

Epistaxis limits the performed activities of daily living in proportion to its severity: a cross-sectional survey among patients with hereditary haemorrhagic telangiectasia*

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Abstract

Background: We examined the severity of epistaxis in patients with hereditary haemorrhagic telangiectasia (HHT) and its relationship with the performed activities of daily living.

Methodology: This cross-sectional survey included 36 patients with HHT in Japan. An anonymous questionnaire survey was conducted regarding the severity of epistaxis, the measures adopted to prevent epistaxis, and the limitations in the performed activities of daily living. The latter was assessed using a visual analogue scale (VAS). The correlation between epistaxis severity and the VAS score was analysed using Spearman's rank correlation coefficient.

Results: Of the 36 participants surveyed, 94.4% had >1 episode of epistaxis/week. The mean epistaxis severity score (ESS) was 4.3 (range, 0.9–8.4). Limitations in daily life, going out (within a day), meeting with others, eating with others, and going on overnight trips were positively correlated with the ESS. To prevent nosebleeds, 44.4% and 41.7% of the participants used medications and avoided drying their nasal cavities, respectively.

Conclusions: Epistaxis impacted the daily life of patients with HHT in proportion to its severity. Nonetheless, less than half of the patients used medications or took precautions. Hence, further educational activities should be considered for medical professionals and patients.

Key words: hereditary haemorrhagic telangiectasia; epistaxis; activities of daily living; quality of life; severity of illness index

Introduction

Hereditary haemorrhagic telangiectasia (HHT), as named by Hanes in 1909 (also known as Osler–Weber–Rendu or Osler's disease^(1–4)), is a systemic disease characterised by telangiectasis and arteriovenous malformations in various organs. In the field of otorhinolaryngology, it is well known as the cause of intractable epistaxis⁽⁵⁾. It is diagnosed based on the Curaçao clinical diagnostic criteria⁽⁶⁾. HHT is an autosomal-dominant genetic disorder caused by mutations in the ENG and ACVRL1 genes, referred to as HHT1 and HHT2, respectively⁽⁵⁾. Although ENG and ACVRL1 mutations account for the majority of HHT cases, muta-

tions in the SMAD4 gene are also related to HHT development⁽⁷⁾. In Japan, the prevalence of HHT is estimated to be one in 5,000–8,000 individuals⁽⁸⁾. Interestingly, approximately 99% of Japanese patients may experience recurrent epistaxis, which is the most common symptom⁽⁹⁾. As epistaxis is one of the major factors impairing the quality of life (QoL) of patients with HHT^(10–13), it is useful for physicians and patients themselves to ascertain the severity of epistaxis and the epistaxis severity score (ESS), as proposed by Hoag et al.⁽¹⁴⁾. According to previous work, patients with severe epistaxis based on the ESS are more likely to have affected Physical Component Summary and present significantly

Please answer the following questions related to your HHT profile.

1. Please write your age. () years old
2. Please write your gender. ()
3. Have you been diagnosed with HHT?
 - A. No, I have not been diagnosed with HHT
 - B. Yes, I have been diagnosed with HHT
 - C. I was suspected of having HHT.
4. At what age were you diagnosed with or suspected of having HHT? () years old

Please answer each of the following questions as they pertain to your TYPICAL nosebleed symptoms DURING THE PAST 3 MONTHS.

1. How often did you TYPICALLY have nosebleeds?
 - Less than monthly
 - One to three times per month
 - Once per week
 - Several per week
 - Once per day
 - Several per day
2. How long did your nosebleed TYPICALLY last?
 - < 1 minute
 - 1-5 minutes
 - 6-15 minutes
 - 16-30 minutes
 - > 30 minutes
3. How would you describe your TYPICAL nosebleed intensity?
 - Not Typically Gushing or Pouring
 - Typically Gushing or Pouring
4. Have you sought medical attention for your nosebleeds?
 - No Yes
5. Are you anemic (low blood counts) currently?
 - No Yes
6. Have you received a red blood cell transfusion SPECIFICALLY for nosebleeds?
 - No Yes

Please answer questions about nosebleeds.

1. When did you start to realize that you have a lot of nosebleeds?
 - A. ≤19 years old
 - B. 20-39 years old
 - C. 40-59 years old
 - D. ≥60 years old
2. Is there anything you are doing to prevent nosebleeds?
 - A. Not touching my nose.
 - B. Taking medication
 - C. Applying ointment to the nose
 - D. Wearing a mask.
 - E. Washing out the nose
 - F. Other ()
 - G. I've never really cared.
3. Overall, to what extent are the activities of daily living limited by nosebleeds? (Please draw a line where appropriate.)

not limited at all completely limited

4. How much are you limited by nosebleeds in going out (within a day)?

not limited at all completely limited

5. How much are you limited by nosebleeds in going on overnight trips?

not limited at all completely limited

6. How much are you limited by nosebleeds in meeting with others?

not limited at all completely limited

7. How much are you limited by nosebleeds in eating with others?

not limited at all completely limited

Figure 1. The questionnaire form regarding the ESS and the performed activities of daily living. This form was translated into English. The actual questionnaire was written in Japanese. ESS, epistaxis severity score.

worse Mental Component Summary scores than those with mild epistaxis⁽¹³⁾. Arai and Akiyama reported that patients with HHT in Japan expected constant updates concerning HHT therapy, convenient access to HHT-specific epistaxis treatment, longer consultation time, acquisition of expert skills by the otolaryngologist, and sufficient knowledge to stop the recurrent nasal bleeding⁽¹⁵⁾. These expectations suggested that these issues had not been satisfied. Recurrent epistaxis may interfere with the patients' daily life. However, the extent to which epistaxis restricts their daily life and the type of treatment that patients with HHT receive have not been investigated. This information would aid medical professionals in gaining better insights into the patients' condition and would help treatment guidance.

We hypothesised that HHT-related epistaxis limited the performed activities of daily living of these patients. It was also considered necessary to investigate the measures taken by patients with HHT to prevent epistaxis, as it would be beneficial for them to be informed if prevention was inadequate. Although the activities of daily living are an indicator of the patients' QoL, we aimed to investigate the restriction of the activity range more directly by conducting a questionnaire survey using the visual analogue scale (VAS). Therefore, with the cooperation of the Japan Osler's Disease Patient Association, we examined the

severity of epistaxis and the correlation between epistaxis and daily behavioural restrictions to obtain knowledge on the severity of epistaxis among patients with HHT in Japan and highlight the importance of epistaxis prevention and treatment.

Materials and methods

Questionnaire

We conducted an anonymous questionnaire survey of patients with HHT who attended the 2017 annual meeting of the Japan Osler's Disease Patient Association. The questionnaire (Figure 1) was distributed at the meeting, and the patients were asked to complete it. We used the REDcapTM system as a questionnaire method for online responses. Patients who were unfamiliar with the use of the Internet were asked to fill out a paper questionnaire. A printed QR code form was distributed to those who wanted to complete the questionnaire online, and a questionnaire form was distributed to those who preferred a paper-based response. Both online and paper responses were received within 2 months. The survey items included age, sex, HHT diagnosis, the severity of epistaxis, and the degree of limitation in the activities of daily living.

Regarding the severity of epistaxis, the questions were focused

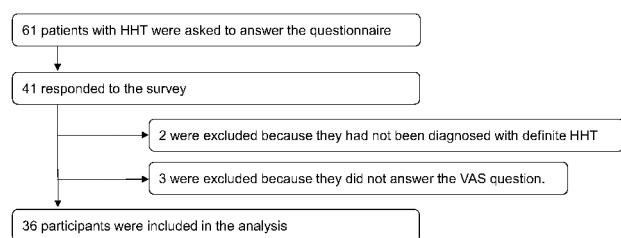


Figure 2. Flowchart of the survey participants. HHT, hereditary haemorrhagic telangiectasia; VAS, visual analogue scale.

on the following: epistaxis frequency, duration, intensity, and history of epistaxis-related medical consultation, anaemia, and blood transfusion. The normalised ESS was calculated from the answers⁽¹⁴⁾. The impact on the activities of daily living was investigated using a 10-cm VAS in five categories: general daily life, going out (within a day), meeting with others, eating with others, and going on overnight trips. The participants were asked the following: 'How much of your daily social life is limited by epistaxis?' and 'To what extent are you restricted from going out (within a day)/meeting with others/eating with others/going on overnight trips because of epistaxis?' Preventive measures taken by the participants were also asked. The questions were primarily focused on the following issues: not touching my nose, taking medication, applying ointment to the nose, wearing a mask, washing out the nose, no care regarding the disease, and others. Multiple answers were allowed.

Table 1. Characteristics of the respondents.

Characteristic		
Sex	Male	19 (52.8%)
	Female	17 (47.2%)
Current age (years)	53.5 (18–83)	
Age at HHT diagnosis (years)	42 (6–70)	
Age of epistaxis onset (years)	≤19	17 (47.2%)
	20–39	9 (25%)
	40–59	10 (27.8%)
	≥60	0 (0%)

Data are presented as numbers (percentages) or medians (ranges). HHT, hereditary haemorrhagic telangiectasia.

Statistical analysis

All statistical analyses were performed using JMP Pro 14 Software (SAS Institute, Cary, NC). The correlation between the ESS and the degree of limitation in the activities of daily living was analysed using Spearman's rank correlation coefficient. The Kruskal–Wallis test was used to compare the limitations in the activities of daily living according to the ESS. For all tests, the level of significance was set at $p < 0.05$.

Ethics

This study was approved by the Ethics Committee of Osaka University Hospital (#17092). All participants provided written informed consent.

Table 2. Characteristics of epistaxis and normalised ESS.

Characteristic		N	(%)
Frequency of epistaxis	Less than monthly	0	0.0%
	Once per month	2	5.6%
	Once per week	3	8.3%
	Several times per week	8	22.2%
	Once per day	9	25.0%
	Several times each day	14	38.9%
Duration of epistaxis	<1 min	2	5.6%
	1–5 min	14	38.9%
	6–15 min	12	33.3%
	16–30 min	4	11.1%
	>30 min	4	11.1%
How would you describe your typical nose bleeding intensity?	Not typically gushing	24	66.7%
	Typically gushing or pouring	12	33.3%
Have you ever sought medical attention for nose bleeding?	No	28	77.8%
	Yes	8	22.2%
Are you anaemic (low blood count) currently?	No	13	36.1%
	Yes	18	50.0%
	I do not know	5	13.9%
Have you ever received a red blood cell transfusion specifically because of nose bleeding?	No	35	97.2%
	Yes	1	2.8%
ESS [median (range), 4.3 (1.0–8.4)]	Severe	3	8.3%
	Moderate	17	47.2%
	Mild	16	44.4%

ESS, epistaxis severity score.

Table 3. Relationship between the epistaxis severity score and the performed activities of daily living.

How limited is the following activity due to epistaxis?	rs	p-value
General daily life	0.59	<0.01
Going out	0.53	<0.01
Meeting others	0.57	<0.01
Eating with others	0.58	<0.01
Going on overnight trips	0.64	<0.01

rs was calculated by Spearman's rank correlation coefficient.

Results

In total, 200 sphenoidal sinuses of 100 human cadaver (43 men, 57 women; mean age: 81 ± 11,3 years) were investigated. Sellar, post-sellar, lateral and combined sinus pneumatization type occurred in 100 (50%), 46 (23%), 26 (13%) and 28 (14%) sides. 44 of the specimens showed on at least one side an OCR. 20 of them had a unilateral OCR whereas the remaining 24 samples showed a bilateral OCR. In total, an OCR occurred in 68 of 200 (34%) sides. Significant differences in OCR presence were found between sinus pneumatization types [χ^2 (3) = 20.09; p < 0.001; V = 0.317]: the combined type showed the highest prevalence of OCR presence (14/28, 50%), followed by lateral (6/26, 23%), post-sellar (8/28, 17%) and sellar (12/100, 12%), respectively. Divided according to the extent of pneumatization, a sub-optical and latero-optical OCR were found in 19% and 15% of the sides (38/200 and 30/200), respectively. Detailed results of OCR subtypes according to sphenoid sinus pneumatization are presented in Table 1.

A bony dehiscence in the OCR area could be identified in 40 of 200 sides. Of the 61 patients with HHT who attended the 2017 annual meeting of the Japan Osler's Disease Patient Association, 41 participated in the survey (Figure 2). Among them, 39 parti-

cipants answered that they had been diagnosed with definite HHT. Three participants who did not answer the VAS questions were excluded; thus, 36 patients were finally included in the analysis.

The respondents were 19 men and 17 women with a median age of 53.5 (range, 17–83) years (Table 1). All respondents reported >1 episode of epistaxis per month, and 34 (94.4%) patients reported >1 episode per week. In total, 23 patients (63.9%) suffered from daily epistaxis. The median ESS was 4.3 (range, 0.9–8.4). There were three severe, 17 moderate, and 16 mild cases of epistaxis (Table 2).

Table 3 shows the correlation between the degree of limitation in the activities of daily living and the ESS. The overall daily activities, going out, meeting people, eating with others, and the extent of travel restrictions for overnight trips had a significant correlation with the ESS (range, 0.53–0.64). When we compared the degree of limitation in the activities of daily living according to the epistaxis severity, the patients in the more severe group showed significantly greater limitations in the performed activities of daily living (Figure 3).

In the survey on measures taken to prevent epistaxis by themselves, most respondents (77.8%) answered that they did not touch their noses (Table 4); 41.7%, 25.0%, and 2.8% of the participants used an ointment, a mask, and performed nasal irrigation, respectively; and a total of 44.4% took preventive measures to prevent dryness of the nasal cavity. In the mild ESS group, only 18.8% of the participants used ointments, and 12.5% performed nasal irrigation. In contrast, a significantly greater proportion (58.8%) applied ointment and nasal irrigation in the moderate ESS group (p < 0.05). In addition, 41.7% of the respondents answered that they had received a type of medication, while 13.9% answered that they did not take any special preventive measures.

Table 4. Preventive measures to avoid epistaxis daily, as reported by the patients (multiple answers were allowed).

	Overall		Mild		Moderate	
	N	Ratio	N	Ratio	N	Ratio
Not touching my nose	28	77.8%	11	68.8%	14	82.4%
Taking medication	9	25.0%	3	18.8%	3	17.6%
Applying ointment to the nose	15	41.7%	3	18.8%	10	58.8%
Wearing a mask	1	2.8%	0	0.0%	1	5.9%
Washing out the nose	15	41.7%	2	12.5%	10	58.8%
Others	7	19.4%	4	25.0%	2	11.8%
No care regarding the disease	5	13.9%	4	25.0%	1	5.9%

* Statistically significant (p<0.05) (moderate vs mild).

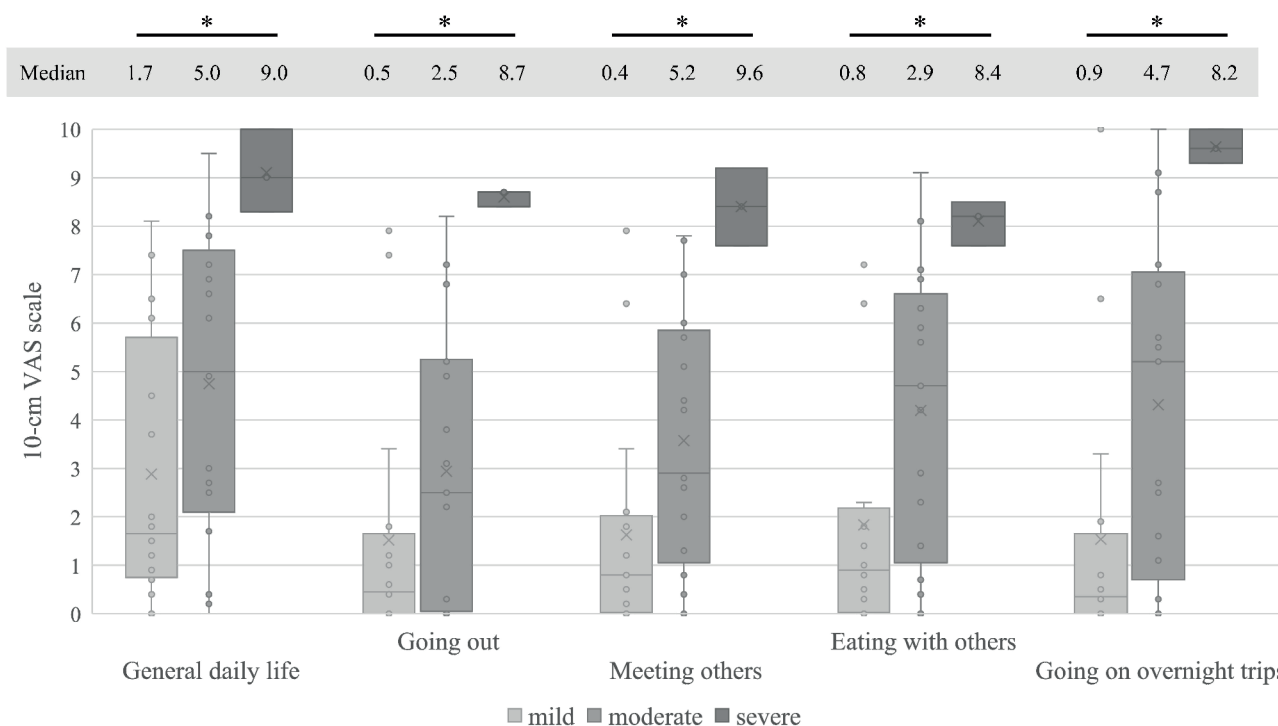


Figure 3. Limitations in the activities of daily living by the severity of epistaxis (10 cm-VAS scale). Each box shows the inter-quarter range. The median VAS score (cm) for the range of actions in each group is presented at the top of the diagram. VAS, visual analogue scale. Comparison of each group was performed using ANOVA.

Discussion

In the present study, we investigated the severity of epistaxis and the correlation between epistaxis and daily behavioural restrictions among patients with HHT in Japan. Most respondents reported >1 episode of epistaxis per week. All activities of daily living were significantly correlated with the ESS. Moreover, patients with severe epistaxis showed significantly greater limitations in the activities of daily living than those with mild and moderate epistaxis. Furthermore, almost one-fifth of the patients answered that they did not take any special preventive measures.

The prevalence of epistaxis in HHT was reported to be 95–99%^(9,14,15). In our study, the prevalence was 94.4%, which was consistent with the results of having >1 episode of epistaxis per week. Gonzalez et al. reported that the severity of epistaxis was mild in children, even in confirmed HHT cases⁽¹⁶⁾. Nonetheless, 50% of patients reported the presence of epistaxis by the age of 20 years, which was consistent with our finding that 47.2% of patients had recurrent epistaxis by the age of 19 years. These findings suggested that most patients with HHT have recurrent epistaxis as a part of their lives.

In this study, we found that the ESS was correlated with the limitations in the activities of daily living in patients with HHT. Merlo et al. reported that the ESS is a major determinant of impaired health-related QoL (HR-QoL) in these patients⁽¹³⁾. Geisthoff et al.

stated that the duration of epistaxis, as well as liver involvement, gastrointestinal bleeding, and the number of visible telangiectases, presented a major influence on the HR-QoL of patients with HHT⁽¹⁰⁾. The management of recurrent epistaxis may be effective for improving the QoL of these patients and for preventing anaemia.

Drug therapy for epistaxis has been tested. In a phase IIIB, randomised, double-blind, placebo-controlled, cross-over study, treatment with tranexamic acid resulted in a decreased ESS by 54%⁽¹⁷⁾. Gaillard et al. also demonstrated a 17% reduction in the mean duration of epistaxis per month in a controlled randomised, double-blind study⁽¹⁸⁾. Topical administration of anti-vascular endothelial growth factor antibodies, bevacizumab, and 5-fluorouracil has been attempted, but these therapies have not been well established^(19–21). The French Society of Otorhinolaryngology recommends the administration of tranexamic acid if there are no cardiovascular contraindications⁽²²⁾. However, in our survey, only 41.7% of the patients received medication, suggesting the necessity of educational activities for medical professionals. These results may indicate why patients with HHT expect expertise from otolaryngologists⁽¹⁵⁾.

Regarding epistaxis prevention, avoiding nasal dryness and crusting may prevent the triggering of bleeding⁽²³⁾. In a British study, in which a questionnaire survey was conducted in patients with HHT, room humidification, nasal lubrication, and

saline treatment were reported to be beneficial⁽²⁴⁾. Therefore, at present, guidance to prevent nasal dryness and crust adhesion can prevent nasal bleeding. In the severe ESS group, all patients (100%) answered that they prevented nasal dryness. However, only 58.8% of the participants stated that they had taken preventive measures in the moderate ESS group. Although this proportion is not low, it is not adequate. Despite the limitations caused by epistaxis in daily life activities, epistaxis prevention is not sufficiently widespread. Given the lack of patient guidance and the inadequacy of drug therapy, otolaryngologists in Japan should be better educated regarding HHT.

This study had several limitations. First, the number of participants was small. Second, as it was a questionnaire survey, the diagnosis of HHT was self-reported, and information regarding cerebrovascular or pulmonary complications was not obtained. Third, only 8.3% of cases were severe; therefore, this study was primarily focused on mild and moderate cases. Fourth, our questionnaire was original and had not been validated. Further prospective studies are needed to determine whether controlled epistaxis can reduce the degree of daily life limitation.

Conclusions

Epistaxis impacted the daily life of patients with HHT in proportion to its severity. In this study, the cohort mainly consisted of cases with mild and moderate epistaxis. Nevertheless, we found that the group with moderate epistaxis, in particular, experienced significant limitations in daily life. In addition, less than half of the patients took medications or adopted precautionary measures. Hence, further educational activities should be considered for medical professionals and patients.

List of abbreviations

ESS, epistaxis severity score; HHT, haemorrhagic telangiectasia; HR-QoL, health-related quality of life; QoL, quality of life; VAS, visual analogue scale.

Authorship contribution

HI and MH supervised the project. YM, TT, HA, and MH analysed the data and wrote the manuscript. YM, TT, HA, AN, SO, YM, and KT provided advice on project planning and data interpretation. All authors participated in the discussion of the results and critically polished and approved the final draft.

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Ethics approval and consent to participate

This report was approved by the Institutional Review Board of Osaka University Hospital.

Consent for publication

Written informed consent was obtained from all participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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