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Unique Considerations in Pediatric Diagnosis of Hereditary Hemorrhagic Telangiectasia

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a disorder of vascular dysplasia characterized by multiple mucocutaneous and visceral arteriovenous malformations (AVMs). The clinical sensitivity of consensus diagnostic criteria has not been well established within the pediatric population. Furthermore, the age-dependent penetrance of the disorder can make timely diagnosis in children challenging. We present three cases of HHT that demonstrate the spectrum of disease presentation within children and adolescents. Early recognition of the manifestations of HHT in pediatric patients can facilitate timely diagnosis and ensure that recommended screenings and interventions are provided to affected children.

ABBREVIATIONS

HHT: Hereditary Hemorrhagic Telangiectasia; PAVM: Pulmonary Arteriovenous Malformation; CVM: Cerebral Vascular Malformation; AVM: Arteriovenous Malformation; TCE: Transcatheter Embolotherapy

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a disorder of vascular dysplasia characterized by multiple arteriovenous malformations (AVMs). The AVMs, which are abnormal connections between arteries and veins without an intervening capillary bed, are distributed throughout mucocutaneous surfaces and viscera. Small telangiectasias may manifest as superficial skin and mucosal membrane lesions with potential to rupture, contributing to epistaxis or gastrointestinal bleeding. Larger AVMs are predominantly found within the lungs, central nervous system, and liver. The presentation of these lesions may range from incidental radiographic findings to catastrophic hemorrhagic events.

HHT has an estimated prevalence between 1:5000 and 1:10,000 [1,2]. Consensus guidelines for HHT are largely expert opinion based upon observational adult data [3]. These guidelines have been extrapolated to managing HHT in children [3,4]. This may lead to delays in appropriate recognition and diagnosis of HHT within the pediatric population, as many characteristic signs and symptoms do not develop until adolescence and early adulthood [1,2,5]. We present here three cases which demonstrate the heterogeneity of HHT presentation within the pediatric population and discuss the challenges this poses for pediatric practitioners.

CASE PRESENTATION

Case 1

A 12-year-old girl presented with difficulty breathing and mild hypoxemia requiring 1 L supplemental O2 via nasal cannula. Chest x-ray was performed and showed findings concerning for a new lung mass (Figure 1a). Physical examination noted several telangiectasias on her tongue and oral mucosa. She had frequent nose bleeds for the past several years with prior history of endonasal electrocauterization which failed to improve her symptoms. High-resolution chest CT subsequently demonstrated pulmonary arteriovenous malformations (PAVMs) in her right lower and left upper lobes measuring 11 mm in diameter (Figure 1b,1c). Transcatheter embolotherapy (TCE) of both lesions was performed which ameliorated her oxygen requirement (Figure 1d). Evaluation for other visceral AVMs was negative. Genetic testing demonstrated a pathogenic indel mutation (c.690-

1_705delinsAC) affecting splicing in the *ENG* gene. Family history was positive for a mother with frequent epistaxis and maternal grandmother that died of a hemorrhagic stroke.

Case 2

A full-term infant boy was delivered via cesarean-section for hydrocephalus, cerebral hemorrhage, and right-sided porencephaly identified on prenatal ultrasound. Post-natal angiography demonstrated a large venous aneurysmal dilation arising from a distal branch fistula of the left anterior temporal artery (Figure 2a, 2b). He underwent TCE and ventriculo peritoneal shunt placement within the first 6 weeks of life. He has since experienced severe developmental delay, left hemiplegia, seizures, and optic atrophy leading to legal blindness. By six years of age, he had developed chronic severe epistaxis and cutaneous telangiectasias of the face and upper extremities. Contrast echocardiography demonstrated a clinically asymptomatic PAVM. Confirmatory genetic testing showed a multi-exonic deletion (EX4_11del) within the *ENG* gene. Family history was positive for a mother with epistaxis and asymptomatic PAVM. Genetic testing of the mother identified the same *ENG* gene mutation.

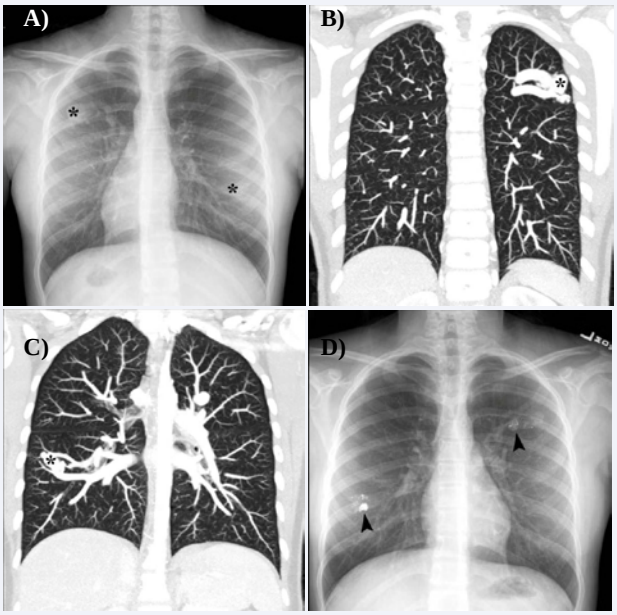

Figure 1 Imaging of Pulmonary Arteriovenous Malformation (PAVM)
A. ** FIGURE 1A IS UPSIDE DOWN**.
B-C. Chest CT with intravenous contrast reconstructed as coronal Maximal Intensity Projection images. PAVMs (*mark) with enlarged feeding pulmonary artery and draining pulmonary vein.
D. Chest X-ray after transcatheter embolotherapy. Endovascular plugs and coils within pulmonary arteries feeding PAVMs (arrowheads).

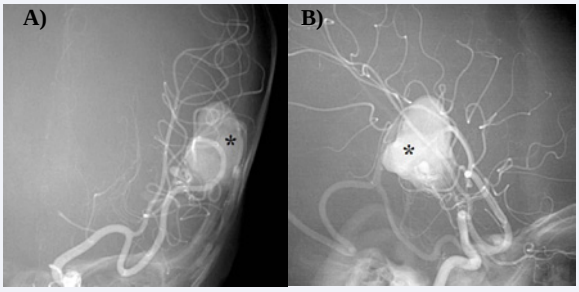

Figure 2 Cerebral angiogram with contrast injection of the left internal carotid artery. The anteroposterior (2a) and lateral (2b) images show an enlarged anterior temporal branch of the middle cerebral artery directly filling a large aneurysmal vein (*mark) with rapid shunting to superficial draining veins.

Case 3

A 5-year-old girl presented to hematology for evaluation of a possible bleeding disorder due to frequent, prolonged epistaxis since 20 months of age. She had symptomatic anemia. Endonasal electrocautery was performed due to bleeding at ages 4 and 6. Her family also reported rare episodes of hematochezia, hemoptysis, and prior pneumonia. She was noted to have a few small telangiectasias on her hands. Contrast echocardiogram demonstrated a clinically asymptomatic PAVM. Evaluation for other AVMs, including upper endoscopy and colonoscopy were negative. *ENG* and *ACVRL1* testing were negative. *SMAD4* testing also demonstrated no pathogenic gene changes. *GDF2* and *RASA1* testing are pending at time of submission. Her mother was subsequently found to meet clinical criteria for HHT including the identification of a large, recently symptomatic PAVM. Hersibling with recurrent epistaxis is also undergoing evaluation.

DISCUSSION

The diagnosis of HHT may be made on either a clinical or genetic basis. Internationally accepted diagnostic clinical criteria, known as the Curaçao Criteria, include spontaneous, recurrent epistaxis, mucocutaneous telangiectasias (characteristically located on the fingers, hands, lips, oral cavity and nose), visceral arteriovenous malformations, and family history of a first-degree relative diagnosed with HHT [4]. A diagnosis of HHT is considered "definite" if three or more criteria are present, "possible" if two criteria are present, and "unlikely" if fewer than two are present [1,4]. As seen in Case 1, older children and adolescents may present the classical clinical findings satisfying the criteria for definitive HHT. However, there are few studies examining the sensitivity of the Curaçao Criteria and no studies that specifically evaluate the application of these criteria to the pediatric HHT population. The Curaçao Criteria have limitations in the pediatric population given the age-related onset of symptoms. The hallmark signs and symptoms of HHT evolve over time, especially within the first decade of life[2,4,6], and recent literature has highlighted the need to revise diagnostic criteria according to age [7].

Molecular genetic diagnosis plays an increasingly prominent role for presymptomatic testing of children with affected family members. HHT is inherited in an autosomal dominant manner with high clinical heterogeneity and an age-dependent natural history [1]. Pathogenic perturbations to several genes involved in the TGF-β/BMP pathway, important for angiogenesis, have been well described, including the endoglin gene (*ENG*), the activin receptor-like kinase 1 gene (*ACVRLK1*), and *SMAD4*. Patients with *ENG* and *ACVRLK1* gene mutations have historically been classified as having HHT1 and HHT2 respectively. In conjunction with mutations to the growth differentiation factor 2 gene (*GDF2*), these four mutations account for up to 87% of HHT diagnoses [1,6]. A causative mutation remains elusive in roughly 20% of patients who meet diagnostic clinical criteria

[8]. Other pathogenic variants have been described, including mutations to *RASA1* and loci for which associated genes have yet to be identified [6,9]. An appropriate pediatric HHT screening evaluation must continue to rely on family history, physical examination, and a lower threshold to proceed with non-invasive screening and imaging.

Physicians caring for children must have a clinical awareness of HHT and a high index of suspicion for the signs and symptoms associated with its manifestations. While pediatric data is limited, available cohorts suggest that the pediatric rates of cerebral vascular malformations (CVMs) and pulmonary arteriovenous malformations (PAVMs) are similar to those reported in the adult population [10,11]. These lesions are often detectable but asymptomatic early in life, and Latino et al. have demonstrated that for children with a genetic or clinical diagnosis of HHT, there is rarely progression to new AVM formation on either subsequent rescreening or in comparison to genotypically-matched adult parents [11,12]. This suggests a window of opportunity exists in which presymptomatic AVMs may be identified in children and the appropriate interventions offered before significant morbidity develops.

Rarely, the presenting findings of HHT may be dramatic, such as the cerebrovascular hemorrhage described in Case 2, for whom additional clinical HHT criteria did not develop until the child was 6 years of age. CVMs occur in 10-20% of patients with HHT [13,14]. Intracranial hemorrhage as the presenting finding has been observed in infants and children [15]. The CNS vascular malformations of HHT exist along a phenotypic spectrum and may include arteriovenous malformations, cavernous malformations, developmental venous anomalies, vein of Galen malformations, or high-flow pial fistulae [3,16]. Children are more likely to develop high-flow arteriovenous fistulae (as seen in Case 2) or spinal AVMs compared to adults [13,16]. Current guidelines recommend screening children with possible or definite HHT with an unenhanced MRI/MRA within the first 6 months of life or at time of diagnosis. Older children and adults may benefit from the addition of contrast blood product sensitive sequences [3]. HHT should be considered when a cerebral or spinal AVM is identified, even in the absence of other Curaçao criteria.

Pulmonary arteriovenous malformations (PAVMs) in patients with HHT are estimated to occur in 40-60% [17,18] of patients over their lifetime. Pulmonary sequelae include hypoxemia, hemoptysis, and pulmonary hypertension, while CNS consequences of PAVMs include migraines, cerebral abscess, transient ischemic attack, and stroke. In children with possible or definite HHT, screening for PAVMs with transthoracic contrast echocardiography is currently recommended at time of diagnosis, after puberty, and every 5-10 years thereafter [3], though recent data suggests that longer intervals may be sufficient given the low rate of observed de novo AVM formation [12]. It is increasingly suggested that PAVMs are a finding specific for HHT. HHT rates in children with PAVMs approach 85-100%; adult HHT rates are similarly high [19-22]. Given the frequency of this association, HHT must be considered in children with isolated PAVMs, even if other criteria are lacking [23].

Hepatic AVMs have been reported in 32-74% of HHT patients [24], and Giordano et al. have demonstrated comparable rates of 52% within the pediatric population [25]. As these lesions are largely asymptomatic, universal screening of children for hepatic AVMs has not been recommended in the absence of abnormal liver enzymes or a clinical picture suggestive of portosystemic vascular pathology (such as high-output cardiac failure, portal hypertension, or encephalopathy) [3,24]. However, sonographically demonstrable findings of hepatic AVMs may enhance the sensitivity of the Curaçao criteria in children with an otherwise "unlikely" or "possible" diagnosis of HHT, and hepatic ultrasound may therefore be considered in the initial diagnostic evaluation.

Table 1: Prevalence of epistaxis and telangiectasia by age of onset.

	Epistaxis		Cutaneous Telangiectasia	
	<10 yrs	10-20 yrs	<10 yrs	10-20 yrs
Guttmacher [1]	37%	70%	10%	30%
Giordano [25]	-	66%	-	50%
Dheyauldeen [28]	56%	77%	-	-
Berg [29]	30-48%*	55-77%*	14-21%*	18-46%*
AAssar [27]	54%	90%	-	-
Plauchu [26]	-	58%	0%	20%

*= Separate values reported for endoglin and ALK1 mutations.

While the manifestations associated with visceral AVMs may lead to dramatic diagnoses of lesions strongly suggestive of HHT, the largely age-dependent onset of disease symptoms makes these presentations in children uncommon [5,26]. As seen in Case 3, children often present with subtle sequelae of mucocutaneous telangiectasias which may precede other clinical manifestations by years. Severe and recurrent epistaxis is often the earliest clinical finding of telangiectasias with a mean age at presentation of 12 to 15 years [26-28]. Visible skin telangiectasias follow about 10 years later [5,26]. Epistaxis is often the only identifiable criteria for HHT in children (Table 1), making the diagnosis challenging. Qualitative differences in frequency and severity of bleeding between HHT-related epistaxis and benign epistaxis of childhood may not develop until later in life [26,28,29]. A thorough clinical and family history of the child with epistaxis may be the only means of identifying patients with HHT before lesions with greater associated morbidity develop. We encourage providers to consider HHT in the differential diagnosis of epistaxis leading to endonasal electrocautery, iron deficiency anemia, or need for blood product transfusion.

CONCLUSION

While the clinical manifestations of HHT are well described, the age-dependent penetrance and clinical heterogeneity of the disease makes its diagnosis in children and adolescents challenging. The Curaçao criteria represent the manifestations of HHT over a lifetime and may fail to adequately screen young children. Appropriate recognition of the disease manifestations, as an isolated symptom or in combination, may help ensure that affected patients receive diagnostic testing and appropriate screening in a timely fashion.

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