1) TITLE: Lifestyle and dietary influences on nosebleed severity in hereditary haemorrhagic telangiectasia

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ABSTRACT

Objective

To identify factors influencing the severity of epistaxis in hereditary haemorrhagic telangiectasia.

Study design

Participants with and without hereditary haemorrhagic telangiectasia were recruited from a specialist UK service, and online following advertisement by the HHT Foundation International. Both groups were asked to complete a non-biased questionnaire.

Methods

The reported effects of specific treatments or lifestyle factors on epistaxis were assigned positive values if beneficial, negative values if detrimental, zero if “no difference,” and summed to enable statistical analysis.

Results

Epistaxis affected 649/666 (97%) participants with hereditary haemorrhagic telangiectasia and was significantly more frequent than in control participants. Specialist invasive treatments were reported as beneficial, laser therapy more frequently than cauterisation. Medical treatments commonly used for HHT epistaxis (female hormones, anti-oestrogens, tranexamic acid, aminocaproic acid, nasal creams and bevacizumab) also had significantly positive (beneficial) scores. Lifestyle and dietary factors were generally detrimental, but room humidification, nasal lubrication and saline treatments were all reported as beneficial (95% confidence intervals greater than zero). Multiple food items were volunteered as being detrimental to epistaxis. The most frequently reported items were alcohol (n=45; 6.8% of participants) and spices (n=26, 3.9% of participants). Remaining foods

reported to exacerbate epistaxis were also found to be high in salicylates (including red wine, spices, chocolate, coffee and certain fruits), natural antiplatelet activity (garlic, ginger, ginseng, ginkgo biloba and vitamin E15) or in omega-3 acids (oily fish, salmon).

Conclusion

This study supports existing treatments and suggests lifestyle and dietary manoeuvres that may also improve nosebleeds in hereditary haemorrhagic telangiectasia.

Keywords: Cautery, Dietary salicylates, Epistaxis, Laser, Lifestyle, Oestrogens, Tamoxifen

Level of Evidence: 2c

Word Count: Abstract 250; Full text (including Abstract) 3000

INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber syndrome,¹ is an autosomal dominant disorder that leads to the development of abnormal vessels. The most common clinical feature is epistaxis (nosebleeds) which often occurs on a daily basis.² Other disease manifestations include gastrointestinal telangiectasia, and arteriovenous malformations (AVMs) particularly in the pulmonary, hepatic and cerebral circulations. Careful epidemiological studies reveal that HHT affects approximately 1 in 5,000 individuals.^{3,4}

HHT is caused by mutations in the *endoglin*, *ALK1/ACVRL1*, or *Smad4* genes.⁵ The mutated genes encode proteins which mediate transforming growth factor-beta (TGF- β) superfamily signalling in vascular endothelial cells. Disruption of signalling pathways in HHT pathogenicity results in remodelled vasculature, with dilation of venules and concomitant arteriovenous communications.^{6,7} The current perspective of pathogenesis is that HHT vessels result from aberrant responses to injury-induced angiogenic stimuli, when the mutated genes in HHT appear to result in the inability of a blood vessel to mature appropriately.^{1,6-8}

More than 90% of HHT patients experience spontaneous recurrent epistaxis secondary to telangiectasia of the nasal mucosa.⁸ Both severity and frequency of HHT-related epistaxis vary widely.⁹ Frequency may range from a few bleeds yearly to several each day, whilst severity may range from a few drops to unmanageable flows with acute haemodynamic disturbances; chronic iron deficiency anaemia and transfusion dependence are common.^{1,9} Increased frequency and duration of epistaxis in HHT sufferers is associated with a decreased quality of life.^{10, 11}

Otorhinolaryngological management of HHT epistaxis includes cauterisation, laser photocoagulation,¹² septal dermoplasty,¹³ and Young's procedure (nostril closure). Ligation and embolisation treatments have also been used.⁹ Medical treatments using both oestrogen and anti-oestrogen therapy are now supported by small randomised controlled trials.^{14,15} There is increasing interest in the use of anti-angiogenesis therapies, such as bevacizumab (Avastin)^{16,17} and thalidomide.⁶ Therapeutic manipulation of coagulation and fibrinolytic pathways,¹⁸⁻²⁰ and antioxidant therapies²¹ are also employed to try to limit blood loss in HHT. Many patients require more than one modality, with more invasive surgical treatments generally reserved for patients remaining transfusion-dependent or severely symptomatic despite standard therapy.²²

Anecdotal reports from patients in our clinic suggested several lifestyle factors and conservative treatments that may have provocative or beneficial effects on nosebleeds in HHT. Only a proportion have been examined in prior formal publications.^{9,23} The goal of this study was to use a non-biased patient survey to identify factors associated with changes in epistaxis severity in HHT.

METHODS

Study Design

To capture patient experiences of treatment and lifestyle factors affecting nosebleeds in an unbiased manner, relevant questions were incorporated into a wider ongoing survey regarding health and treatments for people with HHT and general population controls. The full study addressed general and HHT demographics, factors influencing HHT nosebleed severity, and prevalence and behaviour

of common medical conditions in the participant and their relatives. The study received a favourable Ethics opinion by the NRES Committee East Midlands-Derby 1 Research Ethics Committee before on-line launch at www.imperial.ac.uk/medicine/HHTsurvey2012.

For the current study, relevant data were downloaded on 10th May 2012. Participants were asked “Have you had any of these [.....] treatments for HHT nosebleeds?” and then asked to score the effects of treatments as ‘much better’, ‘a bit better’, ‘no different really’ ‘a bit worse’, or ‘much worse’. Additional options of ‘sometimes better-but not always’ and ‘sometimes worse-but not always’ were provided for invasive treatments (cauterisation, laser treatment, septal dermoplasty, Young’s procedure (nostril closure), arterial ligation, and embolisation) and the opportunity to tick more than box per treatment if it didn't always have the same result, for medical treatments. Participants were also asked to score the effects of specific lifestyle changes as ‘much better’, ‘a bit better’, ‘no different really’ ‘a bit worse’, or ‘much worse’. Finally, they were given the opportunity to provide information on any other medical treatment, lifestyle or dietary item that seemed to lead to a change in their nosebleeds and then asked to detail whether that was a beneficial or detrimental change.

Patient population

Potential participants were recruited through the Imperial College London HHTIC London Clinical Service databases (2001 to present) by post, during attendance at the HHT clinics, and by advertisement by the HHT Foundation International. Answers from individuals who filled in paper format questionnaires were transcribed into the online survey by the study team. Non-HHT

participants were also recruited to provide comparison data for nosebleed frequency in the HHT and general populations.

Statistical methods

Question responses 'much better', 'a bit better'/'better', 'no different', 'a bit worse'/'worse', 'much worse', 'sometimes better-but not always', and 'sometimes worse-but not always' were converted into numerical format (+2, +1, 0, -1, -2, +0.5 and -0.5 respectively) to generate "response means". Interventions volunteered by participants were scored as +1 ('better') or -1 ('worse'), and summed to generate a "score", which could not be compared to "response means" because of the absence of the formal 'no difference' response category (occasional individuals volunteered a 'no difference' effect using free text). GraphPad Prism version 5.00 (GraphPad Software, San Diego, California, USA) was used to calculate descriptive statistics, and to compare variables quantified in the same manner, using Fisher's Exact test (proportions), or Mann Whitney (two variables).

RESULTS

Population characteristics

In total, 771 responses were received at the time of data download, 666 with HHT and 105 controls. The average age of HHT and non-HHT participants were 54 (range 21-87) and 53 years (range 21-86) respectively. 436/663 (66%) of HHT participants and 70/105 (67%) of non-HHT participants were female. The majority of participants were of Caucasian descent, living in the USA, UK, Europe, Canada or Australia. The proportion of HHT participants reporting epistaxis (649/666, 97%) was

significantly higher than the proportion of non-HHT patients (70/105, 67%), $p<0.0001$. The frequency of nosebleeds experienced by the HHT participants was also higher (Figure 1A).

Treatment modalities in HHT-related epistaxis

326 participants reported the use of specialist invasive treatments for HHT epistaxis (Figure 1B). 164/170 (96%) of those requiring emergency packing had used either, or more commonly both, cauterisation and laser therapy. More invasive treatments were almost always used in patients who had also received cauterisation and/or laser therapy.

Approximately 50% of those treated by cauterisation (138/267, 52%) or laser photocoagulation (109/221, 49%), and smaller proportions receiving other modalities, provided a response report (Figure 2). The graded responses to each specified treatment (spanning beneficial, no difference and detrimental options) were scored to generate a response mean. Of those patients reporting an effect, most reported a benefit, and all invasive treatment modalities demonstrated positive responses. For the two major outpatient procedures, laser therapy was more frequently reported as beneficial than cauterisation (Mann Whitney $p<0.0001$).

Medical treatments for HHT epistaxis fell into two categories (Figure 3). Female hormones (which could have been used for any indication including oral contraception and hormone replacement), and 'anti-oestrogens' (tamoxifen/raloxifene) were specified in the questionnaire: The graded responses (spanning beneficial, no difference and detrimental options) were scored to generate a response mean. High proportions of individuals receiving these agents provided a response report—

275/330 (83%) of those receiving female hormones, and 30/33 (91%) receiving tamoxifen/raloxifen. Both were generally reported as beneficial, although the response mean for tamoxifen/raloxifene was significantly higher than that for female hormones (Mann Whitney $p=0.0037$). The other four groups volunteered by study participants (aminocaproic acid, bevacizumab, nasal antibiotic ointments, and tranexamic acid) were also more frequently reported as having a beneficial effect on epistaxis. For these volunteered agents, participant responses (beneficial or detrimental) were summed to generate positive (beneficial) “scores”.

Other medical and lifestyle influences

Other agents used by HHT patients also fell into questionnaire-specified and participant-volunteered categories (Figure 4). Steroid hormones (excluding topical agents or inhalers) and iron tablets were specified in the questionnaire: each was as commonly reported with beneficial as detrimental effects. The other agents were volunteered by study participants. Nasal humidification regimes were all reported as having beneficial effects on nosebleeds (95% confidence intervals for scores greater than zero). Surprisingly, the Chinese herb Yunnan Baiyao was frequently reported as being beneficial (score 1.5 [1.06, 1.94]), as were nasal decongestants (score 1.31 [0.17, 2.45]). As expected, HHT participants using anti-platelet agents, anticoagulants and non steroidal anti-inflammatory drugs were more likely to report a detrimental effect. Similarly, the use of omega-3 acid supplements and allergy treatments were reported as detrimental (scores -1.2, [-0.64, -1.76] and -0.6 [-0.21, -1.41] respectively).

The effects of specific lifestyle variables requested (‘Different foods/drinks’, ‘Season/temperature’, ‘Mood, stress or anxiety’, ‘Lifestyle activities/sports’ and ‘Nasal knock/injury’) were all reported as detrimental (Figure 5). When participants volunteered details, as shown in Figure 5, the majority of

reports (all negative) cited extremes and changes in temperature (n=133), low humidity (n=80), both temperature and low humidity (n=23), or spring time allergies (n=31). For activities and sports, reports were generally negative although two participants reported beneficial effects from aerobic sports.

The most unexpected data were the 25 different food items reported (Figure 6): all except soy were reported only as having detrimental effects on epistaxis. The most frequently reported items were alcohol (n=45, 6.8% of participants) and spices (n=26, 3.9% of participants). We noted that most of the foods reported to exacerbate epistaxis were high in salicylates (including spices, chocolate, coffee and certain fruits),²⁴⁻²⁶ other natural compounds reported to have anti-platelet activities (red wine, garlic, ginger, ginseng, ginkgo biloba and vitamin E)²⁷⁻³⁰ or in omega-3 acids (oily fish, salmon)³¹.

DISCUSSION

Management of HHT epistaxis is difficult and, as a rare disease, individual practitioners rarely treat large number of patients outside of HHT centres. In this study of a non-biased questionnaire of international HHT patients, we highlight the need for multiple different treatment modalities which were generally reported as beneficial. More importantly, the data provide potential options for lifestyle modifications.

The strengths of the study were the use of a non-biased questionnaire amenable to quantification. Limitations were that only a proportion of participants reported the effect of specific variables on their epistaxis: 83-91% for oestrogen and anti-oestrogen therapies, ~50% for laser and cauterisation, low for more invasive modalities, and not ascertainable for other treatments and lifestyle factors. The intention of dedicated treatments was known to the patients and the reported beneficial responses may therefore have included placebo responses. However, the goal of the study was not to evaluate the beneficial effects of specific treatments but to identify other factors modifying nosebleed severity, and overall the findings of treatment benefits strengthened our confidence in the subsequent reports associated with environmental and lifestyle factors: Salicylate content and anti-platelet activities of dietary food items are not generally appreciated, and we suspect, but cannot prove, that this was not known to the participants reporting effects on their nosebleeds. The use of a subjective questionnaire-based study meant that the effects attributable to one particular treatment or variable could not be isolated from potentially independent and/or interactive effects of other therapeutic, lifestyle, pathogenic or genetic variables. The responses were not reported consistently by all patients, and the reasons for this variability are not yet understood.

That said, the data do add to the limited published literature. Use of specific otorhinolaryngological treatments in HHT is guided by expert opinion and the findings of case series. For example, recent international guidance recommended the use of laser therapy over cauterisation.⁹ Our study findings provide direct evidence to suggest that the use of laser treatment may be preferable to cauterisation in HHT. Medical therapies, particularly hormonal therapies which are supported by randomised control trials in HHT,^{14,15} were also reported as beneficial. To date no formal comparisons have been made between oestrogens and anti-oestrogens in the treatment of HHT-related epistaxis. The current study begins to suggest that the use of anti-oestrogen treatment may

be favourable to hormone treatment, although the lower hormonal score may in part reflect the variety of oestrogen/progesterone dosing regimes used by participants. Beneficial effects were also reported for aminocaproic acid, tranexamic acid, antibiotic ointments and bevacizumab. No data were volunteered by participants for thalidomide or antioxidants. Trauma to the nose and high anxiety levels were reported to worsen nosebleeds along with almost all patient-reported variables relating to environmental factors. These findings support both wide anecdotal consensus, and the findings of single questionnaire-based study (n=40)²³ which reported changes in temperature, low humidity, sneezing, bending over, strenuous activity and alcohol as aggravating factors on nosebleeds in HHT. These factors are likely to influence epistaxis through drying of the nasal mucosa by fluctuations in temperature and humidity, external trauma to telangiectasia, and increased perfusion pressure of the vessels whilst bending over. Many of these factors also lead to epistaxis in the general population,³² due to the superficial and easily traumatised multidirectional arterial anastomotic system of the nose.³³

We believe the most important data from this study relate to potential forms of self-management in this chronic condition. Consensus opinion has suggested the use of humidification and regular lubrication of the nostrils,⁹ based on anecdotal reports and the likelihood that crusting and drying of the nasal mucosa will exacerbate damage of the nasal telangiectasia, precipitating haemorrhage.^{8,9} For example, saline irrigation of the nostrils has been postulated as a useful method of preventing deeper crusting where tolerated by the patient.³⁴ In our study, the positive (beneficial) scores for room humidification (1.50 [95% confidence intervals 1.31-1.69]), saline treatments (1.50 [1.23-1.78]) and nasal lubrication (0.61 [0.15-1.08]) provide evidence to encourage use. For individuals with nasal congestion, the beneficial reports for nasal decongestants (score 1.31 [0.17, 2.45]) are intriguing and likely to reflect reduced nasal irritation and damage to telangiectasia secondary to reduced blowing of the nose.

Eight participants reported using Yunnan Baiyao, a traditional Chinese herbal medicine widely used in the treatment of haemorrhages and wounds, and shown in several randomised controlled trials to reduce intra-operative bleeding, attributable to its haemostatic properties.³⁵⁻³⁸ Similarly, two participants reported beneficial effects from soy, which reduced bleeding from mechanically injured vessels in thrombocytopaenic dogs,³⁹ and was associated with decreased risk of subarachnoid haemorrhage in a Japanese population.⁴⁰ For these agents, further study of efficacy, tolerability and mechanisms that may be involved in alleviating HHT epistaxis is indicated in a wider group of patients. As for other potentially prothrombotic agents, examination of side effect profiles is important, particularly with the recent demonstration of the heightened risk of venous thromboemboli in iron deficient HHT patients.⁴¹

Nosebleeds are more frequent and prolonged for individuals in the general population using anti-platelet⁴² and anti-coagulant therapies⁴⁰, and the current study suggests this may be the case for HHT patients. There were also deleterious reports for food items reported to have similar activities. The two most commonly reported groups of agents to exacerbate HHT epistaxis were alcohol (especially red wine) and spices. Total salicylates and salicylic acid are high in a wide variety of spices,²⁴⁻²⁶ with anti-platelet activity of curcumin, a food spice from turmeric, reported by numerous groups.⁴³⁻⁴⁵ Curcumin is also recognised to inhibit vascular smooth muscle cell functions relevant to responses to vascular injury,⁴⁶ the process currently considered to precipitate HHT haemorrhage. There is already a substantial literature regarding the mechanisms by which red wine appears to have a beneficial effect protecting against cardiovascular disease in the apparent “French paradox” (summarised recently in⁴⁷). We can also speculate that the detrimental effects of alcohol in the current study may be attributable not only to vasodilatation, but also to the reported association

between alcohol and reduced platelet aggregation.⁴⁸ Chocolate was the next most commonly reported item to exacerbate HHT epistaxis (Figure 6). Multiple studies have emphasised different anti-platelet effects of cocoa,⁴⁹⁻⁵⁰ its flavonol constituents,^{51,52} and specifically dark chocolate⁵³⁻⁵⁶. Similarly, anti-platelet activity for Omega-3 is recognised,⁵⁷⁻⁵⁹ with reduced microvascular thromboses demonstrated in a porcine model⁶⁰, though it is not clear whether this usually translates to clinically relevant haemorrhagic risk.^{61,62} In the current study, fish oil and omega-3 containing items were reported as worsening epistaxis by 15 HHT patients. Additionally, most fruits, especially berry fruits and dried fruits, many vegetables, tea and honey contain salicylate²⁴⁻²⁶ although functional evidence of anti-platelet activities has generally not been reported to date. Anti-platelet activity is also recognised for a wide variety of additional food and dietary items: Pribitkin,²⁸ Ciocon²⁹ and colleagues emphasised the importance of garlic, ginger, ginseng and Gingko Biloba (the 4 'G's), and in the current study each was reported by multiple different HHT participants as exacerbating their nosebleeds (Figure 6).

Conclusion

This study suggests that HHT patients with troublesome epistaxis may be advised to try simple risk-free strategies including avoidance or monitored intake of high salicylate foods and other dietary items reported as deleterious in this study. Acute aggravation of HHT epistaxis could serve as an activity biomarker for proposed dietary manoeuvres to protect against atherosclerosis and vascular diseases.

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FIGURE LEGENDS

Figure 1: Nosebleed frequency and treatments

A) Comparison of frequency of nosebleeds reported by individuals with and without HHT.

B) Treatment modalities used by HHT patients: The upper Venn diagram indicates the use of emergency and common outpatient modalities; the lower diagrams the use of specialised treatments, stratified according to whether respondents also had cauterisation (left panel), cauterisation and laser treatment (middle panel), or laser treatment (right panel). Four participants reported treatment by specialised treatments (septal dermoplasty, embolisation) without laser and/or cautery: they are indicated on the upper panel.

Figure 2: Reported effect of specialised treatments on nosebleed severity

A) Graphical indication for each treatment, of the number of reports where the treatment was reported as improving nosebleeds, making no difference, or worsening nosebleeds. For clarity, response counts are shown above their respective bars

B) Indication of proportion of respondents and response means (with 95% confidence intervals) for each treatment modality.

Figure 3: Reported effect of recognised medical treatments for HHT nosebleeds

A) Graphical indication for each treatment, of number of reports where the treatment was reported as improving nosebleeds, making no difference, or worsening nosebleeds.

B) The mean treatment effect reported (with 95% confidence intervals) for each treatment. Note that treatment effects cannot be compared between the two different categories (response means, or scores).

C) Indication of proportion of respondents, and mean treatment effect reported for each treatment modality (*response means; ^scores). Note that the total number of respondents using nasal antibiotics aminocaproic acid, tranexamic acid and bevacizumab were not captured, as these were treatment effects volunteered by the participants. The likely absence of individuals where effects on epistaxis would have been reported as 'no difference' means that these scores cannot be compared to the response means for oestrogens or anti-oestrogens

Figure 4: Reported effect of other medical treatments on HHT nosebleeds

A) Graphical indication for each treatment, of the number of reports where the treatment was reported as improving or worsening nosebleeds. Epistaxis responses to steroid therapy and iron tablets were specifically requested: the 'no difference' responses (77.4% (96/124) of steroid users; 88% (403/457) of iron tablet users) are not illustrated for clarity.

B) The mean treatment effect reported (with 95% confidence intervals) for each treatment. Note that response means cannot be compared to scores.

C) Indication of number of respondents and mean treatment effect reported for each treatment modality (^scores; *response means).

Figure 5: Reported effect of lifestyle factors on HHT nosebleeds

A) Graphical indication for the effects of each change reported as improving nosebleeds, making no difference, or worsening nosebleeds.

B) The number of reports of specific environmental changes, grouped according to type (black bars negative/ detrimental, grey bar positive/beneficial).

Figure 6: Reported effect of dietary factors on HHT nosebleeds

The number of reports for specific dietary items, grouped according to type (black bars negative/ detrimental, grey bar positive/beneficial). *There were additional single deleterious reports for vitamin C, cheese, carbonated drinks, red meat, soy and bananas, although two individuals volunteered a beneficial effect with soy.

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Figure 1A

Figure 1B

Figure 2

Figure 3

C

	Total receiving treatment	Total (%) reporting response	Mean treatment effect reported	95% Confidence Intervals
Tamoxifen/raloxifene*	33	30 (91%)	0.53	0.34, 0.72
Female hormones*	330	275 (83%)	0.22	0.15, 0.29
Nasal antibiotics^	?	30	0.80	0.48, 1.12
Aminocaproic acid^	?	11	1.00	0.40, 1.60
Tranexamic acid^	?	14	1.14	0.70, 1.59
Bevacizumab^	?	10	1.30	0.54, 2.06

Figure 4

A

B

C

	Number of reports	Mean effect size	95% Confidence Intervals
Nasal lubrication^	31	0.61	0.15, 1.08
Room humidifier^	9	1.50	1.31, 1.69
Saline treatment^	7	1.50	1.23,1.78
Yannan Baiyao^	8	1.50	1.06,1.94
Nasal decongestants^	5	1.31	0.17, 2.45
Omega 3 acids^	5	-1.20	-1.76, -0.64
Allergy mediations^	15	-0.60	-1.41, -0.21
Acetylated salicylates^	24	-1.79	-1.97,1.62
Non steroidal anti-inflammatory drugs^	33	-1.56	-1.88,-1.24
Steroid treatments (excludes topical/inhalers)*	124	0.03	-0.05, -0.12
Iron tablets*	456	0.015	-0.016, 0.047

Figure 5

Figure 6