FID Score: an effective tool in Hereditary Haemorrhagic Telangiectasia - related epistaxis*

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Abstract

Background: Hereditary haemorrhagic telangiectasia (HHT) is a rare disease characterized by a multisystemic vascular dysplasia and epistaxis, that is the most common cause of disability and social impairment. Patient management strictly depends on the severity of this symptom; therefore, it is of paramount importance for the clinicians to effectively grade epistaxis severity.
The aim of this report was to validate the Frequency, Intensity and Duration score (FID) for grading epistaxis severity in patients with HHT; we studied repeatability and external validity comparing FID score with Epistaxis Severity Score (ESS).

Methods: This is a descriptive, observational study that included 264 adult HHT patients with epistaxis. Diagnosis of HHT was established with Curaçao criteria or positivity at genetic testing. Nosebleed severity was evaluated according to the FID score and the ESS. The first 30 patients were included in the validation of the FID score, which was graded on days 0, 1, 3 and 7. In the remaining 234 patients, a comparison between the ESS and FID score was performed.

Results: The statistical analysis performed in order to validate the FID score showed very good agreement between scores calculated on different days; analysis comparing the FID score with the ESS revealed a high correlation between the two grading systems.

Conclusions: The FID score is a quick, easy and precise tool for evaluating HHT-related epistaxis and could be a possible alternative to the ESS. The FID score meets the need for an intuitive and smart grading system that is easy to manage in clinicians' hands.

Key words: Hereditary haemorrhagic telangiectasia HHT, Rendu-Osler-Weber, epistaxis, grading score, epistaxis severity

Introduction

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disease affecting approximately 1/6000 people [(1)]. The transforming growth factor (TGF)-β / bone morphogenetic protein (BMP) pathway is involved in the pathogenesis of HHT. Two major genes involved in HHT are ENG and ACVRL1, responsible for 85% of HHT cases; mutations in SMAD4 cause another 5% of cases and the remainder are of unknown genetic origin [(2)].
Pathogenesis is related to the presence of arteriovenous malformations (AVMs) in which intervening capillaries are lacking, resulting in direct connections between arteries and veins [(3)].
This vascular dysplasia is multisystemic and causes typical HHT lesions: mucocutaneous telangiectases and visceral AVMs.
Despite the possible heterogeneity of the HHT clinical spectrum, epistaxis is the signature of the disease: it is reported by 95% of patients and is the most common symptom at presentation, with mean age of onset at 12 years [(3,4)].
The clinical spectrum related to epistaxis ranges from mild and rare nosebleeds to life-threatening episodes due to massive blood loss and need for hospitalization, transfusions and, in some selected case, surgical treatment. Epistaxis is also the main complaint of patients and represents the most common cause of disability and social impairment [(5,6)].
Patient management strictly depends on the severity of epis-

taxis, therefore it is of paramount importance for the clinician to effectively grade this symptom. In the literature, many studies have proposed a classification for grading HHT-related nosebleed severity [5,7-16]. The Epistaxis Severity Score (ESS), published in 2010, is the first and only validated grading system and currently the most used grading scale in the scientific literature [16]. However, the ESS has some disadvantages, such as the difficulty of calculation because of the inclusion of weighted factors, the need for a computerized method for calculation and the involvement of factors not necessarily related to epistaxis, such as the need for medical attention, transfusions related to epistaxis and anaemia. Among other reported epistaxis classification systems in HHT patients, Pagella and colleagues in 2009 published a simple score for grading epistaxis severity based on the frequency, intensity and duration of nosebleeds, known as the FID score [17]. The aim of this study was to validate and compare these two scoring systems (FID and ESS) for reporting epistaxis severity in patients affected by HHT.

Materials and methods

This is a descriptive, observational study that included 264 adult HHT patients referred to our department between November 2014 and February 2018. The study was approved by the local ethics committee (Comitato Etico Area di Pavia, reference number 1-29/1/14) and was designed and conducted in compliance with the principles of Good Clinical Practice regulations and the Declaration of Helsinki. Informed and written consent was obtained from all patients before inclusion in the study. Nosebleed severity was evaluated according to the ESS, as reported by Hoag et al., and also the FID score proposed by Pagella et al., based on the average frequency, intensity and duration of epistaxis in the last three months (Table 1 and Addendum A) [16,17].

Subject recruitment

Inclusion criteria were an HHT clinical diagnosis with at least three out of four Curaçao criteria or positivity at genetic testing and presence of epistaxis [18,19]. Informed consent was obtained from all individual participants included in the study.

FID score

According to the FID score, epistaxis severity is calculated as the sum of the scores (1, 2 or 3) for each value, and is considered low if the sum is 3, mild if 4–6 and severe if 7–9 [17]. To evaluate the repeatability (test-retest reliability) of the FID score, it was graded on days 0, 1, 3 and 7. No interventions nor changes in management have been reported by patients between the measurements.

ESS

The ESS classification is determined by six factors: frequency, duration and intensity of epistaxis, need for medical attention, anaemia and need for transfusion. Responses are assigned a weighted integer that must be multiplied by the question's coefficient. These are then added to yield the raw score, which must be normalized to give the normalized ESS. Epistaxis is considered low if the ESS is 0–4, mild if 4–7 and severe if 7–10 [16].

Table 1. The FID score, modified from Pagella et al. [16] with permission of SAGE Publications.

	Epistaxis in the last three months		
	Frequency	**Intensity**	**Duration**
Grade 1	Less than one episode/week	Slight stains on handkerchief	Less than 10 min
Grade 2	At least one episode/week	Soaked handkerchief	From 10 to 30 min
Grade 3	More than one episode/day	Bowl or similar utensil necessary	Over 30 min

Table 2. Patient's demographics.

Patients included in the validation of the FID score (N=30)		
	N	%
Sex	13 males	43%
Age (SD; range)	50.07 (11.83; 30-78)	
Patients included in the comparison between FID score and ESS (N=234)		
	N	%
Sex	125 males	53.4
Age (SD; range)	54.25 (15.36; 18-83)	

Statistical analysis

Data were described as the mean and standard deviation (SD) if continuous and as counts (percentages) if categorical. In order to assess the intra-patient between-day agreement for the FID score, Cohen's kappa coefficients have been used. Agreement levels will be graded as poor ($\kappa \leq 0.20$), moderate ($\kappa > 0.20$ to ≤ 0.40), fair ($\kappa > 0.40$ to ≤ 0.60), good ($\kappa > 0.60$ to ≤ 0.80) or very good ($\kappa > 0.80$ to 1.00), according to Altman [20]. Kappa coefficients will be given with the corresponding 95% confidence interval (95%CI) calculated using the bootstrap method. Comparisons between Cohen's κ-coefficients were performed by evaluating the presence/absence of overlap in their confidence intervals. Spearman's non-parametric correlation coefficients (ρ) will be calculated and presented with 95%CI. The magnitude of an effect size for correlation coefficients was evaluated as follows, as described by Cohen: small for correlation coefficients on the order of 0.1, medium for those on the order of 0.3, and large for those on the order of 0.5 [21].

Table 3. Kappa coefficient of agreement and 95% confidence interval.

	Overall	Day 0 vs. Day 1	Day 0 vs. Day 3	Day 0 vs. Day 7
Frequency	0.848 (0.800–0.949)	1	0.844 (0.531–1.000)	0.697 (0.587–0.805)
Intensity	0.948 (0.898–1.000)	1	0.839 (0.755–1.000)	1
Duration	0.822 (0.656–1.000)	1	0.825 (0.676– 1.000)	0.636 (0.148–1.000)
Total	0.919 (0.843–0.960)	1	0.873 (0.680–1.000)	0.865 (0.698–1.000)

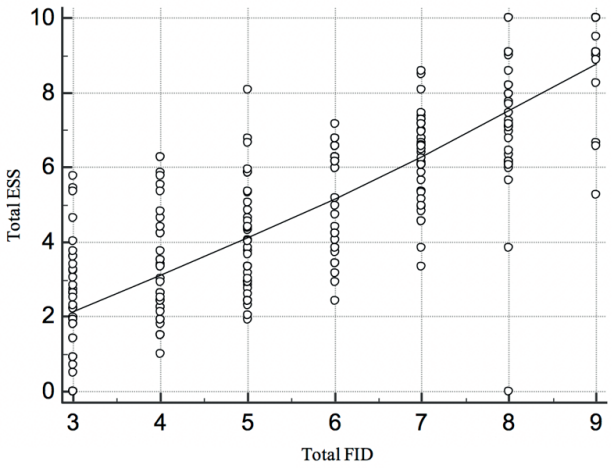

Figure 1. Non-parametric Spearman rank correlation between the FID score and the ESS: statistical analysis revealed a high correlation (ρ = 0.80, 95% CI 0.75-0.84, $p < 0.0001$).

Results

In this report, 264 adult HHT patients were enrolled (demographics in Table 2). The first 30 patients (17 females and 13 males) were included in the validation of the FID score. The mean age of this cohort was 50.07 years (SD = 11.83), ranging between 30 and 78 years. Agreement between the FID score calculated on different days is reported in Table 3. Fourteen out of sixteen (87.5%) kappa coefficients are very good, while the other two are good.

The remaining 234 patients (109 females and 125 males) participated in the comparison between the ESS and the FID score. The mean age of this second cohort of patients was 54.25 years (SD = 15.36), ranging between 18 and 83 years. All respondents had symptoms of epistaxis, with a mean ESS and a mean FID score of 5.7 (SD = 1.9) and 5.0 (SD = 2.5), respectively. Statistical analysis revealed a high correlation (ρ = 0.80, 95%CI = 0.75–0.84, $p <$ 0.0001) between the FID score and the ESS (Figure 1).

Discussion

HHT is a rare and complex disease with a highly variable phenotype due to the multisystemic vascular dysplasia that leads to visceral and mucocutaneous AVMs. Despite the heterogeneity of possible clinical manifestations, epistaxis is the most commonly reported symptom of HHT [22]. It is reported in 95% of adult patients and generally appears before the age of 20 years [2]. Epistaxis severity may change according to several individual and environmental factors, for example, age, season, blood pressure, etc. [6]. It could be mild and infrequent, never requiring medical attention, or severe and life-threatening, leading to anaemia, transfusion dependence and several surgical treatments. Epistaxis severity is a crucial issue among clinicians, surgeons and HHT patients. The scientific literature contains various studies addressing the characteristics of nosebleeds, their association with the nasal distribution and morphology of telangiectases and their association with quality of life [5,12,14,17,23-30].

To date, the means to objectively report epistaxis is still a matter of debate due to its high intra- and inter-individual variability. In fact, epistaxis is a complex symptom most frequently reported by the patient and highly variable over time, therefore it is rather difficult to assess and classify in a truly reliable and reproducible way. Patient management depends on the severity of the epistaxis: in fact, surgical treatment is decided from patients' self-reported symptom severity and impairment of quality of life. Furthermore, postoperative epistaxis evaluation allows surgeons to assess the treatment efficacy in controlling this symptom.

A precise and reliable epistaxis grading system is therefore a fundamental tool.

The first objective of this study was an internal validation of the scoring system proposed by Pagella et al. [17]. The scale was named FID after the frequency (F), intensity (I) and duration (D) of epistaxis episodes occurring in the last three months [17]. The choice to investigate these three aspects of epistaxis came from the characteristics of nosebleeds most complained about by HHT patients and from analysis of the literature already published in this field [14,15]. Test-retest reliability was demonstrated to be very good, showing the reproducibility of the FID score.

The second objective was external validation through comparison with the ESS, the only statistically validated grading system published until now [16]. According to Hoag and colleagues, six factors were independent predictors of epistaxis severity: intensity, frequency and duration of epistaxis, need for medical attention, transfusions related to epistaxis and anaemia. In this grading system, after being weighted by respective coefficients, the single scores are added and normalized to obtain a final

result that may range from 0 to 10. The ESS allowed clinicians to have, for the first time, a validated objective measure of epistaxis severity and to compare different therapeutic strategies. Statistical analysis revealed a high correlation between the FID score and the ESS, thus proving the construct validity of the FID score. This second endpoint was crucial, allowing the use of the FID score as an easy and practical tool to assess epistaxis severity in HHT. In fact, the inclusion of weighted factors and the need for a computerized method of calculation made the ESS a complex model that is not so readily available as a routine clinical tool. Conversely, the FID score allows the clinician to easily and quickly assess epistaxis severity with three questions about the intensity, frequency and length of epistaxis. The final score can be calculated easily, without the need for a computer program, and does not depend on patient awareness of HHT-related factors. Moreover, in the ESS, patients have to assess the need for medical attention, anaemia and transfusion, which could be confounding factors. According to our experience, the need for medical attention is strictly dependent on patients' self-perspective of their own disease: many patients affected by chronic diseases tend to overemphasize or even underestimate their symptoms. HHT patients should be carefully educated on the conditions requiring medical attention but they may not always be compliant to our recommendations. Furthermore, patients with a long history of HHT tend to self-manage nosebleeds and do not seek medical attention unless there is the possibility of being treated in an HHT treatment centre of excellence, as standard management strategies currently provided for epistaxis in primary referral centres (i.e. non-absorbable nasal packings and cautery) are not the most appropriate therapeutic options in HHT patients[31]. Anaemia in HHT could be related to different conditions and this could represent a bias in calculating the ESS. In fact, iron-deficiency anaemia is common in HHT, with a prevalence of 50%, however the main cause is not only recurrent epistaxis but also gastrointestinal (GI) bleeding [32]. Approximately 25% of adults with HHT have GI bleeding due to gastrointestinal AVMs. Slow but persistent bleeding from the gastroenteric tract generally begins after the age of 50 years and becomes increasingly severe with age [3]. GI bleeding in HHT patients could be insidious, that is, it may not be symptomatic because the bleeding is chronic, intermittent and slow, often without notable melaena, until chronic iron-deficiency anaemia develops. GI bleeding not only causes chronic iron-deficiency anaemia but also occasionally determines acute GI haemorrhage [33]. A recent study performed on 680 HHT patients demonstrated that epistaxis and GI bleeding were independently associated with anaemia; nevertheless, in a multivariable model GI bleeding was an independent predictor of anaemia and the association with epistaxis was no longer significant [32]. Therefore, anaemia in HHT patients should not be linked to epistaxis until an appropriate endoscopic evaluation of gastric and duodenal mucosa has been performed.

Moreover, questions about the need for blood cell transfusion may be misleading due to the recent introduction of alternative treatment strategies, such as intravenous iron supplementation. Blood transfusion was the most effective strategy to treat anaemia in HHT patients for a long time. Currently, except for acute haemorrhage, oral and intravenous iron supplementation is considered the first-line therapy of choice for chronic bleeding and mild anaemia in HHT patients [2]. According to McDonald et al., iron replacement therapy should be considered preferable to blood transfusions to manage anaemia resulting from HHT-related haemorrhage [3]. Several studies demonstrated that intravenous iron supplementation is safe, cost-saving and reduces transfusion requirements and the percentage of transfusion-dependent patients [34-38]. This is the reason why the grading scale proposed by Al-Deen and Bachmann-Harildstad in 2008, even if is commonly used and easy to understand for the patients, may be surpassed by the FID score. There are several ongoing clinical trials investigating potential treatment strategies to reduce bleeding in HHT patients. Recent studies confirmed that bevacizumab is highly effective for treating chronic bleeding in HHT; and pazopanib, sorafenib, tacrolimus and thalidomide may have a therapeutic role in reducing HHT-related bleeding [38-48]. So, asking the patients if they ever received a transfusion because of nosebleeds without investigating the use of treatment that interferes with the need for transfusion may be confounding. Moreover, in comparing the FID score with the ESS, the choice of the first score to report characteristics of epistaxis in the last three months is particularly helpful. In fact, epistaxis has a significant intra-individual variability over time, therefore assessment of the current severity of this symptom to a best approximation is crucial to provide a time interval for the patient to refer to. The main limit of the FID score is the evaluation of epistaxis intensity. There are, indeed, a huge number of possible intermediate situations between slight stains on a handkerchief, soaked handkerchief and the need for a bowl to contain the blood flow, therefore intensity assessment may be inaccurate. Rather than a quantitative assessment as in the FID score, Hoag et al. made 'intensity' a qualitative variable ('not gushing or pouring').

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Conclusion

In conclusion, we demonstrate that the FID score could be considered an intuitive, easy and precise epistaxis severity score when compared to the ESS. The FID score, in fact, meets the need for an intuitive and smart grading system that is easy to manage in clinicians' hands. Statistical analysis demonstrated FID accuracy and reproducibility in reporting epistaxis severity, and the external validation revealed a high correlation with the ESS. This is fundamental as the ESS, until now, is considered to be the referral score for the grading of HHT-related epistaxis. Comparative use of the ESS and the FID score proved the comparability of the two scales and supported the use of the FID

score as an efficient tool to evaluate epistaxis severity in HHT patients.

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Authorship contribution

FP, EM and GS study design, data interpretation and manuscript review; EM literature search, data collection, interpretation and writing of the manuscript. CT and ADS data analysis. SU and RL data collection and literature search.

Conflict of interest

The authors declare that they have no conflict of interest.

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