10 or more years (HR 1.45, CI 0.95–2.21, $p < 0.001$). Median age at death was 77 years for cases with HHT (interquartile range 67–85 years) and 80 years for controls (interquartile range 74–87 years). Survival in cases with HHT did not differ between males and females (HR 1.06, CI 0.66–1.70, $p = 0.825$) but was higher in those from the most affluent socioeconomic group compared with the least (HR 1.15, CI 1.04–1.27, $p = 0.007$). After stratification by age, mortality was increased for both those aged 60 years and older on entry to the study (HR 1.60, CI 1.17–2.21, $p = 0.004$) and for those younger than 60 years compared with matched controls (HR 6.74, CI 4.2–10.8, $p < 0.0001$).

Sensitivity analysis. Three hundred seventy-three (55%) cases of HHT had a contemporaneous diagnosis within THIN, with the remaining 302 (45%) cases of HHT coded as historical. ORs for complications in

Table 2 Crude and adjusted ORs of complications in cases with HHT vs controls

Complication	Cases (n = 675), n (%)	Controls (n = 6,696), n (%)	Crude OR (95% CI)	p Value	Adjusted OR[a] (95% CI)	p Value
Neurologic						
Stroke	37 (5.5)	212 (3.2)	1.81 (1.25–2.66)	0.002	1.76 (1.20–2.58)	0.004
TIA	14 (2.1)	92 (1.4)	1.56 (0.87–2.82)	0.146	1.52 (0.84–2.76)	0.167
Intracerebral hemorrhage	4 (0.6)	20 (0.3)	2.00 (0.68–5.85)	0.21	1.99 (0.68–5.84)	0.21
Cerebral abscess	3 (0.4)	1 (0.01)	30.0 (3.12–288.4)	0.003	29.3 (3.03–282.8)	0.004
Migraine	71 (10.5)	448 (6.7)	1.68 (1.28–2.20)	<0.001	1.67 (1.29–2.20)	<0.001
Seizure	8 (1.2)	62 (0.9)	1.29 (0.61–2.71)	0.50	1.26 (0.60–2.66)	0.54
Hemorrhagic						
Anemia	135 (20.0)	401 (6.0)	4.42 (3.51–5.55)	<0.001	4.41 (3.50–5.56)	<0.001
Epistaxis	177 (26.2)	230 (3.4)	11.6 (9.10–14.7)	<0.001	11.4 (8.99–14.5)	<0.001
Gastrointestinal hemorrhage	10 (1.5)	16 (0.2)	6.08 (2.75–13.4)	<0.001	6.13 (2.76–13.6)	<0.001
Hemoptysis	16 (2.4)	77 (1.2)	2.13 (1.23–3.70)	0.007	1.99 (1.14–3.46)	0.015
Cardiovascular comorbidities						
Cardiac failure	30 (4.4)	141 (2.1)	2.39 (1.53–3.71)	<0.001	2.37 (1.53–3.70)	<0.001
Ischemic heart disease	53 (7.9)	429 (6.4)	1.25 (0.90–1.72)	0.184	1.19 (0.86–1.65)	0.289
Myocardial infarction	33 (4.9)	217 (3.2)	1.53 (1.03–2.27)	0.034	1.46 (0.98–2.17)	0.06
Venous thromboembolism	18 (2.7)	154 (2.3)	1.18 (0.71–1.94)	0.527	1.12 (0.68–1.86)	0.643
Malignancies						
Lung cancer	5 (0.7)	37 (0.6)	1.36 (0.53–3.49)	0.524	1.20 (0.46–3.08)	0.712
Breast cancer	10 (1.5)	117 (1.8)	0.85 (0.44–1.63)	0.623	0.86 (0.45–1.65)	0.647
Prostate cancer	3 (0.4)	56 (0.8)	0.50 (0.15–1.63)	0.25	0.49 (0.15–1.60)	0.235
Colon cancer	6 (0.9)	22 (0.3)	2.76 (1.11–6.85)	0.029	2.76 (1.10–6.90)	0.03

Abbreviations: CI = confidence interval; HHT = hereditary hemorrhagic telangiectasia; OR = odds ratio.
[a] Adjusted for smoking status using conditional logistic regression.

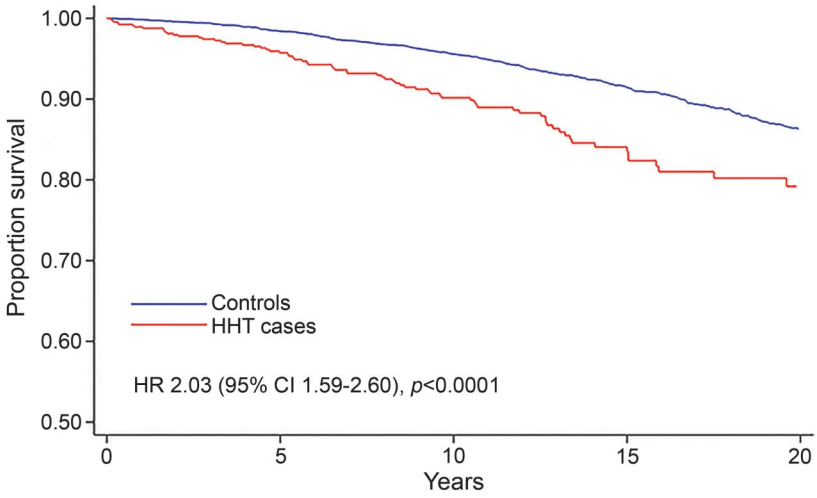
HHT were similar between contemporaneously and historically diagnosed patients (data not shown). Survival in contemporaneous cases was worse than in their matched controls (HR 1.61, CI 1.13–2.30, $p = 0.008$) and the same pattern was evident when looking at the survival of historical cases compared with controls (HR 2.57, CI 1.81–3.66, $p < 0.0001$). Age-adjusted survival in historically diagnosed HHT cases was worse than that in those diagnosed contemporaneously (HR 2.93, CI 1.80–4.75, $p < 0.0001$).

DISCUSSION We have identified several neurologic sequelae (migraine, cerebral abscess, and stroke) and bleeding complications (anemia, epistaxis, and gastrointestinal bleeding) that are more common in patients with HHT. We observed a 2-fold increase in mortality in patients with HHT compared with controls.

The strengths of this study are the combination of a relatively large number of participants (containing data from almost 700 patients with HHT) and the long period of follow-up—in excess of 20 years for some—which would be more challenging to achieve in a prospectively designed clinical study. Our findings are population-based and hence provide representative estimates for complications and survival for the UK population, minimizing certain biases that can arise as a consequence of case-series analysis from specialist centers. The case-control design allows comparative estimates of relative risk to be made against a matched control group providing new data in addition to those generated by previous studies that mainly used descriptive analyses of complication frequencies in HHT-only cohorts. Our survival analysis compares mortality between cases with HHT and matched controls from the general population rather than relying on estimated life expectancies from life tables[14] and includes a population more than 10 times larger than the previous largest case-control study estimating survival.[15]

The potential limitations of this study require consideration. We were only able to study individuals clinically diagnosed with HHT. However, we expect a diagnosis of HHT recorded in THIN to have a relatively high specificity because in the UK National Health Service we anticipate that most diagnoses will be made in secondary care in conjunction with

Figure Kaplan-Meier plot of survival from index date among cases with HHT compared with age-, sex-, and primary care-matched controls



Index date is the first recorded diagnosis of HHT appearing in health records (if a "contemporaneous" case). If a diagnosis of HHT was made before a patient's practice joined the THIN database (a "historical" case), the index date was the date the practice started contributing longitudinal data to THIN. The index date for controls was defined as the index date of the matched case. CI = confidence interval; HHT = hereditary hemorrhagic telangiectasia; HR = hazard ratio; THIN = The Heath Improvement Network.

clinical genetics physicians, with details on diagnosis and complications sent back to the primary care physician. Hence, we consider it unlikely that a primary care physician would code a patient as having HHT unless supported by evidence from a specialist center. Nonetheless, we acknowledge that in the absence of external validation of our cases of HHT, we cannot exclude the possibility of a small degree of diagnostic misclassification that if present may reduce the size of associations observed. We are also unable to exclude the possibility that patients with HHT may visit their primary care physician more often, and may be more likely to have some of the minor complications diagnosed at a lower threshold than the control population. However, we believe this is unlikely for the more severe events, such as cerebral abscess, stroke, and death, which are usually events noted in a secondary care setting and subsequently recorded in primary care records. We did not detect an increased risk of certain complications (such as intracerebral hemorrhage) that are well-documented possible sequelae of HHT.[3] This may reflect issues of ascertainment inherent in primary care databases resulting from the miscoding of complications (e.g., coding intracerebral hemorrhage as stroke). Finally, although our data show a higher mortality in patients with HHT compared with controls, we are not able to comment on whether this poorer survival is related directly to complications of HHT because we could not access patients' clinical notes or death certification to confirm the cause of death. A previous study found that slightly more than a third of deaths in patients with HHT could be attributed directly to complications of the disease.[14] We used all available data, and as a consequence there was no power calculation, and the uncertainty of the estimates is indicated by the 95% CIs.

We found a higher risk of neurologic (cerebral abscess, stroke, and migraine) and bleeding complications (anemia, epistaxis, hemoptysis, and gastrointestinal hemorrhage) in individuals who had HHT compared with controls. A recent epidemiologic study using US health insurance data for surveillance of HHT and its complications found the disease, and hence its complications, to be underrecognized in this database.[24] This may be a consequence of the relatively high costs of US health insurance, because individuals unable to afford health insurance are likely to be underrepresented in the dataset. The UK National Health Service has a much wider coverage, with close to 98% of the population registered with a general practitioner.[25] Most published work looking at complications in the disease are descriptive analyses in cohorts often recruited from specialist HHT centers. On comparing the prevalences of clinical complications, most of our estimates are lower than those cited in the existing literature (table 3). We deliberately included for comparison only studies in which the prevalence of cerebral and pulmonary AVMs in the HHT population was not stated because we did not have this information available for our cohort. The lower prevalence of identified complications in our study may be a consequence of the ascertainment of complications being lower in a primary care database than in a clinical study with access to detailed clinical data that are collected in secondary and tertiary medical care centers. Alternatively, previous studies may have overestimated the prevalences of complications because of a referral and selection bias if more complicated or severe cases are seen in the specialist centers from which the cohort is derived. It is widely acknowledged that many cases of HHT in the general population remain undiagnosed. While some symptomatic patients presenting to health care services elude diagnosis because clinicians do not have a sufficiently high index of suspicion for HHT, there are likely to be other HHT gene carriers who remain undiagnosed simply because they display a milder phenotype of the disease.

We noted higher odds of colonic carcinoma in our cases with HHT (in approximately 1%), which may be a true association or alternatively be the consequence of misclassification with juvenile polyposis syndrome, a disease known to be associated with the HHT phenotype via a shared mutation in the *SMAD4* gene.[26,27] Juvenile polyposis syndrome is associated with up to 40% increased risk of colon

Table 3 Comparison of our prevalence estimates for complications of hereditary hemorrhagic telangiectasia with those made in other studies (excluding any that confirmed the presence of pulmonary arteriovenous malformations)

Complication	Donaldson (current study), %	Range of estimates from other literature, %	References
Stroke	5.5	7.2-9	6, 9, 32
TIA	2.1	4.1	9
Intracerebral bleed	0.6	2.1	3
Cerebral abscess	0.4	0.03-9.1	6, 7, 33-35
Migraine	10.5	33-40	10, 36
Anemia	20	29	37
Epistaxis	26.2	90-99	37-39
Gastrointestinal bleeding	1.5	13-30	38, 40

cancer,[28] and this may explain the increase in bowel cancer risk observed in our population.

Overall, our data from a population-based sample of patients with HHT suggest that the risks of complications of HHT may not be as high as previous studies have suggested. Future work could help to further validate our findings by accessing the primary and secondary care records of the individuals in the THIN database included in this study, although previous audit has shown a relatively high level of completeness of clinical diagnostic data.[29]

Our data demonstrate that patients with HHT have a poorer survival compared with controls. Median age at death was 77 years in cases with HHT compared with 80 years in controls, a decrease of 3 years. The published literature of survival in HHT is relatively small, consisting of 3 articles[13–15] and an abstract[16] studying a total of 283 cases, compared with our analysis of 675 individuals who had the disease. These studies have either compared survival in HHT cases with that in matched controls[14,15] or have examined the parents of HHT-affected offspring and compared the age at death of parents who had HHT with that of parents without the disease[13,16] (studies summarized in table 4). In our data, the HRs for death were highest in the 3 years after initial diagnosis and decline latterly, which may reflect the nature in which some patients with HHT are diagnosed, for example, after a life-limiting complication such as stroke. Our data pertain to the presence or absence of a recorded diagnosis of HHT, and hence we were unable to explore the impact of any differences in clinical management strategies.

A substantial number of the patients with HHT included in THIN had a historical rather than contemporaneous date of diagnosis. While both groups had worse survival than their matched controls, the HR for death was almost 3 times as high in the historically diagnosed group of HHT cases compared with the contemporaneous cases. This may be explained by more severe or symptomatic disease in the historical cases as a consequence of presentation earlier in life compared with those who were diagnosed as incident

Table 4 Summary of studies of survival in HHT

Year published	Authors	Study size (cases)	Methodology	Cases vs controls	Mean Follow-up, y	Mean difference in age at death in cases vs controls (reduction in years)
2014	Donaldson et al. (current study)	675	Prospective epidemiologic study	HHT cases vs age-, sex-, and primary care-matched controls	11.7[a]	3.0[b]
2010	Edwards et al.[16]	113	Cross-sectional questionnaire study of HHT offspring	HHT-affected parents vs unaffected parents	NA	8.3
2006	Sabba et al.[13]	40	Retrospective clinical study	HHT-affected parents vs unaffected parents	NA	6.8[b]
2005	Kjeldsen et al.[15]	73	Prospective clinical/epidemiologic study	HHT cases vs age-, sex-, and location-matched controls	7.5	0
1999	Kjeldsen et al.[14]	57	Prospective clinical/epidemiologic study	HHT cases vs "expected mortality" calculated from life table analysis	21	NA

Abbreviation: HHT = hereditary hemorrhagic telangiectasia; NA = not available.
[a] Median follow-up.
[b] Median age at death.

cases during the course of our period of data collection. This is consistent with our clinical experience that developments such as the formulation of the diagnostic Curaçao criteria,[30] publication of international guidelines for the diagnosis and management of HHT,[31] increasing use of genetic testing, and, perhaps, an increased awareness of the disease, have contributed to diagnosis of more patients before they are severely symptomatic.

We present evidence from a large, representative primary care database confirming that on average a diagnosis of HHT is associated with a 3-year reduction in median age at death and providing quantitative estimates of complication risks in HHT compared with matched controls. While some patients undoubtedly experience significant morbidity due to HHT, our study suggests that complication rates among the diagnosed population may not be as high as previously thought. This may change the information provided in counseling newly diagnosed patients when discussing the natural history of the disease. Because many of these complications are amenable to intervention, early diagnosis and treatment should remain the priority for responsible clinicians.

AUTHOR CONTRIBUTIONS

J.D. (guarantor) was involved in the study design, performed the majority of the data processing and analysis, and drafted the manuscript. A.F., T.M., and R.H. contributed to the study design and interpretation of findings. All authors were involved in revising and approving the manuscript before submission.

STUDY FUNDING

This research was funded jointly by the University of Nottingham and Nottingham University Hospitals NHS Trust. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received July 24, 2014. Accepted in final form January 27, 2015.

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