

Altered quality of life in Rendu-Osler-Weber disease related to recurrent epistaxis*

I. Ingrand¹, P. Ingrand¹, B. Gilbert-Dussardier³, G. Defossez⁴, V. Jouhet⁴, V. Migeot⁴, X. Dufour², J.M. Klossek²

¹ Clinical Investigation Center INSERM CIC-P 802, Centre Hospitalier Universitaire, Université de Poitiers, France

² Department of Otolaryngology Head & Neck, Centre Hospitalier Universitaire, Poitiers, France

³ Competence center for HHT, Department of Medical Genetics, Centre Hospitalier Universitaire, Poitiers, France

⁴ Public Health Department, Centre Hospitalier Universitaire, Poitiers, France

SUMMARY

Objectives: Development and validation of an epistaxis-specific quality-of-life questionnaire (EQQoL) to evaluate the impact on quality of life of epistaxis, during hereditary hemorrhagic telangiectasia (HHT).

Study design: Prospective clinical study using QoL instruments administered twice in HHT patients.

Patients and methods: In total, 109 patients who had epistaxis and a clinical diagnosis of HHT according to Curaçao criteria were included. Invoice of the questionnaire in 2004 and 2006 included SF-36, Jenkins' sleep scale and the new epistaxis-specific 13-item EQQoL.

Results: EQQoL uptake rate was 98%, mean score 58/100 ± 27, and Cronbach alpha 0.96. EQQoL was sensitive to change with a strong correlation with the course of epistaxis. Factorial analysis showed that EQQoL was clearly distinct from SF-36 and Jenkins sleep scales. In stepwise multivariate ordinal logistic regression, frequency and duration of epistaxis were both associated with lower EQQoL. Conversely, visceral involvement and comorbidity had independent impact on SF-36 scores, but not on EQQoL.

Conclusions: This new epistaxis-specific EQQoL questionnaire provides complementary information on the impact of HHT on patients' quality of life relative to the SF-36 generic questionnaire. After international validation, the EQQoL might prove a useful tool for treatment evaluation.

Key words: epistaxis, hereditary hemorrhagic telangiectasia, Osler Rendu Weber disease, quality of life

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber disease, is an autosomal dominant disorder characterized by systemic vascular dysplasia due to a mutation in the endoglin or the activin receptor gene ⁽¹⁾. The worldwide prevalence of HHT ranges from 1/996 in a French county ⁽²⁾ to 1/39216 in northern England ⁽³⁾. The diagnosis is mainly based on clinical grounds, consisting of a combination of epistaxis, telangiectasias, visceral manifestations, and a family history (Curaçao criteria) ⁽⁴⁾. One of the most frequent target sites is the mucous membrane of the nose. Spontaneous irregular nosebleeds, occurring in over 90% of cases, often at night ⁽⁵⁾, are the main manifestation and also the most distressing symptom. Frequently, patients feel they are not adequately taken into account and they complain of being incapacitated by epistaxis and express a strong desire for more effective therapies ^(6,7) that would reduce the frequency and/or the duration of nosebleeds.

It is particularly important to take a multidimensional concept ⁽⁸⁾ into account, during chronic and incapacitating disorders like the quality of life that takes the patient's perception of his or her own health into consideration. Few studies dealt with quality of life in patients with HHT. Most published studies used generic questionnaires such as SF-36, in Italian ⁽⁹⁾, English ⁽¹⁰⁾, and German populations ^(7,11), but to our knowledge, there have been no such studies in France or North America. These studies all showed that patients with HHT had a significantly diminished general quality of life, compared with the general population, but the impact of the rhinological dimension of epistaxis-related quality of life has never been specifically explored because of the lack of validated questionnaires. Epistaxis compromises quality of life ^(11,12), and can impede social life, employment, leisure, hobbies and mental status. Some studies based on generic questionnaires have shown an improvement in quality of life after treatment

for epistaxis by nasal closure or laser therapy^(13,14). However, generic questionnaires, which measure health-related quality of life independently of specific diseases, or even in the absence of disease, have limited sensitivity, and a more clinically sensitive and responsive instrument for therapeutic evaluation in patients with epistaxis is missing⁽⁸⁾.

The main objective of this study was to develop and validate an epistaxis-specific questionnaire that, when combined with the SF-36 generic questionnaire, can simultaneously evaluate all aspects of quality of life in patients with HHT. Secondary objectives were 1) to quantify the impact of HHT on quality of life, by comparison with studies of the general French population, and 2) to identify determinants of quality of life in HHT patients.

MATERIALS AND METHODS

Patients

All patients involved in the study are managed in the Poitou-Charentes region of western France, which represents 2.8% of the French population including a county (Deux-Sèvres) where the prevalence of HHT is particularly high (1/2381)⁽²⁾. To be included, patients must have epistaxis and a clinical diagnosis of HHT according to the Curaçao criteria.

Questionnaires were sent by mail in 2004 and repeated in 2006 to determine reproducibility and sensitivity to changes of the specific questionnaire. The patient population was expanded in the second phase of the study to increase the statistical power.

Survey questionnaires

To study the quality of life of patients with HHT, we used a self-rating questionnaire composed of a generic quality-of-life questionnaire, a sleep questionnaire, and an epistaxis-specific questionnaire. We used the French version of the generic SF-36⁽¹⁵⁾, that comprises 36 items grouped together in eight dimensions: Physical Functioning (PF), Physical Role limitations (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Mental Health (MH), and Emotional Role limitations (RE). To study the impact of HHT, and especially epistaxis (often nocturnal), on sleep, we used the validated Jenkins questionnaire⁽¹⁶⁾ that includes four items with responses in the form of 6-point Likert scales (0 = none, to 5 = 22-31 days/month).

We developed a 13-item epistaxis-specific questionnaire to explore the impact of nosebleeds occurring during the four weeks before the survey. A multidisciplinary team of clinicians (HNT, medical genetics) and biostatisticians elaborated propositions of multiple items based on difficulties frequently reported by the patients. The retained items, with formulations inspired from the Sino-Nasal Outcome Test⁽¹⁷⁾, covered physical problems such as blocked nose, the influence of weather, crusts in the nose, and bad night, functional limitations such as frustration, fatigue, anxiety, precautions, restric-

tions at work, during leisure and mental activities, and emotional consequences of epistaxis (impact on relationships with friends and family), with responses in the form of 7-point Likert scales (all the time = 1, to very rarely or never = 7). The new rating tool was called EQQoL, for Epistaxis Questionnaire Quality of Life.

The survey collected socio-demographic characteristics and comorbidity. Clinically relevant variables^(9,11,12) were the date of the first episode of epistaxis, the frequency and duration of epistaxis during the four-week period before the questionnaire, and visceral involvement. The questionnaire also covered hospitalization and transfusion, and prophylactic treatments during the previous two years.

Statistical analysis

We studied the psychometric properties of EQQoL, and its positioning relative to SF-36 and the Jenkins Sleep questionnaire^(16,18). Relations were sought between the quality-of-life scales on the one hand and socio-demographic characteristics and clinical items on the other hand.

Analysis of EQQoL validity

We analysed EQQoL internal validity from the inter-item correlation matrix and the Cronbach alpha coefficient^(18,19). The internal dimensional structure was assessed by principal components analysis (PCA) followed by factorial analysis with varimax rotation⁽²⁰⁾. The number of factors was determined from a diagram of eigenvalues. A unique overall EQQoL score was calculated, as for the SF-36, by summing the items on a scale of 0 (worst) to 100 (best). The score was computed if at least 50% of the items in the dimension were completed.

EQQoL sensitivity to change was analysed in the population of patients who responded to the questionnaire twice, two years apart, by calculating the correlation between the score change and the outcome of epistaxis. In this correlation analysis, SF-36 scores were used alongside as a global measure of quality of life. In addition, Student's paired *t* test was used to study score differences in patients whose epistaxis frequency changed between the two questionnaires. We assessed reproducibility by the intraclass correlation coefficient in patients whose epistaxis frequency did not change between two questionnaires. Factorial analysis after varimax rotation of the EQQoL, SF-36 and Jenkins Sleep scales was used to assess complementarity between the dimensions of the three scales.

Analysis of determinants of quality of life

Age and sex standardized differences of SF-36 dimensions against a normal French population⁽¹⁵⁾ were tested with a *z* test. Univariate analysis, using nonparametric tests (Mann-Whitney, Kruskal-Wallis and Spearman), was performed to assess the relationship between the clinical variables and dimensions of quality of life (SF-36, EQQoL and Jenkins Sleep). Variables with *p*-values below 0.25 entered a multivariate analysis based on stepwise ordinal logistic regression

Table 1. Sociodemographic characteristics of patients with HHT (n = 109).

Characteristic	n	%
Gender (n = 107)		
Male	56	53
Female	51	48
Educational level (n = 104)		
< baccalaureate	58	56
≥ baccalaureate	46	44
Employment (n = 104)		
Full-time work	39	37
Part-time work	12	12
Unemployed	3	3
Retired	49	47
Other	1	1
Comorbidities (n = 107)		
Arterial hypertension	25	23
Cardiopathy	23	21
Anaemia	23	21
Asthma	7	7
Diabetes	6	6
Age (y) (n = 105)		
Mean (sd) [range]	55.7 (16.8) [15-86]	

Table 2. Clinical characteristics of patients with HHT (n = 109).

Characteristic	n	%
Epistaxis frequency during last four weeks (n = 107)		
Every day	24	22
At least three times a week	40	37
Less than once a week	32	30
Never in the last four weeks	11	10
Average duration of epistaxis during last four weeks (n = 86)		
Less than 5 minutes	38	44
Between 5 and 15 minutes	31	36
More than 15 minutes	17	20
Transfusion in the last two years (n = 95)	22	23
Hospitalization in the last two years (n = 95)	26	27
Prophylactic treatment in the last two years (n = 97)	34	35
Local sclerosis	24	25
Electrical or chemical cauterization	9	9
Embolization	9	9
Laser	4	4
Nasal fossae closure	3	3
Intranasal skin graft	1	1
Visceral involvement (n = 97)		
Gastrointestinal tract	18	19
Liver	12	12
Lung	9	9
Brain	2	2
Time since diagnosis (years) (n = 94)		
Mean (sd) [range]	29.1 (16.0) [1-76]	

analysis. Statistical significance was set at $p < 0.05$. Variables included in the analysis were socio-demographic characteristics (age and sex forced in the model, level of education), disease characteristics (years since diagnosis, duration and frequency of epistaxis, visceral involvement, transfusion, prophylactic treatments) and comorbidities. Occupational status (full or part-time employment, retired) and hospitalization were not included in the multivariate analysis because of their dependency on age and treatment, respectively.

RESULTS

Respectively, 91 and 126 questionnaires were sent to patients during the first and second periods of the survey, with response rates of 87% and 81%. Ten patients with confirmed HHT, but who never had experienced epistaxis, did not meet the inclusion criteria. The analysis was based on 109 cases. Sensitivity to change was studied in the 62 patients who responded to both questionnaires (at baseline and after two years).

The patients' sociodemographic and clinical characteristics are listed in Tables 1 and 2. During the 4 weeks before the questionnaire, the mean duration of epistaxis exceeded 15 minutes in 20% of patients and the frequency was 'daily' in 22% of patients.

EQQoL properties

The uptake rate was 98%. Only two patients completed fewer than 7 of the 13 EQQoL items, meaning that the score could not be calculated. Between 96 and 100% of responses were obtained for each of the different items and 96% of patients responded to all the items. The answers to the EQQoL items were widely dispersed throughout the scale, and no saturation occurred (Table 3). Inter-item correlation coefficients ranged from 0.33 to 0.88. The internal consistency of the EQQoL was reflected by a Cronbach alpha coefficient of 0.96.

The EQQoL was unidimensional, principal components analysis accounting for 68% of the variance explained by the first main axis that included all the items (only one eigenvalue above 1). The mean EQQoL score was 58 ± 27 (range: 0 to 100), and the mean scores were widely dispersed, with no sign of saturation (Table 4).

Sensitivity to change was shown by the strong correlation ($r = -0.53$, $p < 0.0001$) between the EQQoL score changes and the outcome of epistaxis between the two surveys. A change in epistaxis frequency negatively correlated also with every SF-36 dimensions, but significantly only for the vitality score (VT, $r = -0.30$, $p = 0.024$) and social functioning (SF, $r = -0.27$, $p = 0.037$). Moreover, we observed strong positive correlations between change in EQQoL and change in several dimensions of SF-36 (VT, SF, RE, MH), the strongest being the correlation with social functioning (SF, $r = 0.52$, $p < 0.0001$). The EQQoL score increased by an average of 18 points in patients whose epistaxis frequency fell ($p = 0.0047$, $n = 17$), and decreased by

Table 3. Items, floor and ceiling effects, and missing data of the EQQoL epistaxis specific questionnaire in HHT patients (n = 109). Item ratings ranged on 7-point Likert scales from “all the time” = 1 (floor), to “very rarely or never” = 7 (ceiling). This translation is provided solely for the purpose of informing on item content, and is not a validated questionnaire.

Item wording	Floor (%)	Ceiling (%)	Missing (%)
1- Have you felt bothered by having a blocked-up nose?	19	7	0
2- Have you felt restricted by the weather or had to avoid going outdoors because of your nose bleeds?	3	27	1
3- Have you felt frustrated because your nose bleeds have stopped you doing what you wanted?	7	25	2
4- Have you been bothered by the presence of crusts in your nose?	20	8	2
5- Have you ever been afraid you could not stop a nose bleed?	7	34	3
6- Have you been tired or breathless because of your nose bleeds?	5	30	2
7- Have you taken any precautions to prevent your nose bleeds?	23	27	3
8- Have you ever spent a bad night because of your nose bleeds?	7	27	2
9- Have you ever been anxious because you have nose bleeds?	11	32	2
10- Do you nose bleeds restrict your relationships with friends or family?	7	41	2
11- Have your nose bleeds created problems with your work?	5	24	4
12- Have your nose bleeds restricted your leisure activities?	11	29	2
13- Have your nose bleeds restricted your mental activities?	6	37	3

Table 4. SF-36, Jenkins sleep and EQQoL scores descriptive statistics in HHT patients (n=109).

	EQQoL	Physical Functioning (PF)	Physical Role limitations (RP)	Bodily Pain (BP)	General Health (GH)	Vitality (VT)	Social Functioning (SF)	Emotional Role limitations (RE)	Mental Health (MH)	Sleep
N	107	102	104	107	103	105	109	104	105	99
Mean	58.2	70.7	54.3	62.1	46.9	44.3	60.3	54.5	56.0	8.79
Sd	27.2	28.4	44.1	30.5	22.0	19.6	30.0	44.1	21.3	5.77
Minimum	0	0	0	0	0	0	0	0	4	0
25 th percentile	36	56	0	41	30	35	38	0	40	4
Median	60	75	63	62	47	45	63	67	60	8
75 th percentile	82	95	100	100	67	55	88	100	70	13
Maximum	100	100	100	100	92	100	100	100	100	20
% ceiling	1	3	30	4	3	4	6	33	2	3
% floor	2	21	42	25	1	1	18	42	1	4
Skewness coefficient	-.25	-.98	-.13	-.25	-.12	-.27	-.32	-.17	-.43	.30
Cronbach's coefficient	.96	.94	.91	.91	.82	.86	.90	.87	.90	.87

an average of 12 points in patients whose epistaxis frequency increased ($p = 0.031$, $n = 18$). No significant change in the EQQoL scores occurred in the subjects whose epistaxis frequency remained stable (mean difference -1.9 points, $p = 0.46$, $n = 24$). In these 24 subjects, the intra-class correlation coefficient of 0.91 (95% CI 0.80; 0.96), reflected the high test-retest reproducibility.

The SF-36 and Jenkins sleep scale statistics are shown in Table 4. No correlation coefficients above 0.70 were observed between the EQQoL dimensions and the SF36 dimensions. Factorial analysis of all items of the EQQoL, SF36 and Jenkins-Sleep scales identified 9 factors, the first of which corresponded strictly to the 13 EQQoL items, clearly separated from the dimensions of the SF36 and Jenkins Sleep scales. Each EQQoL item correlated much more strongly with the EQQoL score than with the scores for the SF36 dimensions. Likewise, each item of the SF36 correlated more strongly with its corresponding dimension than with the EQQoL.

Impact of HHT on quality of life

Comparison with reported values for the general French population showed that the HHT patients had significantly lower scores for all SF-36 items (Table 5). The largest standardized differences, exceeding 20 points, were for RE, RP, SF and GH. Although statistically significant, the impact of pain (BP) on quality of life was too small to be clinically relevant. The Jenkins sleep score showed a strong impact of HHT on quality of sleep. The mean score of 8.8/20 was far worse than the score obtained in Jenkins' princeps study of 250 subjects (5.5, $p < 0.0001$ in the z test)⁽¹⁶⁾.

Univariate analysis (Table 6) showed that the SF-36 and EQQoL scores fell strongly as the duration of epistaxis increased. The EQQoL score also fell strongly as the frequency of epistaxis increased, while this was the case for only six SF-36 scores (PF, RP, BP, GH, VT and MH), and the amplitude of the difference was also smaller. In the EQQoL, low scores were significantly associated with advancing age, time since

Tableau 5. Comparison of the SF-36 results between patients with HHT (n = 109) and standard French population (n = 3617).

Dimension	Symbol	Content	Sample	Control data	Age-sex adjusted control data	Standardized difference	p-value
Physical Functioning	PF	Measures limitations on physical activities such as walking, climbing stairs, leaning forwards, lifting objects and physical efforts	70.7 (28.4)	84.5 (21.2)	82.0	-11.3	< 0.0001
Physical Role	RP	Measures discomfort due to physical status during daily activities or limitations of some activities or difficulties in executing them	54.3 (44.1)	81.2 (32.2)	78.9	-24.6	< 0.0001
Bodily Pain	BP	Measures the intensity of pain and the discomfort caused	62.1 (30.5)	73.4 (23.7)	71.5	-9.5	0.0015
General Health	GH	Self-assessment of general health, resistance to diseases	46.9 (22.0)	69.1 (18.6)	67.3	-20.4	< 0.0001
Vitality	VT	Self-assessment of vitality, energy, or fatigue	44.3 (19.6)	60.0 (18.1)	59.3	-15.0	< 0.0001
Social Functioning	SF	Measures limitations of social activities due to physical and mental health problems	60.3 (30.0)	81.6 (21.4)	81.0	-20.7	< 0.0001
Mental Health	MH	Self-assessment of mental health: anxiety, depression, well-being	54.5 (44.1)	68.5 (17.6)	68.4	-12.4	< 0.0001
Emotional Role limitations	RE	Measures discomfort due to mental problems in daily activities	56.0 (21.3)	82.13 (32.15)	80.5	-26.0	< 0.0001

Values are given as mean (SD).

diagnosis, low educational status, no paid employment, and a history of transfusion, prophylactic treatment and hospitalization. In the SF-36, significant associations were also found with gender, visceral involvement or comorbidity.

After using a descending procedure to eliminate variables below the 0.05 threshold, ordinal logistic regression analysis (Table 7) retained three mutually independent variables that were associated with a reduction in the EQQoL score, namely the frequency of epistaxis ($p < 0.0001$), the duration of epistaxis ($p < 0.0001$), and a history of prophylactic treatment ($p = 0.0025$). These variables concordantly predicted 75% (c statistic) of the EQQoL scores in this population. The residual standard deviation of the EQQoL score obtained in the model was 15. The mean EQQoL score fell strongly as the frequency of epistaxis increased, from 76 (no epistaxis) to 44 (daily epistaxis). The score also fell as the duration of epistaxis increased, from 73 (epistaxis lasting 5 minutes or less) to 45

(> 15 minutes). The need of prophylactic treatment was associated with a score reduction of about 10 points.

An identical procedure showed that the frequency of epistaxis was associated with none of the SF-36 dimensions, while the duration of epistaxis had a major influence on all the SF-36 scores. Comorbidity, visceral involvement, transfusion or the need of prophylactic treatment were also associated with certain dimensions of SF-36.

In 62 patients who completed the two questionnaires (at baseline and after two years), treatment by embolization ($n = 8$), alone or associated with nasal fossae closure ($n = 3$) or skin grafting ($n = 1$), was related to a significant improvement in the EQQoL score ($P = 0.040$, difference of 17 points, 95% CI 1 to 34). In contrast, there was no significant improvement in SF-36 dimensions.

Table 6. Components of quality of life in relation with sociodemographic and clinical variables: Results of univariate analysis (p values and arithmetic means).

Scale	EQQoL	PF	RP	BP [0 - 100]	GH	VT	SF	RE	MH	Sleep [0 - 20]
Age (y)	.0001	<.0001	<.0001	.0003	.0004	.0029	.0023	<.0001	.13	.070
< 45 (n = 29)	71	88	85	75	59	52	73	77	59	7.0
[45-64] (n = 38)	60	71	59	62	46	43	62	55	57	8.9
≥ 65 (n = 38)	48	60	30	52	40	40	52	36	53	10.1
Sex	.082	.014	.049	.0075	.0031	.0004	.047	.0086	.0002	.0060
F (n = 51)	53	64	46	54	40	37	55	42	48	10.6
M (n = 56)	63	78	63	69	53	51	66	65	63	7.4
Education	.0003	<.0001	<.0001	<.0001	.0010	.0007	.0011	<.0001	.0080	.058
< baccalaureate (n=58)	51	60	38	52	41	39	53	38	51	9.8
≥ baccalaureate (n=46)	70	86	78	75	56	52	72	76	62	7.6
Employment	.0013	<.0001	<.0001	.0012	.0016	.0093	.0006	.0002	.11	.11
Full-time (n = 39)	69	87	76	75	57	52	74	74	62	7.4
Part-time (n = 12)	67	65	73	68	49	45	67	72	53	8.1
Retired (n = 49)	49	59	33	51	40	39	50	38	53	10.0
Comorbidities	.052	.048	.024	.043	.0003	.0005	.011	.020	.0004	.13
yes (n = 58)	54	65	45	57	40	38	54	46	50	9.5
no (n = 49)	64	77	65	69	56	52	68	66	64	7.8
Illness duration (y)	.019	.053	.22	.055	.038	.021	.15	.30	.53	.59
< 20 (n = 29)	63	77	58	67	49	48	61	54	57	9.3
[20-40] (n = 38)	62	73	58	62	49	48	68	56	58	8.0
≥ 40 (n = 27)	47	62	40	51	37	35	48	52	50	10.5
Visceral involvement	.22	.0015	.0008	.016	.017	.17	.027	.045	.10	.0025
yes (n = 32)	55	61	38	53	41	42	54	45	53	11.3
no (n = 65)	62	79	69	69	52	48	68	64	60	7.4
Epistaxis frequency	<.0001	.022	.044	.0036	.026	.0045	.071	.098	.029	.74
none (n = 11)	88	81	57	78	57	54	74	55	69	9.3
< 1d/week (n = 32)	74	78	79	73	55	51	66	75	60	7.4
3d/week (n = 40)	49	66	40	55	40	42	55	43	54	10.1
every day (n = 24)	43	66	52	55	46	39	60	51	52	7.9
Epistaxis duration	<.0001	.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.049
< 5 minutes (n = 47)	80	84	77	78	59	54	76	73	67	7.5
≥ 5 and < 15 (n=31)	49	67	53	55	41	43	58	57	56	9.9
> 15 minutes (n = 17)	30	57	23	41	34	32	43	19	41	10.1
Hospitalization	<.0001	.040	.0014	.0006	.0071	.018	.012	.0023	.029	.0012
yes (n = 26)	38	64	36	47	38	39	52	35	51	12.2
no (n = 69)	68	77	68	71	52	49	68	66	61	7.6
Transfusion	.0002	<.0001	<.0001	<.0001	<.0001	<.0001	.0021	.011	.019	.32
yes (n = 22)	42	50	25	40	30	32	48	35	49	9.9
no (n = 73)	66	79	69	71	54	50	69	64	61	8.4
Prophylactic treatment	.0006	.20	<.0001	.041	.060	.21	.34	.0008	.32	.0037
yes (n = 34)	46	68	35	55	42	43	59	37	55	11.2
no (n = 63)	66	76	72	68	51	48	65	68	59	7.4

DISCUSSION

Epistaxis are the main symptom of hereditary hemorrhagic telangiectasia⁽⁵⁾. They are difficult to manage in this setting, and their recurrent nature has a negative impact on patients' quality of life⁽¹³⁾. Yet this impact is often underestimated by family and caregivers. While some patients have abrupt-onset and abundant bleeding episodes, most have unpredictable minor daily bleeds. Patients have to manage these incidents

themselves, and many do not see them as a real disability. Nevertheless, a good number of patients have to restrict certain activities.

Many questionnaires have been developed over the last few decades to measure health-related quality of life in rhinology⁽²¹⁾, and procedures for their development and validation have now been standardized. Before envisaging the creation of a

Table 7. Multivariate analysis of components of quality of life in relation with sociodemographic and clinical variables (p values and least-squares means).

	EQQoL	PF	RP	BP	GH	VT	SF	RE	MH	Sleep
Age	.0015	<.0001	.0020	.081	.011	.11	.050	.0023	.85	.069
Sex	.75	.0017	.76	.11	.0009	.0004	.13	.016	.023	.0024
Comorbidity	-	-	-	-	.0012	<.0001	-	-	.0076	-
yes					40	38			49	
no					51	49			59	
Visceral involvement	-	-	.033	-	-	-	-	-	-	-
yes			40							
no			59							
Epistaxis frequency	<.0001	-	-	-	-	-	-	-	-	-
none	76									
< 1d/week	61									
3d/week	50									
every day	44									
Epistaxis duration	<.0001	.041	.0023	.0030	.014	.0037	.0009	.0066	.0002	-
< 5 minutes	73	72	67	67	54	51	74	66	65	
5 to 15 minutes	55	62	47	48	42	43	57	54	56	
> 15 minutes	44	64	35	47	41	37	48	32	42	
Transfusion	-	.0099	-	.0089	-	-	-	-	-	-
yes		57		43						
no		75		65						
Prophylactic treatment	.0025	-	.0064	-	-	-	-	-	-	.038
yes	52		38							8.1
no	63		60							10.7

Age and sex forced in each multivariate ordinal logistic regression analysis. P-values for significant variables at the .05 level are displayed. Least-squares means are derived from the linear combination of the retained variables.

new questionnaire, one must ensure that there are no validated questionnaires that are ready to use or simply need local adaptation. In addition, it must be shown that the new questionnaire is truly useful compared with existing instruments⁽²²⁾. The SF-36 questionnaire has already been used in HHT^(10,23), and its relevance in this setting is borne out by the results of our survey. However, the observed lack of correlation between the frequency of epistaxis and the different dimensions of the SF-36⁽¹¹⁾ shows that the SF-36 is not sufficiently sensitive to measure the full impact of epistaxis - the symptom that patients consider most bothersome and that interferes with their leisure activities^(7,9). We therefore created a specific questionnaire, EQQoL, composed of 13 items focusing on the impact of epistaxis and we have obtained significant results showing that the new questionnaire is truly useful compared with existing instruments⁽²²⁾. We found that the EQQoL had satisfactory psychometric properties: it was very well accepted and homogeneous, correlated with characteristics of epistaxis (frequency and duration), was sensitive to change and complementary with SF-36 and Jenkins sleep scales.

Rating scale validation requires large population samples, and this poses a problem when dealing with rare diseases. The HHT population studied here, consisting of 109 assessable patients, is to our knowledge, the largest published to date:

previous studies involved 50 Italian patients⁽⁹⁾, 38 English patients⁽¹⁰⁾, and 77 German patients⁽¹¹⁾. We choose not to reduce the number of items, despite certain strong correlations⁽¹⁹⁾, to maintain clinical relevance. The complementarity of the EQQoL, SF36 and Jenkins Sleep scales was verified by factorial analysis of all the items, which identified 9 factors clearly separating the EQQoL, SF36 dimensions and Jenkins sleep scale. The EQQoL questionnaire therefore meets the necessary requirements for use as a pertinent and sensitive health-related quality-of-life rating scale. It can thus be used as a stand-alone instrument for evaluating the impact of epistaxis. When combined with the SF-36 and Jenkins Sleep questionnaires, it can also contribute to providing a more comprehensive evaluation of epistaxis-related quality of life.

The results of this study underline the strong impact of HHT on patients' quality of life, and more specifically the impact of epistaxis⁽¹²⁾. We found that quality of life was undermined by lengthy episodes of epistaxis, based both on the generic SF36 questionnaire and on the EQQoL. In contrast, only the EQQoL was sensitive to the frequency of epistaxis⁽¹¹⁾. This is important, as epistaxis can engender a feeling of isolation and mental distress⁽⁹⁾ that physicians often underestimate^(7,24). Despite a high correlation with epistaxis frequency, the use of EQQoL questionnaire may be justified by the objective to

assess patient's perception of the impact of his/her illness on his/her quality of life. Visceral involvement was associated with significantly lower scores in several dimensions of the SF-36⁽¹¹⁾, but no relationship was found with EQQoL, an indication that the EQQoL effectively focuses on a specific dimension and provides a complementary picture of the impact of HHT relative to the SF-36 generic questionnaire.

Comparison of the SF-36 results with those reported for the French general population further shows the major impact of HHT on quality of life. The largest standardized differences were found for the General Health, Emotional Role limitations, Physical Role limitations and Social Functioning dimensions; these differences exceeded 20 points, which can be considered highly clinically significant⁽²⁴⁾. Patients with HHT therefore have poorer general health, more problems with their work and activities of daily life (because of their physical and mental state), and more relational difficulties. The Bodily Pain score was altered in the HHT patients, but the difference with the general population was below 10 points on average, meaning that it had limited clinical relevance.

Strong evidence for validity was obtained. However, certain inherent limitations of our study must be taken into account before extrapolating these results and recommending routine use of the EQQoL questionnaire. First, the questionnaire must be validated by international studies, outside of the French sociocultural and medical context. The original American SF-36 questionnaire was adopted in many other countries after 1) translation and validation of the translation, 2) validation of the scale, including psychometric criteria, and 3) norming of the instrument with representative national samples. The same international validation process must now be applied to the EQQoL.

CONCLUSION

Current endpoints in controlled clinical trials of new treatments are the number and intensity of epistaxis^(5,13), but these are assessed with poorly validated tools. Quality-of-life instruments used in clinical evaluation can help orient the use of alternative treatments^(6,8,14), and contribute to meeting patients' strong demand for more effective epistaxis therapies⁽⁷⁾. The EQQoL questionnaire can evaluate the impact of epistaxis on quality of life both at a given time point, and also during treatment, as it is sensitive to therapeutic modifications. Thus, once widely validated, the epistaxis-specific EQQoL quality-of-life rating tool could be useful for therapeutic evaluation.

The EQQoL questionnaire is freely available in French and English, on request from the authors.

ACKNOWLEDGEMENTS

The authors thank the patients for their participation in the study, as well as the AMGORO HHT Patient Association (Association maladie génétique orpheline Rendu-Osler), which provided in part financial/material support for this research and the CITAF multidisciplinary team (Investigation and Treatment Center for Angiomatous Families), based at Poitiers University Hospital.

REFERENCES

1. Thomas B, Eyries M, Montagne K et al. Altered endothelial gene expression associated with hereditary haemorrhagic telangiectasia. *Eur J Clin Invest* 2007; 37: 580-588.
2. Bideau A, Plauchu H, Brunet G, Robert J. Epidemiological investigation of Rendu-Osler disease in France: its geographical distribution and prevalence. *Popul*. 1989; 44: 3-22.
3. Guttmacher AE, Marchuk DA, White RI, Jr. Hereditary hemorrhagic telangiectasia. *N Engl J Med*. 1995; 333: 918-924.
4. Shovlin CL, Guttmacher AE, Buscarini E et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet*. 2000; 91: 66-67.
5. Sadick H, Fleischer I, Goessler U, et al. Twenty-four-hour and annual variation in onset of epistaxis in Osler disease. *Chronobiol Int*. 2007; 24: 357-364.
6. de Gussem EM, Snijder RJ, Disch FJ, et al. The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study. *Rhinology* 2009; 47: 85-88.
7. Slotosch D, Koller M, Werner JA, et al. Recurrent nosebleeds in patients with hereditary hemorrhagic telangiectasia. *Dtsch Med Wochenschr*. 2006; 131: 535-539.
8. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med*. 1993; 118: 622-629.
9. Pasculli G, Resta F, Guastamacchia E, et al. Health-related quality of life in a rare disease: hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber disease. *Qual Life Res*. 2004; 13: 1715-1723.
10. Lennox PA, Hitchings AE, Lund VJ, et al. The SF-36 health status questionnaire in assessing patients with epistaxis secondary to hereditary hemorrhagic telangiectasia. *Am J Rhinol*. 2005; 19: 71-74.
11. Geisthoff UW, Heckmann K, D'Amelio R et al. Health-related quality of life in hereditary hemorrhagic telangiectasia. *Otolaryngol Head Neck Surg*. 2007; 136: 726-33; discussion 734-735.
12. Al-Deen S, Bachmann-Harildstad G. A grading scale for epistaxis in hereditary haemorrhagic telangiectasia. *Rhinology* 2008; 46: 281-284.
13. Hitchings AE, Lennox PA, Lund VJ, et al. The effect of treatment for epistaxis secondary to hereditary hemorrhagic telangiectasia. *Am J Rhinol*. 2005; 19: 75-78.
14. Karapantzos I, Tsimpiris N, Goulis DG, et al. Management of epistaxis in hereditary hemorrhagic telangiectasia by Nd:YAG laser and quality of life assessment using the HR-QoL questionnaire. *Eur Arch Otorhinolaryngol*. 2005; 262: 830-833.
15. Leplège A, Ecosse E, Pouchot J, et al. Le questionnaire MOS SF 36 Manuel de l'utilisateur et guide d'interprétation des scores. Paris ESTEM 2001.
16. Jenkins CD, Stanton BA, Niemcryk SJ, et al. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol*. 1988; 41: 313-321.
17. Piccirillo JF, Merritt MG, Jr., Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). *Otolaryngol Head Neck Surg*. 2002; 126: 41-47.
18. Nunnally JC. *Psychometric theory* 2nd Edit New York: McGraw-Hill 1978.
19. Boyle GJ. Does item homogeneity indicate internal consistency or item redundancy in psychometric scales? *Personality and Individual Differences*. 1991; 12: 291-294.

20. Pedhazur EJ, Pedhazur Schmelkin L. Measurement, design and analysis an integrated approach Hilldale, NJ Lawrence Erlbaum Associates. 1991.
21. Alobid I, Bernal-Sprekelsen M, Mullol J. Chronic rhinosinusitis and nasal polyps: the role of generic and specific questionnaires on assessing its impact on patient's quality of life. *Allergy* 2008; 63: 1267-1279.
22. Apolone G, Mosconi P. Satisfaction surveys: do we really need new questionnaires? *Int J Qual Health Care* 2005; 17: 463-464.
23. Pfister M, Zalaman IM, Blumenstock G, et al. Impact of genotype and mutation type on health-related quality of life in patients with hereditary hemorrhagic telangiectasia. *Acta Otolaryngol* 2008: 1-5.
24. Wyrwich KW, Tierney WM, Babu AN, et al. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res.* 2005; 40: 577-591.

Prof. Jean-Michel KLOSSEK
Department of Otolaryngology Head & Neck Surgery
Centre Hospitalier Universitaire
2 rue de la Milétrie
F-86021 Poitiers
France

Tel: +33-(0)54-944 4328

Fax: +33-(0)54-944 3848.

E-mail: j.m.klossek@chu-poitiers.fr