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Reported cardiac phenotypes in hereditary hemorrhagic telangiectasia emphasize burdens from arrhythmias, anemia and its treatments, but suggest reduced rates of myocardial infarction☆,☆☆

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ABSTRACT

Introduction: Cardiac phenotypes should be pronounced in hereditary hemorrhagic telangiectasia (HHT) due to frequent systemic arteriovenous malformations (AVMs), iron deficiency anemia, hypoxemia, hyperdynamic circulations, venous thromboemboli, and paradoxical emboli through pulmonary AVMs.
Methods/results: In an international survey, 1025 respondents (median age 55 years) met HHT diagnostic criteria: 942 (91.9%) reported nosebleeds, 452 (44.1%) at least daily. AVMs were commonly reported in pulmonary (544, 53%), hepatic (194, 18.9%) and/or cerebral (92, 9.0%) circulations. 770/1025 (75%) had used iron tablets, 256 (25.0%) intravenous iron, and 374 (36.5%) received blood transfusions. Arrhythmias were reported by 113/1025 (11%, including 44 (4.3%) with atrial fibrillation), angina by 36 (3.5%), and cardiac failure by 26 (2.5%). In multivariate logistic regression, these phenotypes were associated with hepatic AVMs/pulmonary hypertension (relatively interchangeable variables), blood transfusions, and intravenous iron. Cardiac insufficiency/failure often provokes intensive anemia treatments, but associations with arrhythmias, particularly with a greater transfusion burden, were less easy to explain.
Myocardial infarction (23/1025; 2.2%), and abnormal coronary angiogram (≤31/76, ≤54%) rates appeared low. Provocative preliminary data were obtained including HHT-affected respondents' parents and grandparents in whom HHT could be confidently assigned, or excluded based on autosomal dominant inheritance patterns: in crude and survival analyses, myocardial infarctions were reported less frequently for individuals with HHT, particularly for males ($p = 0.001$).
Conclusion: Arrhythmias are the most common cardiac phenotype in HHT, and likely to be aggravated by iron deficiency anemia, its treatments, and/or high output states due to AVMs. Myocardial infarction rates may be reduced in this apparently high risk population.

☆ This work was performed at Imperial College London, UK.
☆☆ This study complies with the Declaration of Helsinki. The study received a favorable ethics opinion by the NRES Committee East Midlands-Derby 1 Research Ethics Committee, UK, and informed consent was obtained from the subjects.

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[2] This author assigned respondents' HHT phenotypes, performed preliminary analyses that corroborated the final study findings, and critically revised the manuscript.
[3] This author performed preliminary analyses that corroborated the final study findings, and critically revised the manuscript.
[4] This author assigned respondents' HHT phenotypes, and critically revised the manuscript.
[5] This author assisted in the conception and design of the research, and critically revised the manuscript.

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1. Introduction

Cardiac phenotypes should be pronounced in individuals with the inherited vascular disorder, hereditary hemorrhagic telangiectasia (HHT) which is caused by mutations in the *endoglin*, *ACVRL1* or *SMAD4* genes that encode proteins involved in TGF-beta superfamily signaling [1,2].

HHT results in systemic and pulmonary arteriovenous malformations (AVMs), and iron deficiency anemia, usually attributable to recurrent nosebleeds. As discussed recently [3], significant systemic arteriovenous malformations (AVMs) reduce systemic vascular resistance: supranormal cardiac outputs are required to maintain arterial blood pressure [4] with hemodynamic indices improving if hepatic AVMs are treated by liver transplantation [5]. Bleeding from nasal and gastrointestinal telangiectasia leads to iron losses of such magnitude that diet is usually insufficient to meet the 'hemorrhage adjusted iron requirement' [6]. Resultant iron deficiency restricts erythropoiesis, leading to anemia and increased cardiac output [7,8]. Pulmonary AVMs [9] result in hypoxemia which increases the cardiac output [9,10,11], and also place patients at risk of paradoxical emboli proposed to cause angina or myocardial infarction in patients with normal coronary arteries [12]. Paradoxical embolic stroke risks are greater in iron deficient HHT/pulmonary AVM patients [13] who, as in the general population, can display exuberant platelet aggregation to serotonin (5HT) [13]. Additionally, HHT patients are more prone to venous thromboemboli (VTE) than the general population [14], apparently exacerbated by iron deficiency, and elevated coagulation factor VIII [14] which is an established risk factor for first and recurrent VTE in the general population [15–19].

Despite these additional circulatory demands and stresses, received wisdom in the HHT field is that specific cardiac events may be relatively rare. Undoubtedly high output cardiac failure is a feared complication of hepatic AVMs [20], and arrhythmias can be a presenting feature of pulmonary AVMs [21]. However, a survey published in abstract format in 1997 suggested reduced rates of angina [22].

Furthermore, it is known that despite early deaths [23–25] due to HHT-related phenotypes such as cerebral hemorrhage [26–28], cerebral abscess [29,30], or maternal death during pregnancy [31], life expectancy is remarkably well preserved and approaches normal in the latest series from Denmark [23,32,33], though this has not been seen in all countries [24,25]. Cancer protection has been identified as one potential mechanism for the good life expectancy [34]. We hypothesized that reduced rates of life-limiting cardiovascular diseases may be another.

Here, we report results from a systematic unbiased survey that was designed to evaluate cardiac phenotypes in patients with HHT.

2. Methods

2.1. Study design

To capture cardiac histories in an unbiased manner, relevant questions were incorporated into a wider ethically-approved survey designed to capture multiple datasets from respondents. The questionnaire was approved by the NRES Committee East Midlands-Derby 1 Research Ethics Committee; distributed by post using the Imperial College London HHTIC London Clinical Service databases (2001 to 2012); during attendance at the HHT clinics; and advertised by the HHT Foundation International. The basic study design has been reported previously [6,34–36]. Exact wording of relevant questions is provided in the e-component (Survey Extracts). To facilitate maximal completion, for each set of questions, respondents were directed to one of several alternate "loops", each containing the appropriate questions according to their answers to key preceding questions.

Respondents' answers to HHT-related questions permitted independent assignment of their HHT-status based on the Curaçao criteria [37] that were applied through the algorithm in reference [34], and this was performed blinded to all other data. One of the final survey questions asked respondents to provide their date of birth: this was used as a first check of standard of completion (see below). For each parent and grandparent, the survey stated the gender and relationship to the respondent, and respondents were asked to report using drop down boxes: the final age of the individual (at death or 2012 censor); if HHT was known to be present; whether they had a "heart attack (myocardial infarction)"; and age at first "heart attack (myocardial infarction)". Free text options were provided allowing additional details to be reported.

The survey was open from April 2012 to April 2013. Preliminary analyses of the cardiac phenotypes were performed by students during 2013, and included the assignment of HHT phenotypes used in the current study. To extend for the final analyses reported in the current manuscript, all data from the survey were downloaded from SurveyMonkey in 2015.

2.2. Data analyses and statistics

2.2.1. Proband (respondent) analyses

Personal phenotypes reported by survey participants were downloaded in six anonymized Excel sheets. The data were transformed to numeric indices using Microsoft Excel "replace" commands, and copied to a single Excel sheet that did not include the final HHT diagnostic assignments. Following data transformation, an HHT diagnostic column (yes (1), no (0), unknown (.)) was added in using the Excel "vlookup" command to generate "vlookupHHT", and data were uploaded to a STATA datasheet. Further data analyses and statistical evaluations were performed using STATA IC v11 (Statacorp, Texas).

New variables were generated and populated automatically in STATA, particularly "ageknown" (where date of birth had been provided, required for study inclusion); "smokernonpassive" (counting passive smokers as 0); "txgraded" where blood transfusion history was weighted on a scale of 0–5 for never, once, 2–4, 5–10, 10–50, and greater than 50 transfusions; "gradedNB" where maximum frequency of nosebleeds (NB) was assigned on a scale of 0–5 for never, <5 in life, once a year, once a month, once a week, and once a day; arrhythmiaany (either arrhythmia/tachycardia or atrial fibrillation); and miall (to capture the Mi phenotypes reported in different columns). The original and final datasheets will be supplied upon publication to facilitate further analyses by other groups.

Two group comparisons were performed using Mann Whitney, three or more groups by Kruskal Wallis with p-values for two way comparisons calculated by post-test Dunn's correction. HHT cardiac phenotypes and pulmonary hypertension were examined by logistic regression "if vlookuphht==1 & age known ==1". Following univariate logistic regression, multivariate analyses initially examined simultaneously age, gender, graded nosebleeds, pulmonary AVMs, cerebral AVMs, liver AVMs, gastrointestinal HHT, transfused (yes/no), iv iron (yes/no), iron tablets ever (yes/no), still anemic on iron tablets, smoker (yes/no, and not passive), and alcohol graded; arthritis; asthma; high blood pressure; COPD/emphysema; deep vein thrombosis /pulmonary emboli (venous thromboemboli); diabetes; inflammatory bowel disease; liver problems (not related to HHT); kidney problems; osteoporosis; polyps in colon; pulmonary hypertension; sleep apnea; stroke or transient ischemic attack; and varicose veins. Step wise removal of the least significant variable was used to generate the prefinal model. Phenotypes were then added back individually to see if they increased the strength of the model. The final models reported are the models explaining the greatest proportion of the variance including both HHT phenotypes, and nonHHT disease states that made independent contributions to the model, once adjusted for all other variables in the model.

2.2.2. Familial analyses

The study design also permitted capturing of a more restricted dataset on respondents' relatives. Familial data within the six