Epistaxis in Children and Adolescents With Hereditary Hemorrhagic Telangiectasia

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Objectives/Hypothesis: Our objective was to describe epistaxis onset and severity in pediatric hereditary hemorrhagic telangiectasia (HHT) patients and study the cumulative incidence of epistaxis by age of onset within each genetic subtype.

Study Design: Retrospective cohort chart review.

Methods: Charts were reviewed of patients age 0 to 18 years with a clinical or genetic diagnosis of HHT who were evaluated at a tertiary multidisciplinary HHT clinic from January 2010 to June 2016. The epistaxis severity score (ESS), a validated tool for assessing epistaxis severity, was used to assess epistaxis. Statistical analyses were conducted on the full HHT cohort as well as subgroups stratified by the HHT causative gene (HHT1 = ENG and HHT2 = ACVRL1).

Results: Sixty-nine pediatric subjects were identified; 60 had HHT confirmed by genetic testing, and nine (from families with known mutations) met published clinical diagnostic criteria alone. Fifty-nine (85%) had onset of epistaxis. The median age of onset of epistaxis was 5 years (interquartile range [IQR]: 2–9 years). The median ESS for the entire cohort was 1.6 (IQR: 0–2.6). The median ESS was higher in HHT1 versus HHT2 (2.3 vs. 1.1, P = .002), and age of epistaxis onset was earlier in HHT1 (3 vs. 5 years, P = .03). Sex and age were not associated with ESS.

Conclusions: Epistaxis may present early in HHT, but is typically mild in the pediatric period. Severity in the pediatric population is worse in patients with HHT1. By recognizing the significance of even mild, infrequent epistaxis in a child with a family history of HHT, and understanding that not all HHT patients have epistaxis during childhood, community providers and otolaryngologist can assist in the early detection of HHT.

Key Words: Genodermatoses, hereditary hemorrhagic telangiectasia, epistaxis, pediatrics.

Level of Evidence: 4.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder of vascular formation with an estimated prevalence of 1 in 5,000 and 8,000.1–3 HHT has multiple genetic subtypes, with HHT type 1 and HHT type 2 making up the majority of cases. HHT type 1 (HHT1) is caused by a mutation in the endoglin gene (ENG), whereas HHT type 2 (HHT2) is caused by a mutation in activin A type-II-receptor-like kinase 1 (ALK1/ACVRL1) gene. Mutations in SMAD4 cause a syndrome that combines HHT and juvenile polyposis, but represent only 1% to 2% of patients with HHT.4 HHT-associated vascular lesions include telangiectases and arteriovenous malformations (AVMs).

Epistaxis is the most common symptom of HHT. Recurrent, spontaneous epistaxis has been reported in 66% of pediatric HHT patients5 and 96% of adult HHT patients.6 Despite this, most reports to date on the pediatric HHT population have focused on solid organ AVMs.5,7–9 Reports of epistaxis onset in childhood have largely relied on recall of adult patients,7,10–12 and there are no reports to date of epistaxis severity in the pediatric HHT population.

Overall, HHT demonstrates an age-dependent penetration, with progression of symptoms occurring over a lifetime. HHT1 has been reported as having an earlier onset of epistaxis when compared to HHT2.11,12 Others have reported that HHT2 in the adult population may be associated with greater progression of nosebleed severity and thus more severe epistaxis later in life.13 There is a danger in relying on epistaxis to indicate the presence or absence of HHT.

Severe complications of cerebral, hepatic, and pulmonary AVMs can occur in pediatric patients and are...
often not proceeded by presentation of mucocutaneous telangiectasia or epistaxis. Early detection of patients with HHT allows for solid organ screening for AVMs and treatment to avoid potentially catastrophic complications. Published consensus management guidelines recommend routine screening of all affected individuals in the first year of life. It is previously reported that use of genetic testing to identify affected family members of those diagnosed with HHT is underutilized. The barriers were shown to include lack of knowledge of HHT families of their doctors’ rationale for early diagnosis by genetic testing of asymptomatic or minimally symptomatic at-risk individuals.

There are multiple reports of the prevalence and presentation of solid organ AVMs in children and adolescents with HHT, and it has been reported that complications from these AVMs can occur in pediatric patients with HHT prior to the onset or recognition of epistaxis. However, information on severity and onset of epistaxis in pediatric HHT patients is lacking. Additionally, there are limited analyses of genetic subtypes in children and adolescents with HHT. This study aimed to describe epistaxis onset and severity in pediatric HHT patients and study the cumulative incidence of epistaxis by age of onset within each genetic subtype. We hypothesize that the onset of epistaxis is earlier than previously reported based on adult recall, but is not a constant feature in the affected pediatric population.

MATERIALS AND METHODS

Patient Population

A retrospective chart review was conducted of all pediatric patients (0 to 18 years old) with confirmed HHT seen at the University of Utah HHT Center from 2010 to 2016. Children (aged <10 years) and adolescents (aged 10–18 years), were considered affected with HHT if they met published, consensus clinical diagnostic criteria for HHT or had tested positive for a known familial pathogenic variant in ACVR1L, ENG, or SMAD4. If a pathogenic genetic variant had already been identified in a first-degree relative with HHT, then a pediatric patient who met clinical diagnosis (Curacao score of 3 or higher) was presumed to have the same mutation.

All patients seen at this specialty center are systematically examined for oral and cutaneous telangiectases, as well as a targeted medical history for symptoms and manifestations of HHT. Brain magnetic resonance imaging (MRI) is recommended to screen for cerebral AVMs in all affected patients. Screening for pulmonary AVMs is recommended; the specifics of which are dependent on patient age and symptoms. Nasal endoscopy is not a standard part of the clinical evaluation.

The cohort consisted of children mostly from the Mountain West (Utah, Wyoming, Montana, Idaho, Nevada). Most pediatric HHT patients seen at the Utah HHT Center are referred at least in part due to family history, usually an affected parent. Only rarely was a child the family index case. University of Utah Institutional Review Board (IRB) approval was obtained for this study (IRB 00039582).

Epistaxis Severity Score

Since January 2010, the 3-month recall epistaxis severity score (ESS) has been applied as routine clinical practice for individuals seen at the University of Utah HHT Clinic. The ESS is a validated tool that estimates the severity of epistaxis based on answers to six questions related to typical nosebleed intensity, frequency, duration, whether medical attention has been sought, presence of anemia, and need for blood transfusions secondary to epistaxis. ESS surveys were completed by either the patient, guardian, or both. An ESS score of less than 4 is considered mild, 4 to 6.99 is moderate, and greater than 7 is severe.

Statistical Analysis

Descriptive statistics were used to summarize demographics and clinical characteristics of pediatric patients with genetic subgroup (HHT1, HHT2). Mean and standard deviation or median and interquartile range (IQR) were used to summarize continuous variables, and count (%) was used for categorical variables. Exact Wilcoxon rank sum tests were used to compare genetic subgroup with Curacao score, ESS, and frequency and duration of epistaxis. A t test was used to compare age of evaluation with sex, and exact Wilcoxon rank sum tests were used to compare sex with Curacao score and ESS. Fisher exact tests were used to compare categorical variables with genetic subgroup (and sex). Linear regression was used to compare genetic subgroup with Curacao and ESS outcomes, adjusting for age of epistaxis onset and sex, where ESS was log transformed due to skewness. A Cox proportional hazards model was used to compare genetic subgroup with age of epistaxis onset adjusting for sex. The “experiencing gushing or pouring” and “seeking medical attention for epistaxis” outcomes were not analyzed adjusting for age and sex in a logistic regression framework due to low event rates. The Kaplan-Meier method was used to estimate the median age of epistaxis onset (years) and cumulative incidence of epistaxis at different time points within each genetic subtype. Subjects who did not have epistaxis at the time of our evaluation were censored in this analysis. A log-rank test was used to compare the cumulative incidence curves with genetic subtypes and sex. An exact Wilcoxon rank sum test was used to test whether age group (child vs. adolescent) was associated with ESS score. Because statistical power was reduced by dichotomizing age, we also compared age with ESS using Spearman correlation and its 95% confidence interval (CI) in the full cohort and stratified by sex. A regression model predicting log-transformed ESS was used to test whether the relationship between ESS and age was modified by sex, where the ratios of adolescents to children and corresponding 95% CIs were provided from this model. Statistical analyses were performed with R version 3.4 (The R Foundation for Statistical Computing, Vienna, Austria). All P values were two-sided and were evaluated at a .05 significance level.

RESULTS

Demographics and Clinical Features

Sixty-nine pediatric patients with definite HHT were included in the study. Sixty had HHT confirmed by genetic testing, and nine (from families with known mutations) met published clinical diagnostic criteria alone (Table I). All subjects had a family history of HHT. No de novo mutational cases were identified. The mean patient age at evaluation was 9 years, with similar numbers of male (n = 37, 54%) and female (n = 32, 46%) patients. Over 90% of the patients had either HHT2 (n = 41, 59%) or HHT1 (n = 26, 38%). Only two subjects with a mutation in the SMAD4 gene were identified. Non-nasal clinical manifestations of HHT in these

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patients included the presence of one or more oral/cutaneo-
taneous telangiectases (73%), pulmonary AVMs (28%), and
cerebral AVMs (10%).

**Incidence of Epistaxis and Age of Onset**

The median age of onset of epistaxis was 5 years (IQR: 2–9 years) (Table II). Patients with HHT1 had a younger median age of epistaxis onset at 3 years (IQR: 2–6 years) versus 5 years for those with HHT2 (IQR: 2–12 years) (P = .03), corresponding to a consistently higher cumulative incidence that reached 94% by age 8 years (versus 65% by age 8 years in HHT2) (Fig. 1). Ten of 69 (15%) subjects had not yet developed epistaxis. Of these 10 patients, four had HHT2 (4/41 = 10% without epistaxis) and were evaluated at ages 0.25, 4, 5, and 6 years, and six had HHT1 (6/26 = 23% without epistaxis) at ages 0.20, 0.29, 0.50, 1, 2, and 4 years.

### Table I.

Demographics and Clinical Characteristics of Children and Adolescents With Hereditary Hemorrhagic Telangiectasia for All Patients.*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total, N = 69</th>
<th>HHT1 (ENG), n = 26</th>
<th>HHT2 (ACVRL1), n = 41</th>
<th>SMAD4, n = 2</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.63</td>
</tr>
<tr>
<td>Female</td>
<td>32 (46)</td>
<td>13 (50)</td>
<td>18 (44)</td>
<td>1 (50)</td>
<td>—</td>
</tr>
<tr>
<td>Male</td>
<td>37 (54)</td>
<td>13 (50)</td>
<td>23 (56)</td>
<td>1 (50)</td>
<td>—</td>
</tr>
<tr>
<td>Age of evaluation, yr, mean ± SD</td>
<td>9 ± 6</td>
<td>8 ± 5</td>
<td>10 ± 6</td>
<td>3 ± 3</td>
<td>.065</td>
</tr>
<tr>
<td>Age of evaluation group, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Children (0–9 years)</td>
<td>35 (51)</td>
<td>15 (58)</td>
<td>18 (44)</td>
<td>2 (100)</td>
<td>—</td>
</tr>
<tr>
<td>Adolescents (10–18 years)</td>
<td>34 (49)</td>
<td>11 (42)</td>
<td>23 (56)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Characteristic HHT features, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Oral/cutaneous telangiectases</td>
<td>50 (73)</td>
<td>19 (73)</td>
<td>30 (73)</td>
<td>1 (50)</td>
<td>.99</td>
</tr>
<tr>
<td>Lung arteriovenous malformation</td>
<td>19 (28)</td>
<td>9 (35)</td>
<td>10 (25)</td>
<td>0 (0)</td>
<td>.71</td>
</tr>
<tr>
<td>Brain arteriovenous malformation</td>
<td>7 (10)</td>
<td>4 (15)</td>
<td>3 (7)</td>
<td>0 (0)</td>
<td>.56</td>
</tr>
</tbody>
</table>

*All patients includes recurrent nosebleeds, nonrecurrent nosebleeds, and patients who have never had a nosebleed.

†Comparing HHT1 versus HHT2. SMAD4 was not compared due to the low sample size (n = 2).

ACVRL1: activin A receptor type IL; ENG: endoglin gene; HHT = hereditary hemorrhagic telangiectasia; SD = standard deviation.

### Table II.

Epistaxis in Children and Adolescents With HHT1 Versus HHT2 Among All Patients With a History of Epistaxis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total, N = 57</th>
<th>HHT1, n = 20</th>
<th>HHT2, n = 37</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curacão score,</td>
<td></td>
<td></td>
<td></td>
<td>.13*†</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3 (2–3)</td>
<td>3 (2–3)</td>
<td>2 (2–3)</td>
<td>—</td>
</tr>
<tr>
<td>Min/max</td>
<td>1/4</td>
<td>1/4</td>
<td>1/4</td>
<td>—</td>
</tr>
<tr>
<td>Age of epistaxis onset, yr, median (IQR)*</td>
<td>5 (2–9)*</td>
<td>3 (2–6)*</td>
<td>5 (2–12)*</td>
<td>.03*†</td>
</tr>
</tbody>
</table>
| Cumulative incidence (95% CI) of epistaxis at
  6 years                             | 65%           | 83%          | 56%          | —       |
  8 years                             | 75%           | 94%          | 65%          | —       |
  10 years                            | 81%           | 94%          | 74%          | —       |
  12 years                            | 86%           | 94%          | 82%          | —       |
| Epistaxis severity score            |               |              |              | .002*† |
| Median (IQR)                        | 1.6 (0–2.6)   | 2.3 (1.9–3.0) | 1.1 (0–2.1) | —       |
| Min/max                             | 0/6.8         | 0/6.8        | 0/3.8        |  —     |
| Epistaxis severity score, n (%)     | —             | —            | —            | —       |
| Mild (<4)                           | 54 (95)       | 17 (85)      | 37 (100)     | —       |
| Moderate (4–6.99)                    | 3 (5)         | 3 (15)       | 0 (0)        | —       |
| Patients experiencing gushing or pouring, n (%) | 3 (5) | 3 (15) | 0 (0) | 0.04† |
| Patients seeking medical attention for epistaxis, n (%) | 4 (7) | 2 (10) | 2 (5) | 0.61† |

*Exact Wilcoxon rank sum test.

†Analyses were repeated in a regression framework controlling for age and sex. Findings were consistent except for Curacão score, where the difference became statistically significant (P = .044).

*Estimates came from full cohort of HHT1 and HHT2 (n = 67), using the Kaplan-Meier method to account for censoring in 10 subjects who did not develop epistaxis within the time that they were followed.

Fisher exact test.

HHT = hereditary hemorrhagic telangiectasia; IQR = interquartile range; max = maximum; Min = minimum.
Epistaxis Severity

The majority of patients who did exhibit epistaxis experienced mild bleeding (95% with ESS < 4). Of the subjects who had a history of epistaxis, only three patients (5%) were experiencing epistaxis with an ESS > 4. None of the pediatric HHT patients experienced severe nosebleeds (ESS > 7). Anemia was only noted in two patients. None of the study subjects required a blood transfusion to treat their epistaxis-caused anemia.

Epistaxis Treatment

Four patients out of 69 had sought medical attention for their nosebleeds. Two patients were treated with chemical/electrical cauterization prior to presenting at our specialty center. The first patient (ESS of 3.8) was treated with electrical cauterization once by an outside provider to control his epistaxis. The second patient (ESS of 6.8, highest ESS in the entire cohort) received eight treatments with chemical/electrical cautery from the age of 5 to 9 years old. The last two patients (ESS of 4.2 and 2.6) were referred for laser treatment by our specialty clinic to control their epistaxis.

Genotype/Phenotype Correlations

In a univariate analysis there was no difference in the number of clinical diagnostic criteria in patients with HHT1 versus HHT2 (P = .13), but the slightly higher score in HHT1 (3, IQR: 2–3 vs. 2, IQR: 2–3) was statistically significant after adjusting for age and sex (P = .044) (Table II). Median ESS scores were higher in HHT1 (ESS = 2.3, IQR: 1.9–3, maximum = 6.8) than in HHT2 (ESS = 1.1, IQR: 0–2.1, maximum = 3.8) (P = .002). Of patients with ESS > 4, three had HHT1 and none had HHT2. Notably, the three patients who had described the severity of their epistaxis as gushing or pouring were affected with HHT1.

Epistaxis frequency tended to be lower in HHT2, where less then one per month was most common (n = 15, 41%) versus one per week in HHT1 (n = 9, 45%) (P = .04) (Fig. 2). Epistaxis duration was also lower in HHT2, where the most common duration was less than 1 minute (n = 21, 57%), versus 1 to 5 minutes in HHT1 (n = 12, 60%) (P = .01) (see Supporting Figure 1 in the online version of this article).

Sex and Age Differences

The age of onset of epistaxis, number of clinical criteria, and ESS did not vary significantly by sex or age. The median ESS in males was 1.3 and 2.1 in females (P = .30) (see Supporting Table 1 in the online version of this article), and there was low correlation between age at evaluation and ESS at 0.19 (95% CI: −0.08 to 0.43) (Fig. 3). Similarly, there was no age–sex interaction for the ESS outcome, as the ratios of ESS (adolescents/children) were similar within females and males (see Supporting Table 2 in the online version of this article).

DISCUSSION

This represents the first report of epistaxis severity in a pediatric HHT population. Epistaxis is the most common symptom of HHT and is reported in nearly 100% of affected individuals by middle age.1 Telangiectases of the nasal mucosa is the cause of spontaneous epistaxis that is recurrent in these patients. Our data
illustrate that although epistaxis often presents in the pediatric period, some pediatric patients do not have epistaxis; 14.5% of our cohort had not yet presented with epistaxis. Epistaxis in HHT is age dependent, and the majority of patients without epistaxis in our study were young.

The median age of onset of epistaxis in our pediatric HHT cohort was 5 years (IQR: 2–9 years). This is significantly younger than the frequently cited report of mean age onset of 12 years for epistaxis in HHT, which relied on recall from adult patients.\(^4,10\) This discrepancy could be due to recall bias, as it is likely that adult HHT patients could discount and under-report the beginning of infrequent, mild bleeding in childhood, due to the comparatively more significant, problematic bleeding they experience later in life. This study suggests that epistaxis in HHT presents earlier in life than has been previously reported.

Previous studies that relied on adult recall report that epistaxis has a later onset in HHT2 when compared to HHT1.\(^12\) We report similar findings in our pediatric cohort, with HHT1 having a consistently higher cumulative incidence of epistaxis during the early years of life when compared to HHT2. By the age of 8 years, 94% of patients with HHT1 had developed epistaxis, whereas only 65% of HHT2 patients had developed epistaxis. In patients with HHT2, the cumulative incidence of epistaxis increased from 65% at age 8 years to 82% at age 12 years.

The overwhelming majority of this pediatric cohort had mild bleeding and had not sought, nor were they currently seeking, treatment for nose bleeding. Conservative management relying on home humidification and nasal emollients is typically recommended for pediatric HHT patients with epistaxis. Techniques used to treat severe nosebleeds in adults such as septodermoplasty or nasal closure are never indicated in pediatric HHT patients in our experience. The chemical/electrical cautery procedures performed in the two study patients prior to presentation at our clinic would not have been recommended at our HHT specialty center due to association of chemical and electric cautery with increased severity of epistaxis in HHT patients after multiple uses, and with risk of septal perforation. For a pediatric patient with epistaxis causing anemia, or interfering with quality of life, laser ablation would be recommended in our setting when conservative management fails.

Making the diagnosis of HHT in pediatric patients, despite the lack of significant epistaxis in most, is important. Consensus management guidelines for individuals with HHT recommend a brain MRI in the first six months of life if possible, given the risk for birth for cerebral hemorrhage secondary to AVM. A saline contrast echocardiogram to screen for pulmonary AVMs is also recommended. Although there is less consensus about the age at which the initial echocardiogram should be performed in pediatric HHT patients without symptoms of pulmonary AVM, there is consensus that it should be done by at least late childhood.

Epistaxis severity did not vary significantly between children versus adolescent patients. The patient with the most severe epistaxis (ESS of 6.8) in our cohort was a child of the age of 9 years. This suggests a lack of significant progression in nosebleed severity during the pediatric period. This information also supports that epistaxis in children (aged 0–9 years) with HHT can be problematic and require medical intervention, although it is very rare in this age group. It may be that the physiological changes in puberty do not play a role in worsening epistaxis and that a longer time period is required to show progression. Consistent with one report of adults with HHT, severity of epistaxis did not vary significantly by sex.\(^19\)

In our pediatric cohort, patients with HHT1, when compared to HHT2, presented with more significant epistaxis as measured by ESS (higher frequency of epistaxis, longer duration of epistaxis, more likely to seek medical treatment for epistaxis, and gushing and pouring epistaxis). The opposite findings have been reported in adult cohorts, with epistaxis being a more severe problem as measured by ESS in HHT2 than HHT1.\(^13\) Moreover, in the same study, adult patients with HHT2 had a higher rate of interventions and more aggressive therapy to control their epistaxis as compared to HHT1.\(^11,13\) It is possible that HHT2 has a later onset with regard to epistaxis than HHT1, but may be more progressive in terms of severity.

A limitation of this study is the lack of routine rhinoscopy in the evaluation of patients. Our primary goal in evaluation was confirming HHT with certainty as early in life as possible, prior to embarking on recommended routine surveillance for affected individuals. Rhinoscopy to look for nasal telangiectases may have helped sort out incidental epistaxis from HHT-related epistaxis, and helped confirm the diagnosis in some patients. However, in our experience, most pediatric patients require genetic testing to confirm a diagnosis, due to minimal telangiectases and related bleeding.

This study has an ascertainment bias related to the fact that we studied pediatric patients brought to an HHT specialty clinic for evaluation. Although our institution strongly encourages routine genetic testing for early diagnosis in all pediatric patients with a family history of HHT, regardless of their symptoms, this cohort is expected to over-represent children with HHT who have already developed symptoms. As mildly affected as most pediatric patients were in this study, our study likely overestimates the burden of epistaxis in the pediatric population with HHT because affected children who did not yet have an onset of epistaxis, or had minimal epistaxis, are less often brought by parents for evaluation. It is of note that only five of the 69 pediatric patients confirmed to have HHT were referred because of their own symptoms. All others were referred at least in part due a family history.

**CONCLUSION**

Signs and symptoms of HHT during childhood are typically minimal and are not usually elicited in routine healthcare evaluations. Epistaxis-caused anemia was
exceedingly rare in our cohort. The lack of significant physical findings in many pediatric patients with HHT often makes the diagnosis on clinical grounds difficult. Yet, confirmation of HHT in the pediatric period for affected individuals, as is recommended per published consensus management guidelines, typically requires genetic testing. The majority of pediatric patients with HHT present with mild epistaxis during early childhood, although it is often not recognized or noted by a child’s pediatrician because it is not of a medical consequence in itself. By recognizing the significance of even mild, infrequent epistaxis in a child with a family history of HHT, and understanding that not all HHT patients have epistaxis during childhood, community providers can assist in the early detection of HHT and facilitate referral to an HHT specialty center for the recommended medical management, including surveillance for solid organ AVMs, for this complex vascular disorder.

**BIBLIOGRAPHY**