

The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: A population-based study.

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JD (Guarantor) was involved in the study conception and design, performed the majority of the data processing and analysis and drafted the manuscript. CS retrieved the data. AF, TM

and RH contributed to the study design and interpretation of findings. All authors were involved in revising and approving the manuscript before submission.

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What is the key question?

What is the current prevalence of Hereditary Haemorrhagic Telangiectasia (HHT) in the UK and how does it vary with respect to age, sex, socioeconomic status and geographical location?

What is the bottom line?

Using a representative UK general practice database we estimate the prevalence of HHT to be at least 1 per 9,500 which is more common than previously documented in the UK, though still likely to represent an underestimate of the true prevalence.

Why read on?

We identify particular under-recognition in the diagnosis of HHT in males and those from less affluent socioeconomic groups with a significant variation in diagnostic rates between different geographical regions of the UK.

ABSTRACT

Background

Hereditary Haemorrhagic Telangiectasia (HHT) is an autosomal dominant genetic disorder of aberrant blood vessel development characterised by arteriovenous malformations. HHT is associated with significant morbidity due to complications including epistaxis, gastrointestinal bleeding and stroke and may be associated with reduced life expectancy. We explored the hypothesis that a diagnosis of HHT is associated with sex, socioeconomic status and geographical location.

Methods

We used The Health Improvement Network, a longitudinal, computerised general practice database covering 5% of the UK population to calculate prevalence estimates for HHT stratified by age, sex, socioeconomic status and geographical location.

Results

The 2010 UK point prevalence for HHT was 1.06 per 10,000 person years [95% confidence interval (CI): 0.95-1.17] or 1 in 9400 individuals. The diagnosed prevalence of HHT was significantly higher in females compared to males [adjusted prevalence rate ratio (PRR) 1.53, 95% CI: 1.24-1.88] and in those from the most affluent socioeconomic group compared to the least [adjusted PRR 1.74, 95% CI: 1.14-2.64]. The PRR varied between different regions of the UK being highest in the South West and lowest in the West Midlands [adjusted PRR for former compared to latter 1.86, 95% CI: 1.61-2.15].

Conclusions

HHT is much more common in the UK population than previously demonstrated, though this updated figure is still likely to be an underestimate of the true prevalence. HHT appears to be significantly under-diagnosed in men which is likely to reflect their lower rates of consultation with primary care services, though it is possible that there may be a gender differential in disease severity and hence presentation. There is significant under-diagnosis in patients from lower socioeconomic groups and a marked variation in the prevalence of diagnosis between different geographical regions across the UK that requires further investigation.

INTRODUCTION

Hereditary Haemorrhagic Telangiectasia (HHT) is an autosomal dominant genetic disorder of blood vessel development characterised by mucocutaneous telangiectases and by arteriovenous malformations (AVMs) in solid organs[1, 2]. HHT is associated with significant morbidity due to bleeding complications such as epistaxis and gastrointestinal haemorrhage and from embolic complications including cerebral abscess and stroke[3], which are often associated with pulmonary arteriovenous malformations (PAVMS)[4]. HHT may also be associated with reduced life expectancy[5, 6].

HHT can be identified by clinical or genetic screening of family members of affected individuals but is too often diagnosed as a result of advanced complications of the disease. A recent expert panel has recommended screening all possible or confirmed HHT cases for PAVMs[7]. Population-based epidemiological studies in HHT are the essential first step in

understanding and quantifying the burden of disease and informing healthcare planning for this under-recognised condition. There are few data regarding differences in geographical prevalence of HHT in the UK or associations with sex, age and socioeconomic status, and this is important as understanding these relations may increase knowledge of factors that modify both development and diagnosis of the disease.

Hence, the aim of this study was to determine, using a representative sample of the UK population obtained via an electronic general practice database, a contemporary prevalence of diagnosed HHT and its association with age, sex, geographical location and deprivation status.

METHODS

Study population

This study utilised an anonymised, computerised, longitudinal general practice database known as The Health Improvement Network (THIN) which has been validated for epidemiological research[8, 9]. The THIN database records a variety of patient clinical and lifestyle data from consultations both in primary and secondary care including medical conditions, symptoms, medications and sociodemographic details. At the time of data extraction (September 2011), THIN covered 5% of the UK population with 3.46 million patients actively followed prospectively from 440 general practices[10].

Definition of disease

We initially identified all recorded diagnoses (by medical Read codes) between the years 2000 and 2010 of Hereditary Haemorrhagic Telangiectasia (G770.00) and Rendu-Osler-Weber Disease (G770.11). Given the high prevalence of HHT in individuals with pulmonary AVMs[11] we also searched for Read codes pertinent to pulmonary AVMs (we excluded any individuals previously identified as having Read codes for HHT or Rendu-Osler-Weber disease to prevent double-counting). Population denominator values were derived from the annual mid-year populations contributing to THIN. The results presented in this paper are for patients coded as Hereditary Haemorrhagic Telangiectasia (G770.00) or Rendu- Osler-Weber Disease (G770.11) only. A repeat analysis of a wider population was conducted which included all the Read codes listed in Table 1.

Statistical methods

Data for 2010 (the most recent complete data year) were used to calculate a point prevalence for HHT. We stratified our results by sex, age group (<15 years, 15-49 years and 50+ years), geographical location and socioeconomic status. Geographical location was defined by UK Health Authority areas and socioeconomic status was based on the Townsend index score in quintiles[12]. Given the relatively small numbers available for analysis by health authority in 2010, we used combined data from 2000-2010 to calculate prevalence estimates for HHT between different health authorities in the UK adjusting for the use of repeated measures (see below). We were able to look for any significant changes in the prevalence of HHT over the 10 year period between 2000 and 2010. Prevalence estimates taken over multiple years were adjusted by direct standardisation to the 2010 THIN population. Random effects modelling (Huber's Method) allowed for the non-independent nature of the cases contributing each year to the overall disease prevalence estimate,

adjusting the standard errors of the final model. We used Poisson regression to compare prevalence rate ratios, controlling for year, age, sex, Townsend score and health authority. Statistical tests of significance were performed using the likelihood ratio method unless otherwise stated. All analyses were carried out in Stata SE12 (Stata Statistical Software: Stata/SE12.0 for Windows; Stata Corporation, College Station, Texas, USA). The research protocol for this study was approved by the THIN Scientific Review Committee.

RESULTS

We identified a total of 563 individuals diagnosed with HHT/Rendu-Osler-Weber Disease in the THIN database from the years 2000–2010 with 365 cases contributing to the calculated point prevalence in 2010. Table 1 presents the total number of diagnosed cases identified in 2010 stratified by Read code.

Disease	Read Code	N
Hereditary Haemorrhagic Telangiectasia	G770.00	342
Osler Weber Rendu	G770.11	23
Sub total		365
Pulmonary arterio-venous malformation	P736.12	5
Pulmonary arterio-venous fistula	P736.11	6
Pulmonary arterio-venous aneurysm	P736.00	3
Arteriovenous fistula of pulmonary vessels	G420.00	17
Total		396

Table 1. Prevalent cases identified in 2010 from The Health Improvement Network database summarised by Read code

Overall Prevalence

The point prevalence of HHT in 2010 was 1.06 per 10,000 (95% CI: 0.95-1.17) or 1 per 9,400. In the sensitivity analysis using broader diagnostic criteria (combining all Read codes from Table 1) the point prevalence in 2010 increased to 1.15 per 10,000 (95% CI: 1.04-1.26) or 1 per 8,700.

Prevalence by Sex and Year

The prevalence of a diagnosis of HHT was strongly related to sex, with a higher prevalence rate in females compared to males for all years between 2000 and 2010 (Fig 1). In 2010 the point prevalence in women was 1.29 per 10,000 person years (95% CI: 1.12-1.46) and for men was 0.82 per 10,000 person years (95% CI: 0.69-96). After adjusting for age, deprivation status and geographical location, the prevalence rate ratio (PRR) in 2010 for HHT was higher in women compared with men (PRR 1.59, 95% CI: 1.30-1.94, $p < 0.0001$). The prevalence rate for both men and women has remained relatively constant over the last 10 years.

Prevalence by Sex and Age group

Prevalent cases from 2010 were grouped into 3 different age categories (<15 years, 15-49 years and 50 years and over) and stratified by sex (Fig 2). The unadjusted prevalence rate in both sexes was lowest in those aged <15 years and highest in the 50+ age group though the adjusted prevalence rate ratios across the age groups did not differ significantly (p test for trend =0.29) (Table 2).

	Crude Prevalence rates (95% CI) per 10,000 person-years	Crude prevalence rate ratios (95% CI)	Mutually adjusted prevalence rate ratios (95% CI)*
Sex			
Male	0.84 (0.70-0.98)	1.00	1.00
Female	1.28 (1.11-1.44)	1.56 (1.25-1.95)	1.53 (1.24-1.88)
			P=0.0001
Age group (years)			
<15 years	0.61 (1.15-1.77)	1.00	1.00
15-50 years	0.84 (0.71-0.98)	1.39 (0.88-2.19)	1.39 (0.96-2.02)
>50 years	1.58 (1.35-1.81)	2.62 (1.69-4.07)	2.53 (1.76-3.63)
			p<0.0001
			p=0.29°
Townsend Score			
1 (Least deprived)	1.31 (1.07-1.55)	1.93 (1.29-2.89)	1.74 (1.14-2.64)
2	1.05 (0.81-1.29)	1.55 (1.701-2.38)	1.36 (0.88-2.11)
3	1.10 (0.85-1.35)	1.62 (1.03-2.55)	1.50 (0.97-2.31)
4	0.87 (0.63-1.10)	1.28 (0.79-2.08)	1.23 (0.78-1.94)
5 (Most deprived)	0.68 (0.43-0.93)	1.00	1.00
9 (Missing values)	1.34 (0.77-1.91)	1.98 (1.12-3.52)	2.20 (1.25-3.88)
			P=0.026

Table 2. Crude prevalence rates and prevalence rate ratios of HHT derived from Poisson regression modelling using The Health Improvement Network dataset in 2010.

*Adjusted for sex, age group, Townsend score and health authority

°p-trend across age categories

Prevalence by Deprivation status

The prevalence of HHT was inversely associated with socioeconomic deprivation (Table 2).

The crude prevalence rate in the most deprived group (Townsend score: quintile 5) was 0.68 per 10,000 (95% CI: 0.43-0.93) compared to 1.31 per 10,000 in the least deprived quintile (95% CI: 1.07-1.55). After adjusting for the effects of age, gender and geographical location, the prevalence rate ratio was higher in those in the least deprived socioeconomic group when compared to those in the most deprived group (PRR 1.74, 95% CI: 1.14-2.64, p<0.0001).

Prevalence by Health Authority

There was substantial variation in estimates of the crude prevalence of HHT across the UK when stratified by health authority over the 10 year period 2000-2010 (Fig 3). The adjusted prevalence rate ratio varied almost twofold across the different UK health authority boundaries (PRR 1.86, 95% CI: 1.61-2.15, $p < 0.0001$) with the lowest adjusted prevalence in the West Midlands and the highest prevalence in the South West (Table 3).

Health Authority	Crude prevalence rates (95% CI) per 10,000 person-years	Crude prevalence rate ratios (95% CI)	Mutually adjusted prevalence rate ratios (95% CI)*
West Midlands	0.78 (0.69-0.88)	1.01 (0.85-1.19)	1.00
East Midlands	0.85 (0.71-1.00)	1.09 (0.89-1.34)	1.08 (0.88-1.33)
London	0.78 (0.69-0.87)	1.00	1.13 (0.96-1.34)
South East Coast	1.02 (0.92-1.13)	1.32 (1.13-1.54)	1.30 (1.11-1.52)
Northern Ireland	0.93 (0.77-1.09)	1.20 (0.97-1.48)	1.30 (1.05-1.61)
East of England	1.07 (0.95-1.18)	1.37 (1.16-1.61)	1.35 (1.15-1.59)
Scotland	1.07 (0.97-1.17)	1.37 (1.18-1.59)	1.45 (1.25-1.69)
North West	1.14 (1.03-1.25)	1.46 (1.26-1.70)	1.48 (1.27-1.72)
South Central	1.23 (1.13-1.33)	1.58 (1.37-1.82)	1.54 (1.33-1.77)
Yorkshire & Humber	1.37 (1.18-1.55)	1.75 (1.46-2.10)	1.76 (1.46-2.11)
Wales	1.35 (1.20-1.51)	1.73 (1.47-2.04)	1.77 (1.50-2.09)
North East	1.35 (1.14-1.55)	1.73 (1.42-2.10)	1.80 (1.48-2.19)
South West	1.51 (1.39-1.63)	1.94 (1.68-2.23)	1.86 (1.61-2.15)
			$p < 0.0001$

Table 3. Crude prevalence rates and prevalence rate ratios derived from Poisson regression modelling of HHT prevalence using The Health Improvement Network dataset between 2000 and 2010

*Adjusted for age, sex and Townsend score

Sensitivity Analysis

The above analyses were repeated to include all Read codes listed in Table 1, rather than those for HHT and Rendu-Osler-Weber Disease alone and revealed no significant differences

in qualitative trends of our results nor significance values for these trends. There was a slight change in the prevalence rate ratios calculated for the different health authority areas in the sensitivity analysis, with HHT or PAVMs diagnosed most commonly in Yorkshire rather than the South West (data not shown).

DISCUSSION

Summary of results

This is the first study to use a national primary care population-based database to explore sex, socioeconomic and regional differences in the prevalence of hereditary haemorrhagic telangiectasia, as well as providing national prevalence figures for the United Kingdom. The 2010 point prevalence for HHT in the UK is 1.06 per 10,000 (or 1 per 9,400) which has remained relatively stable between 2000 and 2010. The prevalence estimate is higher when Read codes likely to be associated with HHT are included (1 per 8,700) and is higher still if the prevalence in females is considered to be more representative of the population as a whole (1 per 7,800). The prevalence increases with age. The diagnosed prevalence ratio of HHT was 59% higher in women than in men and 74% higher in those from the least deprived socioeconomic group when compared to those in the most deprived group. In addition, we have demonstrated a substantial geographical variation in the diagnosed prevalence of HHT across the UK.

Strengths and Weaknesses

This is the first population-based study of HHT using a primary care database in the UK general population. With a total of 365 HHT prevalent cases identified in 2010 our study sample size is almost four times larger than the last UK estimate undertaken in 1992[13], is nationally representative and comparable in size with epidemiological studies conducted in other countries[6, 14, 15]. We have been able to stratify our prevalence estimates by sex, age group, deprivation status and geographical location without the risk of bias that may occur either from low response rates (as have been observed in previous surveys of HHT prevalence in the UK[13]) or from case-series in specialist centres which may lack a denominator population or represent cases referred for specialist care with potentially more severe disease.

There are potential limitations to the study which should be addressed. The first is that of the validity of the HHT diagnoses, which are recorded by general practitioners in the THIN database whilst the clinical diagnosis is generally made in secondary care. In practice, we are reasonably confident that the vast majority of these diagnoses will be correct with the increasing involvement of clinical geneticists in the screening and diagnosis of HHT which should result in more reliable information being conveyed to the primary care practitioner, and hence entered into the database. It seems very unlikely that a primary care practitioner would enter a diagnosis of HHT into the database unless it was supported by correspondence from secondary care. The consistency of our calculated prevalence of HHT with other comparable estimates from previous studies also supports the reliability of our findings. One further limitation that complicates all studies of HHT prevalence at present is the likelihood of undiagnosed individuals with HHT at large in the community. This may

explain the higher prevalence of PAVMs as defined by radiological criteria (and by inference, HHT) in patients who were participating in a recent Japanese CT screening program for lung cancer[16] than we observed in our dataset which did not use this radiological definition of the disease. Diagnosis is often confounded by the heterogeneous clinical presentation of HHT due to its variable genetic penetrance and expressivity[17]. An average time lag of 25 years separates disease onset and first definite diagnosis[18]. Hence, our prevalence estimates represent those with diagnosed HHT, and are likely to be lower than the true prevalence defined as all individuals with a mutation compatible with the disease. The fact that our data show the prevalence of the disease has been stable in both sexes over the last decade would suggest that the consistency in coding practice over this period has been maintained.

We used the Townsend score which is a deprivation index based on area as it was not possible to access individual-level deprivation data. This score presumes that individuals living within a geographical area have a similar deprivation status which may not be the case. However, there is evidence to suggest that the Townsend scores calculated at a district level are good proxy measures for individual levels of deprivation[19].

Interpretation of results

Reasons for the marked sex difference between the diagnosed prevalence of HHT require careful consideration. One study from the Dutch Antilles showed a 33% increased prevalence ratio of a 'definite' diagnosis of HHT in females compared with males (using the Curacao criteria)[15], and a recent US paper found a female:male ratio of 1.54, with HHT being diagnosed more commonly in females[20]. Other studies have reported a more balanced distribution between sexes[14, 17]. Given HHT is an autosomal dominant disorder,

the offspring of affected individuals will have a 50% chance of inheriting a mutation and this should not *per se* be associated with a sex bias. Our data show a significant difference in diagnosis of HHT in women compared with men which appears to be greatest between the ages of 15 and 49. One possible explanation for this observation is that the higher diagnosed prevalence of HHT in females we observed is due to a difference in access to healthcare resources. Women have significantly higher rates of consultation with primary care providers during the ages of 15 to 70 years with many consultations due to issues surrounding contraception, pregnancy and childcare, and this may explain an increased ascertainment of symptomatic females with HHT[21, 22]. A possible alternative explanation for the disparity between sexes may be that the expression of the HHT phenotype is more common in females with the gene mutation. Little is known about the role of other genetic factors (such as moderator genes) or environmental factors that may modify the HHT phenotype but there is limited evidence that symptoms such as epistaxis may be amenable to treatment via manipulation of oestrogen and progesterone levels[23]. During pregnancy there is an increased risk of developing complications of HHT[24, 25] and it has been suggested that this may represent a modification of the HHT vasculature by female hormones or be secondary to the haemodynamic changes of pregnancy. Clarifying whether the sex differential in diagnosis of HHT is due solely to behavioural factors or may be partly due to biological reasons is an important area for further research.

The reduced prevalence of diagnosed HHT in those from lower socioeconomic groups has multiple potential explanations which encompass controversial issues such as the proximity and quality of healthcare services provided in more deprived areas, as well as differentials in individuals' thresholds for accessing these services across different socioeconomic groups. It

is internationally recognised that health and healthcare access inequities vary along social gradients[26] and one study looking at health seeking behaviour in those from more deprived areas with asthma found that these populations reported a higher prevalence of respiratory symptoms but had lower consultation rates for those symptoms[27].

Explanations such as varying access to health care, differing perceptions of symptom severity or less positive views of health care services were postulated to explain this disparity[27, 28].

Finally, we have observed an almost two-fold difference in diagnosed prevalence throughout the UK; least common in the West Midlands and most common in the South West. A pattern of geographical variability has been seen in other studies, most notably in the landmark French paper which first identified a particularly high concentration of affected individuals in the Ain, Jura and Deux-Sevres regions of the country[29]. They attributed their findings to a local founder effect where an initial new mutation had given rise to a cluster of affected individuals that then gradually moved by diffusion to involve other nearby regions[30]. It is not possible to say whether our findings could represent genetic clusters of the disease in the UK or if they are the result of variations in local primary or secondary care recording practice or access to healthcare resources. Further work should try to address this as there may be regions of the UK with a disproportionate under-diagnosis of HHT, thus exposing individuals to the avoidable risk of the complications of this disease.

Comparison with existing literature

Table 4 provides a summary of the HHT prevalence estimates of different studies conducted worldwide over the last 25 years. Each study has investigated different populations using

different methodologies which, in part, explains the differing results. Certain areas such as the Dutch Antilles and the Ain department of France have shown particularly high prevalence of the disease. Elsewhere, most studies indicate a prevalence between 1 and 1.6 per 10,000 (or between 1 per 6,000 and 1 per 10,000) and our study estimate falls within this range, although data from individuals with health insurance in the USA provide estimates as low as 1 per 33,000[20]. Our findings with respect to age are consistent with previous work with the prevalence of HHT being higher in older age groups, suggesting that the disease has an age-related penetrance[17] or alternatively that the likelihood of diagnosis is related to longevity. No other studies have looked at the prevalence of diagnosis by deprivation status and most studies have been restricted to a small geographical area excepting the epidemiological data from France which also shows a wide variation in prevalence depending on geographical location[29, 31, 32]. Further research should consider the influence of disease severity on the diagnosed prevalence rate and its potentially confounding effect on our observations with respect to sex, socioeconomic status and geographical location.

Year of study	Year of estimate	Authors	Study setting and methodology	Study size	Prevalence rate (per 10,000)	Prevalence rate
2013	2010	Donaldson <i>et al</i>	UK primary care database	365	1.06	1 per 9,400
2013	2005-2010	Grosse <i>et al</i> [20]	US health insurance database	1203	0.3	1 per 33,000
2003	1998	Westermann <i>et al</i> [15]	Screening extended pedigree of previously identified cases in Antilles, Netherlands	112	7.51	1 per 1,300
2002	2002	Dakeishi <i>et al</i> [14]	Screening extended pedigree of cases referred to tertiary centre in Akita prefecture, Northern Japan	23	1.25	1 per 8,000
1999	1995	Kjeldsen <i>et al</i> [6]	Regional patient database, Fyne county, Denmark	73	1.56	1 per 6,400
1995	1994	Guttmacher <i>et al</i> [33]	Postal questionnaire of identified cases in Vermont, USA	34	0.61	1 per 16,400
1992	1991	Jessurun <i>et al</i> [34]	Study of cases hospitalised to one centre in Leeward Islands, Antilles, Netherlands	32	1.94	1 per 5,200
1992	1990	Porteous <i>et al</i> [13]	Postal questionnaire study of cases in Newcastle, "Northern Region", UK	79	0.25	1 per 40,000
1989	1989	Bideau <i>et al</i> [29]	Postal questionnaire study of cases identified by physicians in France (52 departments)	406	1.20	1 per 8,300
1984	1983	Plauchu <i>et al</i> [31]	Postal questionnaire study of cases identified by physicians in Ain department, France	150	4.25	1 per 2,400

Table 4. Summary of previous prevalence studies of HHT

Implications

This is the first contemporary study in a representative UK population to estimate the prevalence of HHT and suggests that it is much more common than the previously thought, and similar to the prevalence seen in other countries. Assuming that the prevalence of HHT in males is the same as for females, the "true" estimate of total prevalence would be closer to 1.28 per 10,000 or 1 per 7800 (the figure calculated for females alone). A similar approach extrapolating the "true" prevalence from females living in the South West of the

UK (the health authority with the highest crude prevalence of HHT) estimates a prevalence of 1.9 per 10,000 and would equate to at least 11,800 cases of HHT in a population of 62.3 million in 2010[35]. The lower diagnostic rate of HHT in males and those from less affluent social backgrounds suggests a sociological (or alternatively a biological role) in the presentation of HHT, while the previously unreported regional differences is an observation that requires validation in other datasets. Future research would ideally draw on a national rare disease database with integrated clinical information and genetic samples allowing greater understanding of the presentation of the disease, the genotype-phenotype relationship in HHT and the influences upon it of moderator genes and external environmental factors.

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Competing Interests None

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CAPTIONS TO FIGURES

Fig 1. The UK prevalence of hereditary haemorrhagic telangiectasia by sex and year (2000-2010) with total prevalent cases tabulated

Fig 2. The prevalence of hereditary haemorrhagic telangiectasia by sex and age group in 2010

Fig 3. The crude prevalence of hereditary haemorrhagic telangiectasia (per 10,000) by UK health authority area (2000-2010)

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