Applicability of the Curaçao Criteria for the Diagnosis of Hereditary Hemorrhagic Telangiectasia in the Pediatric Population

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Objective To evaluate the accuracy of the clinical Curaçao criteria in the diagnosis of hereditary hemorrhagic telangiectasia (HHT) in children and adolescents.

Study design This was a retrospective, multicenter chart review of 673 patients evaluated between 2002 and 2016; 290 were eligible for the study. Genetic testing for a pathogenic mutation was considered the gold standard against which the clinical Curaçao criteria were compared. Patients were divided into 4 age categories: 0-5, 6-10, 11-15, and 16-21-years. Sensitivity and specificity were calculated for each age group, and for the overall population.

Results Overall the Curaçao criteria had a sensitivity of 68% (95% CI 60%-76%) and a specificity of 98% (95% CI 91%-100%). Sensitivity was lowest in the 0- to 5-year group, and increased with advancing age. The Curaçao criteria had the highest sensitivity in the 16- to 21-year-olds. Specificity was 100% in all age groups except for the 11- to 15-year-olds.

Conclusions This study evaluated the use of the Curaçao criteria for the diagnosis of HHT in the pediatric population with a family history of HHT. In those between the age of 0 and 21 years who meet 1 criterion (unlikely HHT) or 2 criteria (possible HHT), genetic testing is preferred for diagnosis. The Curaçao criteria appear to reliably diagnose HHT in children and adolescents who meet 3 or 4 criteria (definite HHT). *(J Pediatr 2018;197:207-13).*

Hereditary hemorrhagic telangiectasia (HHT) is a rare disease characterized by mucocutaneous telangiectasia and arteriovenous malformations (AVMs) in visceral organs. It is an autosomal dominant disorder that affects approximately 1 in 5000-8000 individuals.[1] Endoglin (*ENG*), activin A receptor like kinase 1 (*ACVRL1*), and SMAD family member 4 (*SMAD4)* are all part of the transforming growth factor beta pathway, which is integral to angiogenesis.[2] Pathogenic mutations in any of the aforementioned genes cause disruption of the intricate balance between pro- and antiangiogenic signals necessary for normal vascular development,[3] resulting in HHT. HHT is diagnosed based on the presence of deleterious mutations in *ENG, ACVRL1,* or *SMAD4,*[2] or clinically through application of the Curaçao criteria.[4]

The clinical Curaçao criteria were developed in 2000 (**Table I**). These criteria include (1) multisite mucocutaneous telangiectasia, (2) recurrent spontaneous epistaxis, (3) visceral organ AVM, and (4) family history of HHT in a first-degree relative. Patients who meet 3 or 4 criteria are said to have definite HHT, those who meet 2 criteria as possible HHT, and those with 0 or 1 criteria as unlikely to have HHT.[4,5] Approximately 85% of patients who meet 4 Curaçao criteria will have a mutation in either *ENG, ACVRL1,* or *SMAD4*. The remaining 15% of patients are deemed to have an unidentified mutation, or contain mutations in deep introns that are not sequenced in standard clinical genetic testing.[6,7] In symptomatic adults, the Curaçao criteria are routinely used to diagnose HHT and genetic testing is often not pursued. In adult patients who have a first-degree relative with a HHT mutation, the Curaçao criteria have been validated and perform well with reported sensitivity of 90%.[8] Thus, the criteria can reliably diagnose HHT in adult patients. In patients with possible HHT (2 of 4 criteria present), genetic testing is recommended to confirm diagnosis.[5]

HHT symptoms develop over time, and children with HHT are less likely to manifest symptoms of the disease when compared with adults.[9,10] If epistaxis begins

ACVRL1	Activin A receptor like kinase 1
AVM	Arteriovenous malformation
CI	Computerized tomography
ECHO	Echocardiography
ENG	Endoglin
GI	Gastrointestinal
HHT	Hereditary hemorrhagic telangiectasia
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
SMAD4	SMAD family member 4

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Table I. Curaçao criteria

Criterion	Definition
Epistaxis	Spontaneous, recurrent nosebleeds
Telangiectasia	Multiple at characteristic sites (lips, oral cavity, nose, fingers)
AVM	Any of the following: (1) Cerebral AVM (2) Spinal AVM (3) Pulmonary AVM (4) Hepatic AVM (5) Gastrointestinal telangiectasia (with or without bleeding)
Family history	A first degree relative with HHT according to the criteria Definite HHT: if 3 criteria present Possible HHT: if 2 criteria present Unlikely HHT: if fewer than 2 criteria are present

in childhood, it is typically after 10 years of age, and rarely necessitates cautery or other significant interventions to control bleeding.[11,12] Telangiectasia, which characteristically appear on the lips, oral cavity, nasal mucosa, and fingers, usually develop in the second to third decade of life.[10,13] Children can, and do, experience AVM-related complications, but this is believed to occur at a lower rate when compared with adults.[14-16] Gastrointestinal (GI) bleeding or complications from hepatic AVMs are rarely reported in children.[17,18] Because 3 of the 4 Curaçao clinical criteria are typically absent in children with HHT, the applicability of the criteria to the pediatric population is unclear.

Although it is generally accepted that the Curaçao criteria may be of less utility in the pediatric population compared with adults, no prior studies have specifically addressed this question. In this study, we sought to evaluate the accuracy of the Curaçao criteria for the diagnosis of HHT in patients between the age of 0 and 21 years. We performed a multicenter chart review comparing the Curaçao criteria with the gold standard of a pathogenic mutation on genetic testing for the diagnosis of HHT in the pediatric population.

Methods

Patients were recruited from the HHT Centers at the University of North Carolina, Cincinnati Children's Hospital, Yale University, and Washington University-St Louis between the period 2002 and 2016. Subjects were eligible if they were between the age of 0 and 21 years. Children with genetic variants were included if these variants were classified as "likely to be pathogenic."

Inclusion criteria included genetic testing for HHT within 1 year of documentation of the Curaçao criteria, and documented HHT mutation in a first-degree relative, or clinical diagnosis of HHT in a first-degree family member with documented mutation in any family member diagnosed with HHT. Subjects were included if they were tested for sporadic HHT (ie, they did not have a family history of HHT or HHT symptoms). Exclusion criteria included incomplete documentation of the Curaçao criteria, patients in whom genetic testing was not conducted or results were not available, and patients with a first-degree family member with a diagnosis of HHT or symptoms of HHT, but who had not undergone genetic testing or had tested negative for a known pathogenic mutation. These criteria were designed to maximize the likelihood that patients who tested negative for a pathogenic mutation in fact did not have HHT, rather than being among the 15% of individuals who have HHT based on the Curaçao criteria but test negative on standard mutation analysis.

A total of 673 patients in the target age group were evaluated (**Figure**). A total of 339 patients were excluded because genetic testing was not done or not available, 19 were excluded due to incomplete documentation of clinical criteria, 17 because genetic testing and clinical evaluation were greater than one year apart, and 8 because of a family history of HHT by Curaçao criteria but with negative testing for a pathogenic mutation. Thus, 198 subjects were analyzed in the primary analysis (including those who met 1, 3, or 4 Curaçao criteria), and 290 subjects were eligible for the secondary analysis (including those who met 1, 2, 3, or 4 Curaçao criteria).

Data abstracted from the medical record included patient age, sex, ethnicity, results of genetic testing (with specific mutation if positive), Curaçao criteria met, and location and treatment of AVMs when applicable. Indication for treatment was not collected. Medical record review was approved by a waiver from the University of North Carolina Institutional Review Board (IRB), which also served as the IRB of record for Yale University. The remaining study sites obtained individual institutional IRB approval.

Screening for Visceral Organ AVMs

The international guidelines for the management of HHT acknowledge a lack of evidence regarding the specific age at which AVM screening should begin in children, but they do recommend screening be pursued.[5] Given this, individual HHT Centers of Excellence often have varying practices regarding AVM screening in children, and this was the case across the 4 sites included in this study. Therefore, children were not required to have completed pulmonary and brain AVM screening to be included in this study.

In general, brain AVM screening with magnetic resonance imaging (MRI) is obtained at diagnosis, or in early childhood when sedation is not needed to obtain imaging. Some centers perform a head ultrasound (US) in infancy if diagnosis of HHT is confirmed, and then pursue a MRI at an older age. There is no data regarding the accuracy of head US to detect brain AVMs in this context.

Screening for pulmonary AVMs is typically pursued around 10-12 years of age, although some centers begin imaging based screening at an earlier age. Contrast echocardiography (ECHO) is the initial test of choice, and if positive, a computerized tomography (CT) is performed to assess AVM size, number, and location.[5] Contrast ECHOs are graded on a scale of 1-3 corresponding to shunt size, which is based on opacification of the left ventricle after contrast administration.[19] A grade 1 ECHO can be positive from either a patent foramen ovale or micro-AVM, depending on the delay between appearance of bubbles in the left ventricle after detection in the right ventricle.[20] Prior studies have shown that patients with grade 1

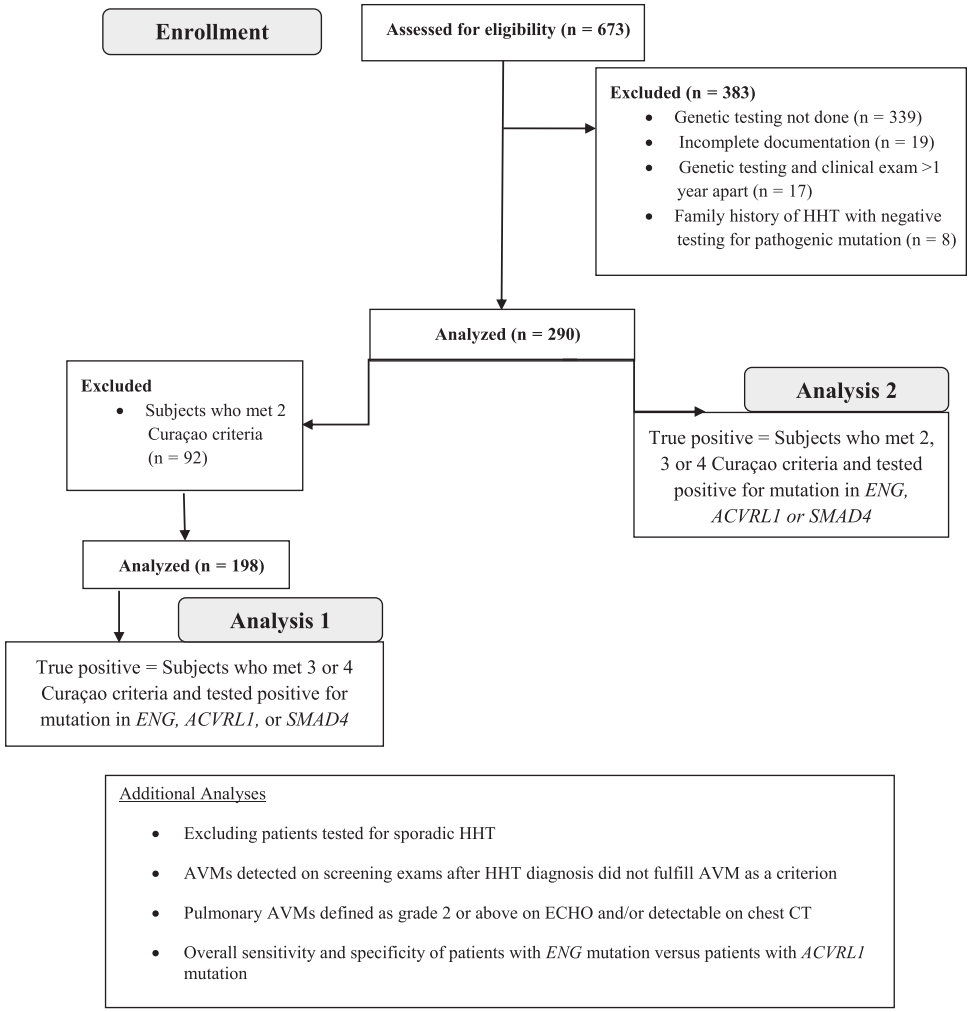

Figure. Selection of study population and analysis.

ECHOs are unlikely to have detectable AVMs on CT.[19] It is speculated that in such instances, the patients indeed have pulmonary AVMs, but these are too small to be detected on CT scan.[19,21] Improved specificities and a correlation between CT and ECHO for diagnosing pulmonary AVMs is observed in those with grade 2 or 3 ECHOs.[19]

Screening for liver and GI AVMs are conducted only in those with symptoms concerning for their presence. Liver AVM symptoms include right upper quadrant pain, liver dysfunction, or high output cardiac failure.[22] GI symptoms include bleeding, which can be either acute or chronic in nature.[23]

Curaçao Criteria

Family history was considered positive if a patient had a first-degree relative with a pathogenic mutation in either *ENG*, *ACVRL1*, or *SMAD4*, or a first-degree family member who met clinical criteria for HHT (3 or 4 Curaçao criteria). Telangiectasia were deemed present if subjects had at least 1 telangiectasia in more than 1 characteristic site (lips, oral cavity, nose, and fingers). Nosebleeds had to be spontaneous in nature and occur at least 2 times a year. There was no stipulation as to duration, as this is not included in the Curaçao criteria. Imaging reports and medical records were reviewed, and an AVM was considered present if there was documented evidence of brain, spinal, lung, GI, or liver AVM either prior to genetic diagnosis, or after genetic diagnosis on screening examination(s). Brain or spinal AVMs had to be documented by MRI or CT. A positive contrast ECHO of any grade and/or CT was considered evidence for a pulmonary AVM. Patients with grade 1 ECHO whose chest CT scan did not detect an AVM were still considered to have pulmonary AVMs, as these positive ECHOs could represent micro-AVMs not detectable on CT scan. Given that there is evidence that grade 1 ECHOs are unlikely to have clinical significance (thus, there is a question as to whether they should count as a clinical criterion),[24] we completed an additional analysis that defined a pulmonary AVM as either a grade 2 (or above) contrast ECHO and/or a documented lesion on CT scan. GI telangiectasia had to be documented by endoscopy, and liver AVM by either CT, US, or MRI. If an imaging report questioned AVM vs nonspecific findings, we examined the medical record to determine how the treating physician interpreted these results.

Statistical Analyses

Subjects were divided into 4 groups at initial evaluation based on age: 0-5, 6-10, 11-15, and 16-21 years. Presence or absence of a pathogenic mutation in either *ENG, ACVRL1,* or *SMAD4* was considered the gold standard for HHT diagnosis. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for each age group, and for the overall population; 95% confidence intervals (CIs) were included for each sensitivity and specificity calculation.

The **Figure** depicts the analysis groups. In the primary analysis of 198 children, true positive subjects were those who tested positive for a pathogenic mutation in *ENG, ACVRL1*, or *SMAD4* and met 3 or 4 Curaçao criteria. True negative subjects were those that tested negative for a pathogenic mutation in *ENG, ACVRL1,* or *SMAD4* and met 0 or 1 criteria. Additional analysis, using the above definitions for true positive and true negative subjects, examined changes in sensitivity and specificity under the following considerations: (1) excluding patients tested for sporadic HHT; (2) if AVMs detected on screening examinations after HHT diagnosis did not fulfill AVM as a clinical criterion; (3) if the presence of pulmonary AVMs was defined as a grade 2 or above contrast ECHO and/or detectable on CT; and (4) comparing *ENG* vs *ACVRL1* genotype.

Two hundred and ninety patients were eligible for the secondary analysis, which examined how modification of the Curaçao criteria impacted sensitivity and specificity. For this sensitivity and specificity analysis, true positive subjects were those that met 2, 3, or 4 Curaçao criteria and tested positive for a pathogenic mutation in *ENG, ACVRL1*, or *SMAD4,* and the definition of true negative patients remained the same.

We used simple logistic regression to determine if there was a statistically significant relationship between genotype and nosebleeds, telangiectasias, or AVM presence. The Wald test determined the *P* value of the regression coefficients, and the Woolf approach determined the CI of the odds ratio (OR).

Results

Of the 290 patients (**Table II**), 214 were diagnosed with HHT based on genetic testing and 76 tested negative for a known pathogenic mutation in *ENG, ACVRL1,* or *SMAD4.* One hundred forty-two were female (49%). Caucasian ethnicity was most common (92%), followed by African American (4%), Hispanic (2%), Asian/Pacific Islander (1%), and unknown ethnicity (1%). Eighty-eight (30%) patients were between the age of 0 and 5 years, 68 (23%) between ages 6 and 10 years, 93 (33%) between ages 11 and 15 years, and 41 (14%) between ages 16 and 21 years. Of the 214 patients with HHT, 141 (66%) possessed a mutation in *ENG*, 63 (29%) in *ACVRL1*, and 10 in (5%) *SMAD4*.

Table II. Patient characteristics

Clinical parameters	n (%)
Sex	
Male	148 (51%)
Female	142 (49%)
Ethnicity	
Caucasian	267 (92%)
African American	12 (4%)
Hispanic	5 (2%)
Asian/Pacific Islander	2 (1%)
Unknown	4 (1%)
Genotype of HHT subjects	
ENG	141 (66%)
ACVRL1	63 (29%)
SMAD4	10 (5%)
Age	
0-5 y	88 (30%)
6-10 y	68 (23%)
11-15 y	93 (33%)
16-21 y	41 (14%)

Curaçao Criteria

Epistaxis was least common in the 0- to 5-year age group (n = 28, 32%), and increased steadily with age, with 31 (76%) patients aged 16-21 years experiencing recurrent nosebleeds. Telangiectasia were also uncommon in the youngest age groups, present in only 14 (16%) of patients in the 0- to 5-year group. The incidence of telangiectasia also increased with age: 20 patients in the 16- to 21-year age group (49%) had developed telangiectasia.

Of the 214 patients with HHT, 48% (n = 103) had an AVM. Seventy-four patients had a pulmonary AVM, 11 a brain AVM, 14 pulmonary and brain AVMs, and 1 patient had a liver AVM. In addition, 1 patient had pulmonary and GI AVMs, 1 patient pulmonary and liver AVMs, and 1 patient pulmonary, brain, and liver AVMs. In these 214 patients with HHT, 156 patients completed screening for pulmonary AVMs, and 91 (58%) of these patients had ECHO (of any grade) and/or CT evidence of an AVM. One hundred eighty-eight patients with HHT completed screening for brain AVMs, and of those 26 (14%) had a brain AVM detected on MRI or CT. If the definition of pulmonary AVM presence was limited to those with grade 2 ECHO or above and/or documented AVM on CT, 64 of the 156 patients screened (41%) had a pulmonary AVM.

Patients with *ENG* mutation were more likely to have epistaxis (*P* value: <.001, OR 6.4 with 95% CI of 3.5,12.0), telangiectasia (*P* value: <.001, OR 5.6 with 95% CI of 2.7,12.8), and AVMs (*P* value: <.001, OR 15.2 with 95% CI 6.9, 38.4) when compared with those with *ACRVL1* mutation.

Pulmonary AVM

In total, 91 patients with HHT had a pulmonary AVM alone or in combination with an AVM in another organ. Of these 91 patients, 80 (88%) had an *ENG* mutation, 6 (7%) an *ACVRL1* mutation, and 5 (5%) a *SMAD4* mutation. Sixty of the 91 (66%) patients with a pulmonary AVM were diagnosed at the time of screening, at a median age of 9 years (range 0-21 years). The diagnosis of pulmonary AVM in the remaining 31 patients (34%) was made at a median age of 11 years (range 0-20 years) as a result of further evaluation of pulmonary AVM-related symptoms. Symptoms included chest pain, shortness of breath, hypoxia, and hemoptysis. Forty (44%) patients underwent treatment of their AVM, and 51 (56%) were observed without intervention during the study period.

Table III. Sensitivity and specificity of the Curaçao criteria

	0-5 y	6-10 y	11-15 y	16-21 y	Overall
Sensitivity % (95% CI)					
Analysis 1	42% (28%-57%)	79% (59%-92%)	82% (66%-92%)	91% (72%-99%)	68% (60%-76%)
Analysis 2	42% (28%-58%)	79% (59%-92%)	83% (67%-94%)	91% (71%-99%)	69% (61%-77%)
Analysis 3	33% (21%-48%)	75% (55%-89%)	79% (64%-91%)	91% (72%-99%)	64% (55%-72%)
Analysis 4	22% (11%-36%)	69% (49%-85%)	70% (51%-84%)	91% (71%-99%)	56% (47%-65%)
Analysis 5	58% (46%-70%)	88% (75%-95%)	89% (78%-95%)	94% (80%-99%)	79% (73%-85%)
Specificity % (95% CI)					
Analysis 1	100% (81%-100%)	100% (79%-100%)	95% (74%-100%)	100% (48%-100%)	98% (91%-100%)
Analysis 2	100% (80%-100%)	100% (79%-100%)	100% (81%-100%)	100% (48%-100%)	100% (94%-100%)
Analysis 3	100% (82%-100%)	100% (79%-100%)	100% (82%-100%)	100% (49%-100%)	100% (94%-100%)
Analysis 4	100% (82%-100%)	100% (79%-100%)	100% (81%-100%)	100% (48%-100%)	100% (94%-100%)
Analysis 5	95% (74%-100%)	80% (56%-94%)	60% (41%-77%)	71% (29%-95%)	75% (64%-84%)

Analysis 1, True positive patients defined as those who met 3 or 4 Curaçao criteria and tested positive for a mutation in *ENG, ACVRL1,* or *SMAD4*; *Analysis 2*, Excluding patients tested for sporadic HHT (those without a family history of HHT); *Analysis 3*, Pulmonary AVM defined as contrast ECHO grade 2 or above and/or detectable on CT scan; *Analysis 4*, AVMs detected on screening exams after HHT diagnosis did not fulfill AVM as a criterion; *Analysis 5*, True positive patients defined as those who met 2, 3, or 4 Curaçao criteria and tested positive for a mutation in *ENG, ACVRL1,* or *SMAD4*.

Brain AVM

Twenty-six patients with HHT had a brain AVM of which 23 (88%) had an *ENG* mutation, 3 (12%) an *ACVRL1* mutation, and none had a *SMAD4* mutation. Fifteen of the 26 patients (58%) were diagnosed at the time of screening, and the remaining 11 patients (42%) were diagnosed secondary to symptoms. Symptoms included persistent headache, or were related to intracranial hemorrhage. Median age of brain AVM diagnosed by screening was 5 years (range 0-21 years), compared with a median of 6 years (range 0-15 years) in those who developed symptoms. The brain AVM was treated in 14 (54%) of the patients.

Sensitivity and Specificity

Table III lists sensitivity and specificity values for each analysis. In the primary analysis of 198 children, test positive was defined as subjects who met 3 or 4 Curaçao criteria and test negative those who met 1 criteria. Sensitivity was 42% (95% CI 28%-57%) in the 0- to 5-year age group, 79% (95% CI 59%-92%) in the 6- to 10-year age group, 82% (95% CI 66%-92%) in the 11 to 15-year age group, and highest in the 16- to 21-year age group at 91% (95% CI 72%-99%). All age groups had 100% specificity except for the 11- to 15-year-olds, in which specificity was 95% (95% CI 74%-100%). This lower specificity was the result of 1 patient who was tested for sporadic HHT and met 3 Curaçao criteria (epistaxis, telangiectasia, and AVM) but tested negative for a known pathogenic mutation. Overall sensitivity was 68% (95% CI 60%-76%), and specificity was 98% (95% CI 91%-100%), with a positive predictive value of 99% and a negative predictive value of 54%. Excluding patients from this analysis who were tested for sporadic HHT (ie, those who did not have a family history of HHT) did not alter the overall sensitivity, which remained at 69% (95% CI 61%-77%), but did increase the overall specificity to 100% (95% CI 94%-100%). Sensitivity and specificity of the different age groups was essentially identical in the 2 populations.

Further analysis included restricting the definition of pulmonary AVMs to those that were grade 2 or above on ECHO and/or demonstrated CT evidence of an AVM. Compared with analysis 1, in which pulmonary AVM was defined as any grade ECHO and/or CT evidence of an AVM, the overall sensitivity of the Curaçao criteria decreased to 64% (95% CI 55%-72%). The sensitivity for the different age groups, with the exception of the 16- to 21-year-olds in which no one had a grade 1 ECHO result, declined as well. Specificity was 100% for all age groups. The sensitivity of the Curaçao criteria further declined compared with analysis 1 if AVMs detected on screening examinations after HHT diagnosis did not fulfill AVM as a clinical criterion. The overall sensitivity was 56% (95% CI 47%-65%), with the most dramatic change in the 0- to 5-year-olds, in which sensitivity was 22% (95% CI 11%-36%). Specificity remained at 100% overall and throughout all age groups.

Analyzing sensitivity and specificity based on genotype showed that the Curaçao criteria had improved sensitivity in those with *ENG* mutation when compared with *ACVRL1*. Overall sensitivity was 76% in the *ENG* patients (95% CI 67%-84%) compared with 40% in *ACVRL1* patients (95% CI 22%-59%), although specificity was the same in both at 98% (95% CI for *ENG* and *ACVRL1* 90%-100%).

Modifying the definition of test positive to include patients who met 2, 3, or 4 Curaçao criteria increased the population analyzed to 290 patients, with the following sensitivity: 58% (95% CI 46%-70%) in the 0- to 5-year-olds, 88% (95% CI 75%-95%) in the 6- to 10-year-olds, 89% (95% CI 78%-95%) in the 11- to 15-year-olds, 94% (95% CI% 80-99%) in the 16- to 21-year-olds, and 79% (95% CI 73%-85%) overall. Overall specificity was lower at 75% (95% CI 64%-84%) and was 95% (95% CI 74%-100%) for the 0- to 5-year-olds, 80% (95% CI 56%-94%) for the 6- to 10-year-olds, 60% (95% CI 41%-77%) for the 11- to 15-year-olds, and 71% (95% CI 29%-95%) for the 16-to 21-year-olds. Thus, expanding the criteria for definite HHT to include patients that met 2, 3, or 4 Curaçao criteria increased the sensitivity in all groups but at the expense of specificity.

Discussion

The Curaçao criteria have been validated in adults and are routinely used to make a clinical diagnosis of HHT. This study

evaluated the performance of these criteria in the pediatric population.

In children between the age of 0 and 15 years with a family history of HHT, the Curaçao criteria have a low sensitivity for the diagnosis of HHT. Sensitivity was higher in 16- to 21-year-olds, although CIs were wide given the smaller number of subjects in this age group. The low sensitivity of the Curaçao criteria was likely due to the age-dependent development of HHT symptoms, such as epistaxis and telangiectasia. Not uncommonly, the only criterion present in children is a family history of HHT in a first degree relative. Relying exclusively on the Curaçao criteria in this context increases the likelihood of a missed (false negative) diagnosis of HHT in a large proportion of children.

In contrast to sensitivity, the specificity of the Curaçao criteria remained high across all age groups. This high specificity was due to the low false positive rate observed. Children who exhibit 3 or 4 Curaçao criteria (definite HHT), especially those with a family history of the disease, are likely to have HHT. We also evaluated whether modifying criteria for definite HHT to include patients who met 2, 3, or 4 criteria improved performance. Although this improved sensitivity, it resulted in a greater false positive rate in all groups. Thus, modifying the criteria requirements for the diagnosis of HHT in children is not helpful.

Additional analysis, in which AVMs detected on screening examinations after the diagnosis of HHT were not used to fulfill the clinical criteria, or restricting the diagnosis of pulmonary AVMs to those with grade 2 ECHO or above and/or AVMs detected on CT scan, lead to decreased sensitivity of the Curaçao criteria. This impacted the youngest age groups most significantly, which is not surprising. Compared with older children and adults, younger children are more likely to have AVMs detected on screening examinations, and less likely to exhibit AVM-related symptoms. In addition, micro-sized pulmonary AVMs, which may be characterized as grade 1 on ECHO in younger children, can grow with time and result in a higher grade ECHO (and, thus, may be sufficiently large to detect on CT) in older children. Specificity, which was already high across all analyses, was not significantly impacted as the false positive rate was not increased.

This study has enabled us to evaluate the performance of the Curaçao criteria in children who have a family history of HHT. Based on our findings, we recommend that patients between the age of 0 and 21 years who meet 1 (usually positive family history) or 2 Curaçao criteria undergo genetic testing to make a definitive diagnosis of HHT, if possible. Even though children 16-21 years old who meet 1 criterion are unlikely to have HHT, the wide CIs for sensitivity indicate genetic testing would still be prudent in this group. On the other hand, 0- to 21-year-olds who meet 3 or 4 Curaçao criteria are most likely have HHT, and genetic testing would not be required for diagnosis.

The large sample size provided us the opportunity to evaluate genotype-phenotype correlations in children with HHT. Children with *ENG* mutations were more likely to exhibit nosebleeds, telangiectasia, and AVMs. Although both adult and pediatric patients with *ENG* mutations have been shown to have higher rates of pulmonary AVMs,[16,25] this study shows that children with *ENG* mutations are also more likely to exhibit epistaxis and telangiectasias. Given this finding, not unsurprisingly, the Curaçao criteria had improved sensitivity in patients with *ENG* mutations compared with those with *ACVRL1* mutations.

Although screening for pulmonary and brain AVMs is recommended in children in the international guidelines, there is a lack of evidence regarding the specific age this should occur.[5] Thus, there is significant variability between HHT centers in the implementation of these guidelines. Previous studies have demonstrated that the overall prevalence of lung and brain AVMs in children is similar to that reported among adults.[14-16] Our study replicated and validates these previous observations. Our finding that the prevalence of HHT associated brain and lung AVMs is similar in children and adults suggests that AVMs do not exhibit the age-dependent penetrance which is observed with epistaxis and telangiectasia.

This study does have limitations, most of which are inherent to any retrospective chart review. The original Curaçao criteria stipulate "recurrent nosebleeds" and "multiple telangiectasia at multiple characteristic sites" without defining a specific number for either manifestation to satisfy criteria. For the purpose of this study, recurrent nosebleeds were defined as greater than 2 per year. Telangiectasia had to be present in more than one site, with at least 1 telangiectasia per site. This approach ensured uniformity in assessing patients across multiple study sites, although sensitivity and specificity may change depending on how these criteria are defined. Excluding patients tested for sporadic HHT, all patients who tested negative for HHT with a reported history of nosebleeds met 2 Curaçao criteria (family history and nosebleeds). These patients did contribute to the lower specificity (because of higher false positive rate) that was seen when our test positive definition included patients meeting 2, 3, or 4 Curaçao criteria. It is possible that a stricter definition of nosebleeds would eliminate some of these false positive patients and lead to higher specificity. Unfortunately, this study was not designed to assess variation in the definition of epistaxis or telangiectasia, but this could be addressed in future studies.

The vast majority of children who present to HHT Centers of Excellence have a family history of HHT, therefore, parents are aware of HHT-related symptoms. Children who are symptomatic are more likely to be tested for HHT when compared with those who are not. This bias could impact our sensitivity and specificity calculations, and limit the generalizability of our study data to unselected populations. In addition, sporadic cases, in which no family history of HHT is present, are rare. Patients tested for sporadic HHT were included in the original analysis to ensure the study population was representative of patients referred to HHT centers for evaluation. Analysis of sensitivity and specificity that excluded these patients did not significantly alter the results. Further studies analyzing the accuracy of the Curaçao criteria in children tested for sporadic HHT is necessary, although obtaining sufficient numbers for generalizable conclusions is likely to be difficult.

Given that the majority of patients with HHT in our study possessed an *ENG* mutation, and the observation that patients with *ENG* mutation are more likely to exhibit symptoms of HHT, there may be concern regarding applicability of these results to patients with *ACVRL1* genotype. Because we recommend genetic testing in any patient aged 0-21 years who meets 1 or 2 Curaçao criteria, this should account for the variability in symptoms between genotypes. Interestingly, the 2 false negative subjects in the 16- to 21-year group (ie, those who met only 1 criterion—family history—but had HHT by genetic analysis) possessed the *ACVRL1* genotype.

Given the lack of evidence-based guidelines on diagnosis of HHT in children, this study provides data and guidance on how best to diagnosis children who have a family history of HHT. ■

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