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;■■:■■-■■).*

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

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