Localization and age distribution of telangiectases in children and adolescents with hereditary hemorrhagic telangiectasia: A retrospective cohort study

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Background: The location of telangiectases in hereditary hemorrhagic telangiectasia (HHT), as set forth in the consensus diagnostic (Curaçao) criteria, is based primarily on adults.

Objective: Document the locations and numbers of telangiectases in a cohort of pediatric patients with HHT.

Methods: A retrospective chart review using a standardized data collection form for site and number of telangiectases was performed for pediatric patients with HHT (age, 0-18 years) from 2005 to 2016.

Results: Of 90 pediatric patients with HHT, 71% had one or more telangiectases. Of all the telangiectases counted (N = 319), cutaneous telangiectases were more common (73%) than oral telangiectases (27%). The hands were the most frequent site, accounting for 33% of all telangiectases. Adolescents were more likely than children to have cutaneous telangiectases (85% vs 50% [Q = 0.005]). The most frequent sites in children younger than 10 years were the hands excluding the fingers (27%), fingers (25%), and face (23%). Only 23% of subjects (21 of 90) presented with multiple (≥3) telangiectases at locations considered characteristic for the current consensus diagnosis guidelines (lips, oral cavity, and fingers).

Limitations: Ascertainment bias based on recruitment.

Conclusions: In this pediatric population, telangiectases at sites not included as "characteristic" by the Curaçao diagnostic criteria were common. The Curaçao criteria in regard to both number and location of telangiectases may be inadequate in the pediatric HHT population. (J Am Acad Dermatol 2019;81:950-5.)

Key words: genodermatoses; hereditary hemorrhagic telangiectasia; Osler-Weber-Rendu; pediatrics; telangiectasia; vascular dysplasia; vascular malformation.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant condition with high penetrance by middle adulthood but extremely variable age-dependent penetrance and expression before adulthood. It is characterized by telangiectases and arteriovenous malformations,

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high-flow lesions that result from an abnormal direct arterial-to-venous connection. HHT has multiple genetic subtypes, with HHT type 1 and HHT type 2 making up the majority of cases. HHT type 1 is caused by a mutation in the endoglin gene (*ENG*), whereas HHT type 2 is caused by a mutation in activin A receptor like type 1 gene (*ACVRL1*) (also known as *ALK1*).[1]

Clinical diagnostic criteria for HHT were first published in 2000 and are referred to as the Curaçao criteria (Table I).[2,3] The Curaçao criteria are based on expert opinion at a time when detailed descriptions of the location and number of telangiectases in patients with HHT of all ages were limited. These criteria, which are still considered to be the consensus diagnostic criteria almost 2 decades after publication, did not attempt to note all locations of telangiectases in patients with HHT; rather, they noted those locations that experts considered most helpful in making the diagnosis: the lips, finger, nasal mucsosa, and oral cavity.[2,3] The number of telangiectases required to constitute a criterion is not specified—only that there should be "multiple" telangiectases. Detailed information about the presentation of visible telangiectases in pediatric patients was and is scarce. Telangiectases of HHT classically present as punctate, 1- to 2-mm, pink to bright red, blanchable macules or thin papules. They are easily missed on physical examination owing to their subtle presentation. In our experience, children with HHT tend to present with relatively smaller, less bright, pink telangiectases.

Telangiectases of the oral cavity and skin are known to increase in number with age in HHT.[4,5] The third decade of life was reported in 1 study as being the most typical decade in which telangiectases were first noted, with only 20% of adults with HHT (10 of 51) reporting telangiectases before the age of 20 years and no reports of telangiectases before the age of 10.[5] Since then, multiple studies have shown, however, that telangiectases commonly appear in HHT before the age of 20.[4,6-9] Some previous studies have relied on adult recall of when telangiectases appeared, which likely does not capture subtle telangiectases during childhood. Other reports were limited by small numbers or lack of data regarding numbers of telangiectases at specific sites in pediatric patients with HHT.

CAPSULE SUMMARY

- The locations of telangiectases considered characteristic of HHT are the lips, fingers, and oral cavity. The hand and face were common sites in children and adolescents with HHT; but not all of them had telangiectases during childhood.
- The established clinical diagnostic criteria are likely less sensitive in the pediatric population with HHT.

Appropriate medical management of HHT dictates that the diagnosis be made in affected individuals as early in life as possible. Solid organ AVMs of the lung and brain can cause sudden, catastrophic complications, sometimes before presentation of the characteristic epistaxis and oral or cutaneous telangiectases.[10-12] International guidelines for the diagnosis and management of HHT recommend a magnetic resonance image of the brain to rule out cerebral AVMs in affected individuals in the first 6 months of life. Surveillance for pulmonary AVMs should also begin during childhood.[3] Thus, HHT is an inherited disorder in which appropriate medical management requires routine surveillance even in currently asymptomatic or minimally symptomatic patients.

Uncertainty regarding common locations and frequency of telangiectases in children and adolescents contributes to the difficulty in diagnosing HHT in pediatric patients. In this article, we examined in detail the specific locations and number of telangiectases in a large cohort of pediatric patients with HHT based on standardized physical examinations and stratified by age group (children vs adolescents). We also compared patient characteristics (age at evaluation, sex, and genetic subtype) with telangiectasia prevalence. We hypothesized that the occurrence and locations of telangiectases in children and adolescents differ from those in adults with HHT.

METHODS

We performed a retrospective review of all pediatric patients (0-18 years old) with HHT evaluated at the HHT Center of Excellence in Salt Lake City, Utah, from January 2005 to June 2016. A total of 174 pediatric patients (age <19 years) had been referred because of an affected parent and/or because of 1 or more suggestive symptoms. The inclusion criteria for this study were a diagnosis of HHT by the Curaçao criteria or a pathogenic variant in an HHT gene (*ACVRL*, *ENG*, or SMAD family member 4 gene [*SMAD4*]).[3] We assumed "multiple" telangiectases to mean 3 or more for the purpose of applying the diagnosis criteria. If molecular testing of a family member had previously shown a pathogenic variant in 1 of the known HHT genes, other relatives determined to be affected on clinical grounds were

Abbreviations used:

AVM: arteriovenous malformations
HHT: hereditary hemorrhagic telangiectasia
IQR: interquartile range

considered to have the same mutation. University of Utah institutional review board (IRB_00039582) approval was obtained for this study.

A standardized form was used during physical examination to document the site and frequency of telangiectases. Examination included careful inspection for telangiectases of the skin and oral mucosa. Questionable telangiectases were excluded from the analyses. The term *hand* was defined as the palm and dorsal aspect of the hand, excluding the fingers. Telangiectases of the nasal mucosa were not included in this study because nasal endoscopy is not a standard practice in the diagnostic evaluation of patients with HHT. Information regarding hemorrhagic events from telangiectases and previous treatment was systematically collected and recorded.

Data were collected and grouped by telangiectasia location. Telangiectases categorized as cutaneous included lesions of the ears, face, neck, arms, hands. and fingers. Some locations were further subdivided. The location face excluded the lips. Oral telangiectases included telangiectases of the lips, oral mucosa, palate, and tongue.

Statistical analyses

Descriptive statistics were used to summarize patient demographics and HHT disease severity. Count (%) was used for categoric variables, and mean, standard deviation, and range (minimum/maximum) were used to summarize continuous variables with approximately normal distributions. Skewed continuous variables were summarized by median and interquartile range (IQR). Demographic variables were compared with presence of 1 or more telangiectases by using a chi-square or Fisher exact test. Telangiectases were summarized by specific locations at both the telangiectasis and patient levels by using count (%). Percent of telangiectases at a subset of locations (cutaneous, face, arm, hand, palmar/dorsal, fingers, oral, lip, and tongue) were compared at the patient level between children (age, 0-9 years) and adolescents (age, 10-18 years) by using a series of chi-square or Fisher's exact tests followed by Benjamini-Hochberg false discovery rate adjustment to reduce false-positive findings.[13] These analyses were also repeated with adjustment for age and sex by using logistic regression, and again we reported false discovery rate q values. Age at evaluation, sex, and HHT genetic subtype were compared with telangiectasis counts by using univariable and multivariable negative binomial regression (with a log link), as the telangiectasis count outcome was notably overdispersed. The model coefficients were exponentiated to report incident rate ratios, their 95% confidence intervals, and P values. Statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc, Cary, NC). All P values and q values were 2 sided and evaluated at a .05 and 0.05 significance level, respectively.

Table I. Consensus clinical diagnostic criteria (also known as the Curaçao criteria) for HHT

Criteria	Definition
Epistaxis	Spontaneous and recurrent
Telangiectases	Multiple, at characteristic sites: lips, oral cavity, fingers, and nasal mucosa
Visceral lesions	Pulmonary, hepatic, cerebral, or spinal AVM; gastrointestinal telangiectasia
Family history	A first-degree relative with HHT according to these criteria
HHT diagnosis	
Definite HHT	≥3 criteria present
Probable HHT	2 criteria present
HHT unlikely	<2 criteria present

AVM, Arteriovenous malformation; *HHT*, hereditary hemorrhagic telangiectasia.

RESULTS

A total of 90 pediatric patients with HHT were identified; 78 of them had HHT confirmed by genetic testing and 12 (from families with known mutations) met the published clinical diagnostic criteria alone (Table II). Of the 78 patients with a known pathogenic variant for HHT, 28 (36%) met the Curaçao clinical diagnostic criteria for HHT.

Of our cohort of 90 patients, 44 were children (age, 0-9 years) and 46 were adolescents (age, 10-18 years); the median age at evaluation was 9 years. More than 90% of the subjects in this cohort had HHT type 1 (n = 41 [46%]) or HHT type 2 (n = 46 [51%]); 3 patients had a *SMAD4* mutation. Of the pediatric subjects with HHT, 26 (29%) had no telangiectases on physical examination. The majority of patients had a history of epistaxis (n = 65 [72%]) and met 2 or fewer Curaçao criteria (56%). The median number of telangiectases differed between children (1 [IQR, 0-3]) and adolescents (5 [IQR, 2-5]) ($P < .001$ [data not shown]). Only 23% of pediatric patients (21 of 90) presented with multiple (≥3) telangiectases at sites considered to be characteristic mucocutaneous locations (lips, oral cavity, and fingers). Most were

Table II. Demographics and clinical features of children and adolescents with HHT

Feature	All patients (N = 90)	Children (age, 0-9 y) (n = 44)	Adolescents (age, 10-18 y) (n = 46)
Sex, n (%)			
Male	46 (51)	23 (52)	21 (46)
Female	44 (49)	21 (48)	25 (54)
Proband, n (%)			
HHT type 2 (*ACVRL1*)	46 (51)	18 (41)	28 (61)
HHT type 1 (*ENG*)	41 (46)	24 (55)	17 (37)
SMAD4	3 (3)	2 (5)	1 (2)
Curaçao criteria,* n (%)			
1	18 (20)	16 (36)	2 (4)
2	32 (36)	20 (45)	12 (26)
3	29 (32)	8 (18)	21 (46)
4	11 (12)	0 (0)	11 (24)
Telangiectasis, n (%)			
0	26 (29)	19 (43)	7 (15)
1	8 (9)	6 (14)	2 (4)
2	12 (13)	6 (14)	6 (13)
3	6 (7)	4 (9)	2 (4)
4	9 (10)	4 (9)	5 (11)
5-10	25 (28)	4 (9)	21 (46)
≥11	4 (4)	1 (2)	3 (7)
Frequency of telangiectasia, median (IQR)	2 (0-5)	1 (0-3)	5 (2-5)
History of recurrent, spontaneous epistaxis, n (%)	65 (72)	22 (50)	43 (93)
Age at evaluation, y			
Mean (SD)	9 (5.6)	4 (2.8)	14 (2.5)
Minimum/maximum	0.2/18	0.2/9	10/18

ACVRL1, Activin A receptor like type 1 gene; *ENG*, endoglin gene; *HHT*, hereditary hemorrhagic telangiectasia; *IQR*, interquartile range; *SD*, standard deviation; *SMAD4*, SMAD family member 4 gene.

*Curaçao criteria for clinical diagnosis of HHT include (1) spontaneous and recurrent epistaxis, (2) multiple telangiectases at characteristic sites (lips, oral cavity, fingers, and nasal mucosa), (3) visceral arteriovenous malformations, and (4) a first-degree relative with HHT according to these criteria.

pink-red, punctate, blanchable macules or thin papules measuring 1 to 2 mm; a radiating linear or branching component was usually not evident (Fig 1). The presence of telangiectases was not associated with sex or HHT genetic subtype.

The average number of telangiectases increased with age ($P < .001$). Around the age of 7 years, patients had 3 or more telangiectases on average; the locations of these telangiectases varied but were not limited to the classical locations defined by the Curaçao criteria. However, telangiectases were also detected in neonates (in 2 of 7 neonates). By the age of 15 years, almost every adolescent (20 of 21) had at least 1 telangiectasis detected on physical examination.

Of the subjects who had telangiectases, more had at least 1 cutaneous telangiectasia (95%) than had oral telangiectases (50%) (Table III). In patients with telangiectases, the hands (63%), fingers (56%), lips (41%), and arm (28%) were the most common locations. In terms of telangiectasis density, the hands and fingers were the most frequent sites, comprising 33% and 22% of the total of 319 documented telangiectases.

At least 1 cutaneous telangiectasia was evident in 85% of adolescents, compared with in only 50% of children ($Q = 0.005$ [Table IV]). The most common sites for telangiectases in children were the hands (27%), fingers (25%), and face (23%); for adolescents, the most common sites were the hands (61%), fingers (54%), and lips (41%). Oral involvement was relatively uncommon in children (in only 20%). In contrast, 50% of adolescents had oral telangiectases.

One subject reported a hemorrhagic event involving a non-nasal telangiectasis. A 14-year-old, who was noted on physical examination to have 5 telangiectases on the hands and 1 on the lip, reported that the lip telangiectasis had bled once. The bleed was self-limiting and required no intervention.

DISCUSSION

In this single-center retrospective study of pediatric patients with HHT, we found that telangiectases in children are not uncommon, despite earlier studies that refer to oral or cutaneous telangiectases as having an onset typically in the third decade or years after the onset of nosebleeds. Although telangiectases were more common in adolescents than in children, telangiectases were detected as early as during the neonatal period of life. With increasing age, development of telangiectases in the characteristic locations, particularly oral telangiectases, became more prevalent whereas fewer younger children had oral involvement.

Only 23% of 90 patients with HHT presented with multiple (≥3) telangiectases at the characteristic locations defined by the Curaçao diagnostic criteria (lips, oral cavity, and fingers). However, 44 subjects (49%) had 3 or more telangiectases at any site (not necessarily at the characteristic sites of HHT). The international guidelines do not define the term *multiple* in terms of the number of telangiectasia at the characteristic locations.[2] The diagnosis of HHT in pediatric patients may be missed if the patient presents with 1 or 2 rather than multiple telangiectases or with telangiectases not considered to be at

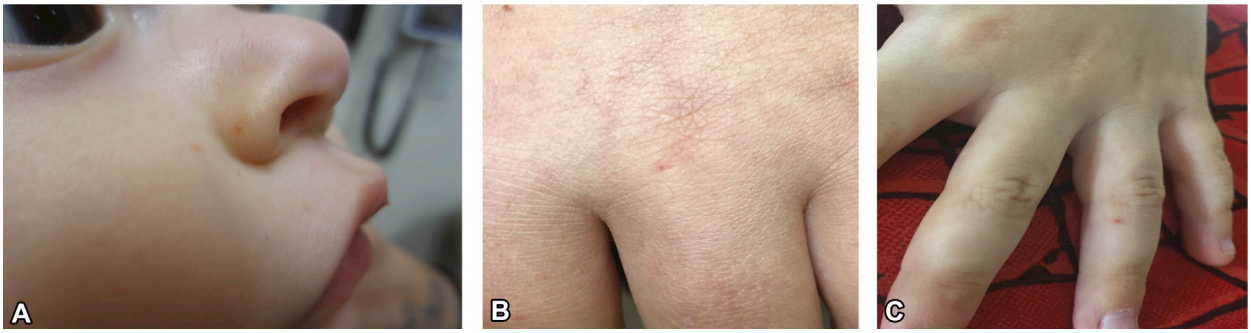

Fig 1. A-C, Telangiectases typical of those seen in pediatric patients with hereditary hemorrhagic telangiectasia.

Table III. Location and prevalence of mucocutaneous telangiectases in pediatric HHT

Location	Patients with telangiectasia,* n (%) (n = 64)	Total telangiectases,† n (%) (n = 319)
Cutaneous	61 (95)	233 (73)
Ears	3 (5)	4 (1)
Face	15 (23)	21 (7)
Neck	2 (3)	2 (0.6)
Arm	18 (28)	29 (9)
Elbow and forearm	12 (19)	21 (7)
Wrist	7 (11)	8 (2.5)
Hands	40 (63)	105 (33)
Palmar aspect of the hand	25 (39)	48 (15)
Dorsal aspect of the hand	25 (39)	57 (18)
Fingers	36 (56)	71 (22)
First digit	12 (19)	13 (4)
Second digit	19 (30)	26 (8)
Third digit	12 (19)	17 (5)
Fourth digit	9 (14)	10 (3)
Fifth digit	5 (8)	5 (2)
Back	1 (2)	1 (0)
Oral	32 (50)	86 (27)
Lips	26 (41)	48 (15)
Upper lip	15 (23)	17 (5)
Lower lip	19 (30)	31 (10)
Buccal mucosa	1 (2)	1 (0)
Palate	3 (5)	3 (1)
Tongue	12 (19)	34 (11)

HHT, Hereditary hemorrhagic telangiectasia.
*Summaries at the patient level (includes patients with at least 1 telangiectasia [n = 64]). Percentages calculated by dividing by the total number of patients with telangiectases (n = 64).
†Summaries at the telangiectasis level. Percentages calculated by dividing by the total number of telangiectases (n = 319).

Table IV. Site-specific analyses stratified by age group

Location	Children, n (%) (n = 44)	Adolescents, n (%) (n = 46)	*q* value*	Adjusted *q* value†
Cutaneous	22 (50)	39 (85)	**0.004**	**0.005**
Face	10 (23)	5 (11)	0.14	0.37
Arm	6 (14)	12 (26)	0.14	0.22
Hands	12 (27)	28 (61)	**0.006**	**0.007**
Palmar aspect of the hand	6 (14)	19 (41)	**0.008**	**0.013**
Dorsal aspect of the hand	8 (18)	17 (37)	0.07	**0.037**
Fingers	11 (25)	25 (54)	**0.009**	**0.013**
Oral	9 (20)	23 (50)	**0.008**	**0.013**
Lips	7 (16)	19 (41)	**0.013**	**0.015**
Tongue	3 (7)	9 (20)	0.09	0.14

Boldface values indicate statistical significance.
*False discovery rate *q* values from chi-square tests.
†Adjusted for genetic subtype and gender using logistic regression.

the characteristic locations. It is also of note that 50 of the 78 pediatric patients with HHT confirmed by molecular genetic testing (64%) did not meet the Curaçao diagnostic criteria. The findings of this study suggest that the Curaçao diagnostic criteria are not sensitive for diagnosing HHT in the pediatric population.

The rate of hemorrhagic events involving extranasal telangiectases has been reported to be as high as 25% in HHT, with 13% patients requiring treatment for a prolonged hemorrhage.[7] In our pediatric cohort, only 1 patient reported having had 1 bleed. It was of the lip, bled once, and required no treatment.

There are some limitations to our study. First, a full-body skin examination was not performed because the standardized data collection form that was used included only inspection and palpation of the skin of certain regions (face, ears, arms, hands, and neck) and oral cavity (tongue, lips, palate, and buccal mucosa) for telangiectases. The standard diagnostic clinical examination for patients in whom HHT is suspected is limited to these body locations because they have previously been

established as those relevant to the clinical diagnosis of HHT. Also, the morphology of each individual cutaneous telangiectasis was not noted during data collection. However, they were mostly punctate 1- to 2-mm lesions resembling those seen in adults with HHT rather than the spider telangiectases with radiating fine linear "legs" that are commonly found on the face and hands of unaffected children. That said, it is both a limitation of this study and a challenge in clinical practice that the telangiectases associated with HHT are not always distinguishable from those seen in the general population.

Ascertainment bias exists in that only individuals referred by providers or scheduled by concerned parents for a clinical encounter were included. Although consensus management guidelines recommend diagnostic evaluation for HHT for all children with a parent affected by HHT as early in life as possible,[3] in our experience most are brought in for evaluation by their parents only after development of 1 or more symptoms. Because the majority of patients in this study had at least 1 symptom or manifestation of HHT previously identified, the clinical manifestations of HHT present in this cohort are likely an overestimate of the entire pediatric population with HHT. However, this likelihood only strengthens our conclusion that the clinical diagnosis of HHT is difficult to make in childhood and confirmation of the diagnosis typically requires genetic testing.

Cutaneous and oral telangiectases are the external manifestation of a potentially life-threatening disease. A careful examination for these lesions in patients is relatively simple and can instigate further evaluation for HHT. Clinicians should use caution, however, when applying the Curaçao criteria in the diagnosis of HHT in children and adolescents, as the locations, frequency, and overall presentation of telangiectases in our pediatric cohort (hands, fingers, and face) differed from the classic adult presentation (lips, oral cavity, and fingers). Because the Curaçao criteria do not include cutaneous telangiectases of the dorsal aspect of the hand, palmar aspect of the hand, forearm, or face and because the majority of pediatric patients with HHT do not have multiple telangiectases, the diagnosis may be overlooked in this population.

The findings of this study support the expert opinion set forth in the published international guidelines for HHT that asymptomatic children of a parent with HHT should be considered to have possible HHT unless it has been excluded by genetic testing. Our findings suggest that the same is the case for minimally symptomatic children who do not meet the Curaçao criteria. The presence of multiple punctate cutaneous telangiectases (particularly of the hands, fingers, face, and lips) in a pediatric patient with a history of recurrent nosebleeds and/or concerning family history should prompt a diagnostic evaluation for HHT.

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