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An evaluation of the severity and progression of epistaxis in hereditary hemorrhagic telangiectasia (HHT) 1 vs. HHT 2

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Abstract

Objective—Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia whose hallmark symptom is spontaneous recurrent epistaxis. Two major genetic subtypes of this syndrome are HHT1 and HHT2. Severity of epistaxis ranges from occasional low-volume bleeding to frequent large-volume hemorrhage. This study evaluated the severity and progression of epistaxis in HHT1 vs. HHT2.

Study Design—Retrospective cohort study

Methods—Retrospective chart review was performed for 183 genotyped HHT patients seen at our Center from 2010-2013. Data collected included epistaxis severity score (ESS), age of epistaxis onset, number and type of treatments, age at which treatments were sought, complete blood count values, ferritin, number of telangiectases, blood transfusions, iron therapy history, and patient demographics.

Results—115 subjects with HHT2 were compared to 68 with HHT1. Subjects with HHT2 had a higher ESS compared to HHT1 (p=0.043) and a later age of onset of epistaxis (p=0.005). HHT2

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Conflict of Interest Statement
No authors of this study have any conflicts of interest.

Associated Presentations
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subjects were more likely to use oral iron (p=0.032) and were more likely to seek interventions to control their epistaxis (p= 0.029).

Conclusion—HHT2 is associated with more severe epistaxis and a subsequent higher rate of interventions, requiring more aggressive therapy as compared to HHT1.

Keywords

Hereditary Hemorrhagic Telangiectasia; HHT; HHT1; HHT2; Osler–Weber–Rendu disease; Osler–Weber–Rendu Syndrome; Laser photocoagulation; Young's procedure; Nasal closure; Epistaxis treatment

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), or Osler-Weber-Rendu Syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of multiple arteriovenous malformations (AVMs) and telangiectases. The diagnosis of HHT is made when a patient has at least three of the four Curacao criteria, which are: recurrent spontaneous epistaxis, family history of HHT, telangiectases in characteristic sites (lips, oral cavity, nose, and fingers), and proven visceral AVM(s).[1] This condition has an estimated worldwide prevalence of 1/5,000.[2] Two major sub-types of this syndrome now recognized are: HHT1 caused by mutations in the endoglin (ENG) gene ([1] and HHT2 caused by mutations in the activin receptor-like kinase 1 (ACVRL1) gene.[3,4]

Telangiectases of the nasal mucosa are prominent in both HHT sub-types and can have a significant negative impact on quality of life as they frequently cause epistaxis. Epistaxis is the hallmark symptom of HHT and the most common complaint of patients with HHT. Severity of epistaxis ranges from nosebleeds occurring every couple of months lasting less than one minute to multiple hemorrhages daily resulting in transfusion dependence.[5] Between 80-90% of diagnosed individuals report having nosebleeds by the age of 21 and nearly 95% develop recurrent epistaxis sometime in life.[6,7]

The overlapping phenotypes and genetic heterogeneity of HHT has stimulated evaluation and description of the clinical heterogeneity and natural history of this group of disorders. A limited number of genotype-phenotype correlation studies have been conducted comparing epistaxis in HHT1 to HHT2. Of these, it has been reported that telangiectases of the nasal and oral mucosae present earlier in life in patients with HHT1 as compared to patients with HHT2.[8] It has also been suggested that patients affected by HHT1 have an earlier onset of epistaxis than those with HHT2.[6,9] Yet one study indicated that adults over 30 with HHT2 may experience epistaxis at a higher frequency and also sought treatment for nosebleeds more often than those with HHT1.[10] This suggests that HHT2 may be more progressive with age. Prior studies have been unsuccessful in their attempts to find a relationship between the number of telangiectases at characteristic sites and epistaxis, although a higher frequency of telangiectases in the HHT1 population has been described.[9] The same group observed incomplete penetrance of epistaxis in HHT2 compared to complete penetrance in HHT1. Subsequent to these previous studies, a validated tool to quantify epistaxis severity has been described.[11] The Hoag Epistaxis Severity Score is a significant improvement over previous

subjective grading schemes and provides greater precision to explore modifiers of epistaxis severity.

The purpose of this study is to evaluate the severity and progression of epistaxis in HHT1 vs. HHT2 and also to examine the relationship between prevalence of characteristic telangiectases and epistaxis.

MATERIALS AND METHODS

Data Collection & Evaluation

A retrospective chart review was performed for all patients seen at the University of Utah HHT Center between January 2010 and June 2013 who had a confirmed diagnosis of HHT, and an identified family mutation in either the ENG or ACVRL1 gene. Beginning in January 2010 the epistaxis severity score (ESS) has been administered as part of each patient's clinical evaluation. The ESS is a validated tool involving a series of questions that objectively measure epistaxis severity.[11] Genetic testing is performed routinely on family probands suspected to have HHT, regardless of clinical presentation or severity. We further collected all of the following: 1) age of onset of epistaxis; 2) number and type of treatments sought for epistaxis; 3) age at which treatments were performed; 4) lab values which included hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), red cell distribution width (RDW), and ferritin (Ferr); 5) number of telangiectases in characteristic sites; 6) current and past medications and supplements; 7) blood transfusion and iron infusion history; and 8) patient age and gender. Lab data was evaluated no more than four times annually. In the event that a patient had more than four labs drawn in a year, we chose the lab with the lowest Hb in each quarter to represent that quarter. The number of telangiectases was recorded for lips, mouth (included the tongue, palate, and oropharynx), face (included face, ears, and conjunctiva), and hands. We specifically documented history of oral iron, multi-vitamin with iron, and a complete medication history.

Data Analysis

This study was conducted under approval of the University of Utah Institutional Review Board. Data was collected and compiled into a database supported by Mathsoft MatLab software. Two sample two tailed t tests with pooled variants and box plots, scatter plots, and bar graphs were plotted to evaluate data.

RESULTS

Of the 183 patients in this study, there were similar percentages of males and females represented in the two disease subtypes. There were nearly twice as many HHT2 patients than there were HHT1 patients. The average age of patients did not differ significantly between the two groups ($p=0.08$). Males with HHT1 were slightly younger ($p=0.02$) but there was no difference in age for females ($p=0.88$) between the two groups (Table I).

The profile and comparison of telangiectases at four common, characteristic sites in HHT1 and HHT2 was found to be similar. There was a trend for HHT1 patients to have more telangiectases on the face and lips relative to HHT2 patients, while HHT2 patients had more

telangiectases on the mouth and hands relative to HHT1 patients. It was more common that HHT2 patients reported use of oral iron (p=0.032). It was also more common that HHT2 patients underwent either laser photocoagulation or cautery (p=0.029) as interventions for epistaxis when compared to intervention rates in HHT1 patients (Table II).

We found no statistically significant differences between groups when comparing the worst recorded ESS, hemoglobin and ferritin values (Figure 1a). However, patients with HHT2 were found to have a more severe average ESS value over time when comparing all reported ESS assessments ($p<0.05$) (Figure 1b).

Age of onset of epistaxis was earlier in HHT1, (p=0.005). In the HHT1 group, there was an outlier who reported an age of onset of epistaxis of 68. The patient was 5.44 standard deviations from the mean and thus was excluded from this plot. There was no difference when comparing age of first procedure (p=0.585) (Figure 2).

HHT2 patients were more likely to undergo intranasal cautery or laser photocoagulation (p=0.029) to control epistaxis than HHT1 patients. Because there were more HHT2 than HHT1 patients, we controlled for group size when comparing these frequencies. Under the same conditions, there was no significant difference in either the number of septal dermoplasties or Young's nasal closure surgeries between the two groups (Figure 3).

DISCUSSION

This study examined data relating to the severity of epistaxis and oral/dermal telangiectases in a large cohort of HHT patients with the two common types of HHT (HHT1 and HHT2). The cohort includes all patients seen at our multi-disciplinary center for HHT, not just patients presenting for management of epistaxis. In fact, many patients had not been seen by an otolaryngologist. It suggests that patients with HHT1 mutations have an earlier age of onset of epistaxis than HHT2; however, patients with HHT1 were not found to have more severe lifelong complications of epistaxis. In fact, the opposite may be true; patients with HHT2 may have more severe lifelong complications of epistaxis. This is suggested in part by the inclusion of all reported ESS' by patients of both types (Figure 1b), which indicates that HHT2 has a more severe epistaxis phenotype. This may be biased because the "severe" patients included in this calculation are likely overrepresented since patients with more severe epistaxis are seen more often in clinic and thus have ESS' recorded more often. However, this observation may be interpreted to mean that there are more severe patients in the HHT2 group than in the HHT1 group. For the purpose of analysis, we divided ESS' into three ranges of severity: <3 (mild), 3-7 (moderate), and >7 (severe). In Hoag's study that originally described ESS, three ranges were used to correlate the ESS with intensity of intervention. The ranges used were: <4 (mild), 4-7 (moderate), and >7 (severe). In this study, the ranges were slightly modified with a lower threshold separating mild from moderate. This lower threshold was chosen to create relatively equal intervals, given this 1-10 severity scale; but also reflects our groups' experience having seen more than 1100 unique HHT patients over two decades, and is in line with the threshold for inclusion into clinical trials for epistaxis.[12] There were similar percentages of patients who fell within each

group and no notable differences were observed when comparing subgroups. Thus it cannot be assumed that HHT2 is associated with a benign epistaxis phenotype.

Over a lifetime, patients with HHT2 have equally severe or perhaps even worse anemia than those with HHT1. Patients with HHT2 were more likely to use oral iron supplements (p=0.0321) yet this did not translate into improved anemia status. There was no difference in hemoglobin or ferritin levels between the two groups. While not significant, there was a trend for hemoglobin (Figure 1a) to be lower in HHT2 patients. It is possible that without increased utilization of supplemental oral iron, HHT2 patients would be more often anemic than HHT1 patients. Patient history of RBC transfusion and/or iron infusion was often based on patient report, since many patients received these therapies at outside institutions, making quantification of the number of required treatments difficult.

This is a retrospective study. With the exception of the data regarding iron infusions/blood transfusions, all other data collected is part of the routine, systematic evaluation of all patients who present to our multi-disciplinary clinic for HHT, and is captured in patients' medical record as such. Our HHT center may be unique in that genetic testing to identify a disease causing genetic mutation is recommended to all patients (or at least one family proband) with a clinical diagnosis of HHT, regardless of symptoms or clinical presentation. This is routinely recommended primarily to allow for diagnostic testing in at risk, but clinically undeclared, family members. Thus, in general, this study population represents the spectrum of HHT that presents in the medical arena.

CONCLUSION

For anticipatory guidance of HHT patients, it is helpful to know that although HHT2 has a later average age of onset of epistaxis, it cannot be assumed to be a "milder" form of HHT. In fact it may progress to a more severe disease state with regards to epistaxis, leading patients to seek surgical management more often than patients with HHT1. However, from a clinical management standpoint the difference is not striking. Given the variability of epistaxis, even between patients with the same type of HHT, counseling regarding medical and surgical therapies for epistaxis should be based on individual history and current presentation.

The suggestion from this study that HHT2 may be a more progressive disorder than HHT1 with regards to epistaxis raises the question as to whether the natural history of other symptoms and manifestations of HHT behave similarly. Future investigation of potential differences in progression over time between the HHT subtypes may have interesting implications with regards to the underlying pathogenesis of this group of vascular disorders.

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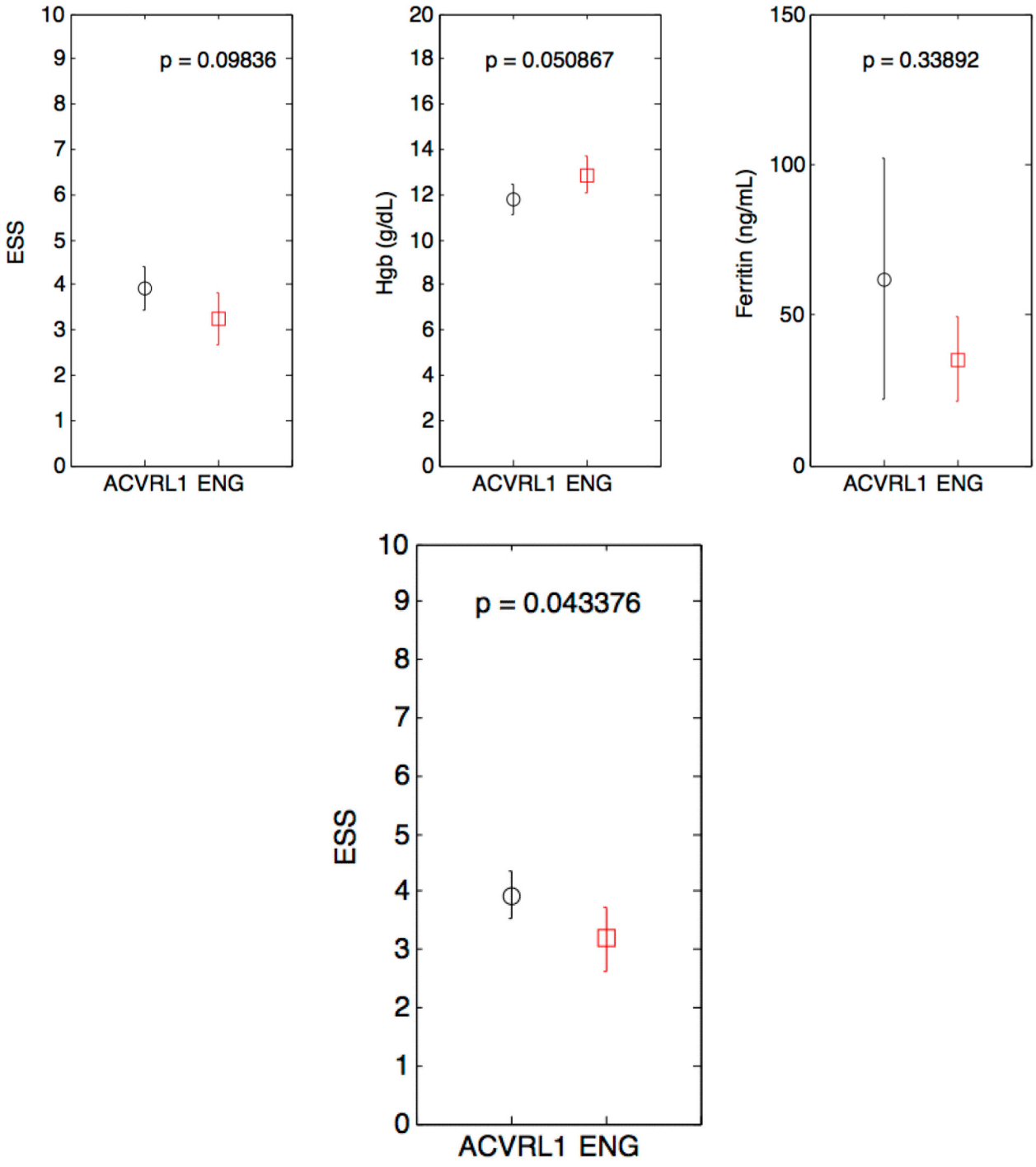

Figure 1.

1a—Box plots depicting comparison of worst recorded ESS, Hgb, and Ferritin between HHT subtypes.

1b—Box plot depicting comparison of total reported ESS' among HHT subtypes

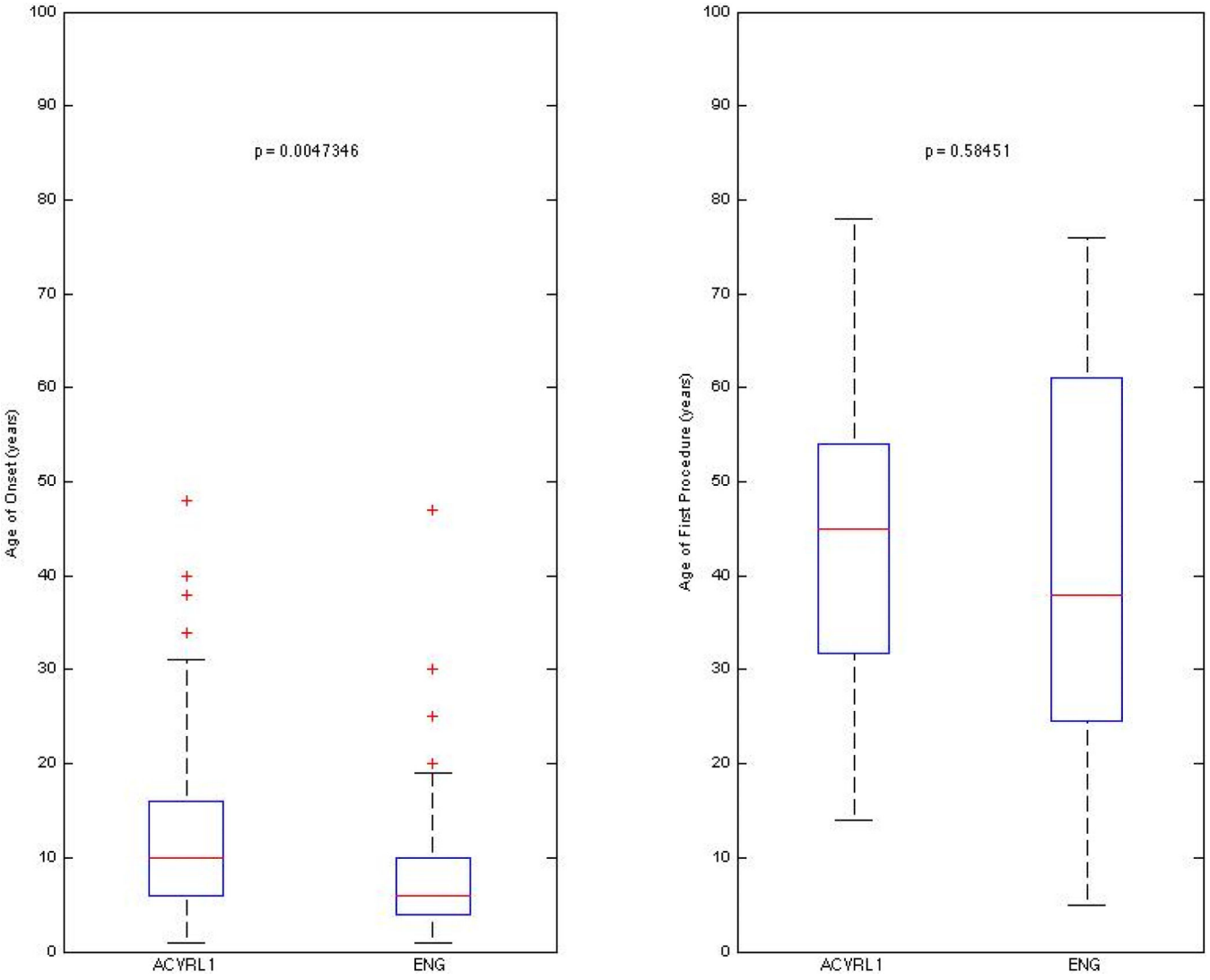

Figure 2.

Box plots comparing age of onset for epistaxis, and age of first procedure in HHT subtypes. Procedures included cautery, laser photocoagulation, septal dermoplasty, and Young's procedure.

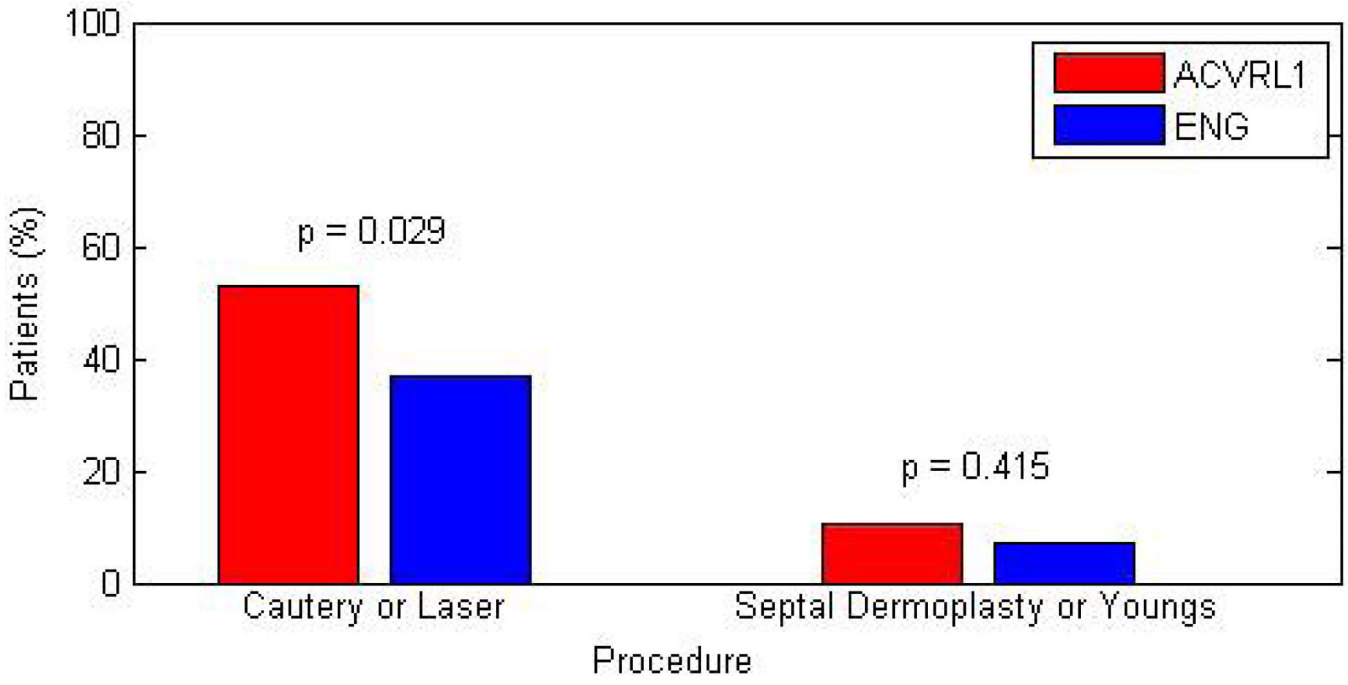

Figure 3.
Bar graph depicting frequency at which major interventions were performed among HHT subtypes.

Table I

Proportion of males and females with mean age, range and respective gene status.

Gene	# of patients	Mean age (range)	# of males (%)	Mean age (range)	# of females (%)	Mean age (range)
HHT1	68	36.5 (2-82)	32 (47.1%)	32.5 (5-78)	36 (52.9%)	40 (2-82)
HHT2	115	42.7 (1-85)	59 (51.3%)	44.5 (2-85)	56 (48.7%)	40.8 (1-81)

Abbreviations:

• HHT- hereditary hemorrhagic telangiectasia

Table II

Profile of HHT patients by gene status.

	HHT2	HHT1	p
Number of telangiectases	*avg (range)*	*avg (range)*	
Face	2.7 (0-24)	2.8 (0-56)	0.9618
Lips	4.2 (0-36)	5.7 (0-36)	0.1561
Mouth	4.5 (0-30)	4.9 (0-50)	0.7459
Hands	18.8 (0-165)	13.6 (0-129)	0.2306
Age of onset for epistaxis	12.2 (1-48)	9.4 (1-47)	0.0047
Age at first intervention	43.8	41.5	0.5845
Treatments/Interventions			
Oral iron	39.0%	23.9%	0.0321
Iron infusion	19.5%	12.7%	0.2222
RBC transfusion	22.8%	12.7%	0.0849
Laser or cautery (electric or chemical)	52.8	36.6	0.0291
Young's procedure or septal dermoplasty	10.6	7	0.4147
ESS range	3.94 (0-10)	3.18 (0-9.1)	0.0434
Mild (1-3)	50.8%	52.6%	0.8162
Moderate (3-7)	38.3%	40.4%	0.7898
Severe (7-10)	10.9%	7.0%	0.4062

Abbreviations:

• ESS- epistaxis severity score

• HHT- hereditary hemorrhagic telangiectasia