Symptomatic Children With Hereditary Hemorrhagic Telangiectasia

A Pediatric Center Experience

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Objective: To assess the clinical and genetic characteristics of symptomatic children with hereditary hemorrhagic telangiectasia (HHT).

Design: Cross-sectional study.

Setting: The HHT clinics in Toronto.

Participants: All children with symptomatic HHT treated from April 1, 1996, through December 31, 2002.

Interventions: Participants were screened for visceral arteriovenous malformations (AVMs). Molecular testing was performed in the children or their affected family members.

Main Outcome Measures: Prevalence of epistaxis, telangiectases, pulmonary and cerebral AVMs, and genetic characteristics.

Results: Fourteen children presented with manifestations of HHT. Seven had cardiorespiratory symptoms related to pulmonary AVMs. Three had neurological symptoms secondary to bleeding from spinal or cerebral AVMs. Two were referred because of skin telangiectases and 2, because of multiple episodes of epistaxis. Screening results revealed a cerebral AVM in 1 of 11 neurologically asymptomatic children. Of the children without respiratory symptoms, 1 was diagnosed as having definite and 1, suspected pulmonary AVMs. Four children with pulmonary AVMs carried an endoglin gene mutation (HHT type 1), and 1 carried an activin receptor–like kinase 1 gene mutation (HHT type 2). The 2 children with spinal AVMs belong to the same HHT type 2 family. No mutation was found in 1 child with pulmonary and 1 with cerebral AVMs.

Conclusions: Visceral AVMs and mucosal telangiectases are present in children with HHT and can lead to life-threatening events. Failure to identify a disease-associated mutation for each child suggests complex mutations or novel HHT genes.

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HEREDITARY HEMORRHAGIC telangiectasia (HHT), or Rendu-Osler-Weber syndrome, is an autosomal dominant vascular dysplasia. Although initially thought to be rare, recent reports suggest a prevalence of 1:5000 to 1:10,000.1,2 Hereditary hemorrhagic telangiectasia is characterized by mucocutaneous telangiectatic lesions, resulting in epistaxis in 90% of patients3 and gastrointestinal tract bleeding in 20% to 30%.4 Visceral arteriovenous malformations (AVMs) are predominantly found in the pulmonary, cerebral, and hepatic circulations.5,6

The clinical characteristics of HHT in children are not well described. Symptoms and signs tend to develop in later childhood and early adulthood,3,5,6 and many children do not experience epistaxis or develop skin telangiectases in the first decade of life.6 Multiple reports7-12 of cerebral and pulmonary AVMs in children have been published; however, prevalence of such AVMs has not been established, and there are no published series describing the clinical presentations and genetics of HHT in childhood.

We aimed to characterize the clinical presentation, presence of asymptomatic visceral AVMs, and genotype in children symptomatic for HHT.

METHODS

Pediatric and adult HHT clinics were established at The Hospital for Sick Children and St Michael’s Hospital, respectively, in Toronto in 1996. Both are tertiary care referral centers affiliated with the University of Toronto. All children and adolescents (aged 0-18 years) presenting with symptoms of HHT from April 1,
1996, through December 31, 2002, were included in the current study. Children referred because of a family history and found to have HHT were not included.

The children were examined carefully for skin and mucosal telangiectases. Thorough examinations of the oral and conjunctival mucous membranes and anterior rhinoscopy for nasal telangiectases were also performed.

The children were screened for visceral AVMs. Pulmonary AVMs were diagnosed by means of echocardiography with agitated saline contrast and enhanced chest computed tomography followed by pulmonary angiography when indicated. Cerebral AVMs were diagnosed by means of head magnetic resonance imaging, followed by cerebral angiography when indicated.

Clinical diagnosis of HHT was based on the established clinical diagnostic criteria for HHT. These criteria include recurrent epistaxis, multiple skin telangiectases, visceral AVMs or telangiectases, and a first-degree family member with HHT.13 Having 3 criteria confirms the diagnosis, whereas having 2 criteria leads to a diagnosis of suspected HHT.13 Molecular testing for HHT mutations was performed as part of a research project aimed at developing a clinically applicable diagnostic test and at understanding basic mechanisms of the disease. Informed consent was obtained from participating patients and/or their parents, as appropriate, and the research protocols were approved by the Ethics Committee of the Research Institute at the Hospital for Sick Children.

Genomic DNA was extracted from blood lymphocytes using commercially available DNA extraction kits (DNAzol [Gibco BRL, Gaithersburg, Md] or Puregene DNA isolation kit [Gen- tra Systems Inc, Minneapolis, Minn]). Mutation analysis for the endoglin gene (ENG; for HHT type 1 [HHT1]) was performed by means of quantitative multiplex polymerase chain reaction and exon sequencing as described previously.14,15 Mutation analysis for activin receptor–like kinase 1 (ACVRL1; for HHT type 2 [HHT2]) was performed by exon sequencing according to published procedures.16,17

**RESULTS**

We examined 127 children in the Toronto HHT clinics from April 1, 1996, through December 31, 2002. One hundred thirteen were referred because of a family history of HHT, and 14 (age range, 0–15 years; median age, 9 years) because of symptoms or signs of HHT. This report describes these 14 children. Their clinical presentation, disease characteristics, and results of molecular analysis are summarized in the Table. Nine (64%) had a family history of HHT, and mutations were found in 8.

Seven children (50%) presented with pulmonary AVMs; 3 (21%), with cerebral or spinal AVMs; and 4 (29%), with mucocutaneous telangiectases. Epistaxis was common, being observed in 12 children (86%), but usually mild; severe nosebleeds were described in only 3 children.

**CLINICAL PRESENTATION OF PULMONARY AVMs**

Of the 7 children with pulmonary AVMs, 5 had a prolonged history of dyspnea and cyanosis that started years before the diagnosis, 1 presented with congestive heart failure, and 1 presented with hemoptysis. The pulmonary presentation and outcome of patients 1 through 5, 7, and 10 were reported in a large series summarizing the outcome of transcatheter embolotherapy for pulmonary AVMs28 and diffuse pulmonary AVMs.19 However, complete screening for other AVMs and HHT mutation analysis were not described previously.

Patient 1 was diagnosed at 11 months of age as having lactic acidosis and mitochondrial myopathy, probably unrelated to HHT. The diagnosis of HHT was established 3 years later, after referral because of epistaxis, dyspnea, and cyanosis. A large pulmonary AVM was found in the left lower lobe and required embolization. After 5 years of follow-up, the child is well, with no evidence of pulmonary AVMs. This child was the first in the family to show signs of HHT. Molecular analysis revealed an ENG splice-site mutation (g.IVS3+1G>A), which leads to an exon 3 skip and expression of an in-frame smaller and unstable ENG-mutant protein. The child's asymptomatic mother was subsequently shown to have pulmonary and hepatic AVMs. She had passed on the mutation to her child but had not inherited it from her parents, who did not carry the mutation and showed no signs of HHT. Results of DNA fingerprinting with 8 different markers confirmed that the child and her mother share the expected alleles with their respective parents.15 This mutation was thus occurring de novo in the mother. This same splice-site variant has also been reported in an unrelated family with several generations of HHT,20 confirming that the same mutation can arise in distinct families.

Patient 2 had a very complicated course characterized by multiple-organ involvement. She was diagnosed in early childhood as having hypothyroidism and developmental delay. She was noted to have long-standing cyanosis and multiple mucocutaneous telangiectases. However, the diagnosis of HHT was only established at 12 years of age, when she manifested diffuse pulmonary AVMs and an occipital cerebral AVM. She also had liver disease, with elevated transaminase levels and with coagulopathy that remained enigmatic even after a liver biopsy. Transcatheter embolotherapies resulted in only transient improvement. Lung transplantation was offered but refused. Epistaxis appeared at 17 years of age. The patient continued to have severe cyanosis and died at 18 years of age. A novel ENG exon 5 substitution (c.640G>A), which converts glycine to serine at codon 214, was identified. The patient did not have a family history of HHT. The same sequence variant was found in her asymptomatic mother and is likely disease associated because it was not identified in more than 200 individuals who underwent testing. However, confirmation of this sequence variant as disease associated requires further study.

Patient 3 presented at 7 years of age with multiple telangiectases and prolonged cyanosis. During 13 years of follow-up, multiple pulmonary AVMs were embolized on 3 occasions (Figure, second embolotherapy), with symptomatic improvement and resolution of hypoxemia. A previously unreported ENG mutation was found in the patient and 2 affected relatives: a 4-base insertion c.982_983insGCCT in exon 7, which causes a frame shift.

Patients 4 and 5 presented with severe cyanosis. Diffuse pulmonary AVMs required multiple transcatheter embolizations (and right lower lobectomy in patient 4), with only transient improvement.

Patient 6 presented with severe respiratory distress soon after birth. A large pulmonary AVM, causing congestive heart failure, was found in the left upper lobe, and lo-
Table. Clinical and Molecular Characteristics of Children Presenting With HHT

<table>
<thead>
<tr>
<th>Patient No./Sex/Age at Diagnosis, y</th>
<th>Presenting Symptom</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Other Clinical Characteristics at Presentation and Follow-up</th>
<th>Pulmonary AVMs</th>
<th>Spinal and Cerebral AVMs</th>
<th>Skin Tel and Epi</th>
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<tr>
<td>1/M/4</td>
<td>Cyanosis</td>
<td>Embolotherapy</td>
<td>Well</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/F/12</td>
<td>Cyanosis</td>
<td>Embolotherapy; x&lt;2</td>
<td>Dead</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/F/7</td>
<td>Cyanosis</td>
<td>Embolotherapy; x&lt;3</td>
<td>Well</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/F/9</td>
<td>Cyanosis</td>
<td>Lobectomy, multiple embolotherapies</td>
<td>Mild cyanosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5/M/15</td>
<td>Cyanosis</td>
<td>Multiple embolotherapies</td>
<td>Mild cyanosis</td>
<td></td>
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<tr>
<td>6/F/0‡</td>
<td>Congestive heart failure</td>
<td>Embotherapy; &lt;2, laser ablation of airways Tel</td>
<td>Well</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7/F/11</td>
<td>Hemoptysis</td>
<td>Embotherapy; &lt;2, laser ablation of airways Tel</td>
<td>Well</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8/M/5</td>
<td>Paraplegia, urinary retention</td>
<td>Ligation of feeding artery</td>
<td>Prolonged rehabilitation, new AVM embolized</td>
<td>Normal</td>
<td>Normal</td>
<td>Y (6) N Y</td>
<td>ACVRL1 exon 8, missense, c.1232G&gt;A</td>
</tr>
<tr>
<td>9/M/9</td>
<td>Loss of consciousness, seizures</td>
<td>Embolotherapy</td>
<td>Well</td>
<td>Normal, only chest radiography performed</td>
<td>Normal</td>
<td>Y (7) N Y</td>
<td>ACVRL1 exon 8, missense, c.1232G&gt;A</td>
</tr>
<tr>
<td>10/F/15</td>
<td>Right hemiparesis, seizures</td>
<td>Embolotherapy</td>
<td>Prolonged rehabilitation</td>
<td>PAVM embolized</td>
<td>Y Y Y</td>
<td>No ENG or ACVRL1 mutation found in family</td>
<td>7</td>
</tr>
<tr>
<td>11/F/8</td>
<td>Skin Tel, Epi, TIA</td>
<td>No treatment</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Y (6) N Y</td>
<td>No ENG or ACVRL1 mutation found in family</td>
</tr>
<tr>
<td>12/M/8</td>
<td>Skin Tel, Epi</td>
<td>No treatment</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Y (3) Y Tel in family</td>
<td>No ENG or ACVRL1 mutation found in patient</td>
</tr>
<tr>
<td>13/M/10</td>
<td>Epi</td>
<td>Cauterization</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Y (10) Y Epi and Tel in family</td>
<td>No ENG or ACVRL1 mutation found in patient</td>
</tr>
<tr>
<td>14/M/11</td>
<td>Epi</td>
<td>Laser ablation</td>
<td>Well</td>
<td>Suspected PAVMs</td>
<td>Normal</td>
<td>Y (4) Y</td>
<td>ACVRL1 exon 8, missense, c.1232G&gt;A</td>
</tr>
</tbody>
</table>

Abbreviations: ACVRL1, activin receptor–like kinase 1 gene; AVM, arteriovenous malformation; CAVM, cerebral AVM; ENG, endoglin gene; Epi, epistaxis; HHT, hereditary hemorrhagic telangiectasia; N, no; PAVM, pulmonary AVM; Tel, telangiectases; TIA, transient ischemic attack, Y, yes.

*Numbers in parentheses indicate years of follow-up since the patient first presented with symptoms.
†Arteriovenous malformation was diagnosed and treated as part of the clinical course.
‡Diagnosis was neonatal.

After 14 years of follow-up, except for a few cutaneous telangiectases that appeared during follow-up, she is asymptomatic with no evidence of pulmonary AVMs. A missense mutation in exon 4 of ACVRL1 (c.383C>A), which changes alanine to aspartic acid at codon 128, was found in this child and her affected parent.21

Patient 7 presented at 11 years of age with recurrent hemoptysis. Chest imaging revealed multiple pulmonary AVMs, which were embolized with significant improvement. Recurrent hemoptysis due to laryngeal and tracheal telangiectases responded well to laser ablation. Six years later, she required transcatheter embolotherapy of bilateral pulmonary AVMs causing hypoxia, with resolution of symptoms. Skin telangiectases were noticed at 15 years of age. A duplication of ENG exons 3 through 8 was found in this patient and her affected parent, and a large unstable intracellular protein could be observed, as previously reported for an unrelated family.12

**CLINICAL PRESENTATION OF CEREBRAL AND SPINAL AVMs**

Three children presented with neurological symptoms. Patients 8 and 9, first cousins, were diagnosed as having spinal AVMs, and their initial course was described elsewhere.22 Patient 8 experienced new neurological symptoms 3 years after the feeding artery to the AVM was ligated. A new spinal AVM was found and embolized. These 2 children belong to the same family with HHT2, characterized by an ACVRL1 missense mutation (c.1232G>A), which converts arginine to glutamine at codon 411, and was reported as a disease-causing mutation in seemingly unrelated families.23
Patient 10 presented with right hemiparesis, headache, and seizures. Two cerebral AVMs were found and embolized. Complete sequencing of ENG and ACVRL1 genes failed to identify a mutation in her clinically affected relatives. All 3 patients required rehabilitation, with resolution of most symptoms.

MUCOCUTANEOUS TELANGIECTASES AND EPISTAXIS

Only 4 children were referred because of mucocutaneous telangiectases and epistaxis; however, all children presented with mucocutaneous telangiectases and/or epistaxis during follow-up. Epistaxis appeared as early as 3 years of age (mean±SD age of first episode, 7.5±4.0 years).

Patient 11 was referred because of multiple skin telangiectases, epistaxis, and an episode of a transient ischemic attack, with no family history of HHT. Results of a physical examination revealed multiple skin telangiectases on her palms and nasal mucosa. Echocardiography with agitated saline injection and chest computed tomography failed to demonstrate pulmonary AVMs. Pulmonary angiography was not performed because the probability of finding an AVM large enough to be embolized was very low. Head magnetic resonance imaging did not display any ischemic or hemorrhagic changes. No cerebral AVMs were seen. The cause of the transient ischemic attack could not be determined, and migraine remains a probable diagnosis. However, the presence of minute pulmonary AVMs cannot be ruled out. Molecular analysis failed to reveal a mutation in the ENG or the ACVRL1 gene.

Patient 12 presented with multiple telangiectases on his face and extremities and epistaxis that started at 3 years of age and tended to be frequent (up to few times a week) and difficult to control (each episode lasting up to 1 hour). However, epistaxis was not treated before referral to our clinic. Patients 13 and 14 presented with epistaxis and were both treated successfully with cautery or laser ablation. Patient 14 was found to carry the previously reported familial ACVRL1 missense mutation (c.1232G>A) and is unrelated to patients 8 and 9.17

ASYMPTOMATIC AVMs DETECTED ON SCREENING

Thirteen children were screened for pulmonary and cerebral AVMs. Of the 11 neurologically asymptomatic children, patient 2 was found to have a cerebral AVM. Of the children with no respiratory symptoms, patient 10 was found to have pulmonary AVMs and underwent transcatheter embolotherapy. Patient 14, with genetically proven HHT2, had echocardiographic and computed tomographic findings suggestive of small pulmonary AVMs. He is being followed up conservatively.

CLINICAL DIAGNOSTIC CRITERIA FOR HHT

Eleven of the 14 children currently meet the established diagnostic criteria for definite HHT. However, because epistaxis or telangiectases appeared in 5 children after their first presentation, 4 of them did not meet these criteria at presentation. As of this writing, 3 children did not have sufficient criteria for a definite diagnosis of HHT. The transient ischemic attack in patient 11 raises a major concern that she has pulmonary AVMs; however, extensive workup failed to demonstrate any. Thus, according to the diagnostic criteria, she is suspected of having HHT. Patients 12 and 13 have telangiectases and severe epistaxis with no evidence of visceral AVMs and no family history of HHT. However, telangiectases and/or epistaxis exist in these families, and screening for visceral AVMs was not performed in family members.

A pediatric HHT clinic was established in Toronto for treating children with HHT. In a recent series24 describing 15 children with HHT, epistaxis was common, appearing as early as 4 years of age. However, symptoms of visceral AVMs were rare, and screening for visceral AVMs was performed in only 6 children.

Five of the symptomatic children in our series presented with acute life-threatening events, including stroke, hemoptysis, and congestive heart failure. Five presented with chronic hypoxia. Previous reports25-28 have established the prevalence of cerebral and pulmonary AVMs at 5% to 10% and 15% to 33%, respectively, in adults with HHT. Much less attention has been given to children with this disease. It was also shown that most pulmonary AVMs grow during life,26 but it is not known whether all pulmonary AVMs are present at birth or some develop later. Multiple cases of fatal complications of cerebral AVMs have been reported in children with HHT.7,10-12 We examined 127 children, 113 of them because of a family history and 14 because of symptoms. Ten children presented with symptomatic visceral AVMs.
Considering the autosomal dominant inheritance of the disease, we estimate that 50% of the children do have HHT. A prevalence of symptomatic visceral AVMs of 16% (10/63) is suggested by these data. In our series, we also demonstrated that the first symptom of HHT in children can be life threatening and can occur at any time from birth onward. A family history of HHT was known for at least 9 children, and screening might have revealed these lesions earlier. The probable reported outcomes of transcatheter embolotherapy in adults and children²⁹ suggest that early intervention could have prevented life-threatening events.

Although epistaxis was common in our series, it was usually mild, in contrast to that found in adults. The application to children of the clinical diagnostic criteria established mostly for adults with HHT¹¹ can be misleading. As mentioned, symptoms and signs of HHT generally develop during childhood and adolescence, such that the absence of epistaxis, telangiectases, or symptoms of visceral AVMs is common in children. We noted the appearance of epistaxis and telangiectases during follow-up in 5 patients. We also demonstrated the presence of asymptomatic visceral AVMs diagnosed on the basis of screening results in 3 children (patients 2, 10, and 14). Folz et al³⁰ concluded that findings in 15 children referred because of symptoms and signs suggestive of HHT could establish the diagnosis in only 2 children. Therefore, the clinical diagnostic criteria should be used cautiously in children, and the diagnosis of HHT and screening for visceral AVMs should be considered in all children with a family history of HHT regardless of symptoms.

Genetic analysis was helpful in establishing the diagnosis of HHT in children. We confirmed 8 cases by identifying the disease-causing mutation. However, we were unable to find ENG or ACVRL1 mutations in 5 cases with a clinical diagnosis. For patients 11 through 13, in whom family history was minimal and no mutation was found, one could argue that the diagnosis is questionable and remains to be confirmed by additional criteria. In patients 5 and 10, in whom clinical diagnosis was definite, the mutation might be complex and require techniques other than quantitative multiplex polymerase chain reaction and exon sequencing. It can also be postulated that these patients have a different type of HHT. A possible HHT type 3, now linked to chromosome 5, was suggested in a family with a high frequency of pulmonary AVMs.²⁹,³⁰ Mutations in the MADH4 gene, which encodes Smad4, were recently described in patients with a combined syndrome of juvenile polyposis and HHT.³¹ Another method shown to be valuable in the diagnosis of HHT is capillary microscopy,³² which can help in establishing the diagnosis of HHT in future studies.

Our study also shows that AVMs occur in children with different types of ENG mutations, including a single base-pair substitution, a large and a small insertion, and a splice variant, in agreement with haploinsufficiency as the underlying model of HHT¹.₁⁴,₁₅,₂₀,₂₃,₃₃,₃₄ Furthermore, one child with HHT2 had a pulmonary AVM (patient 6), and another had suspected pulmonary AVMs (patient 14). Although pulmonary AVMs are less frequent than in HHT1,²⁹ they do occur in HHT2.²⁷ We also observed the appearance of spinal AVMs in 2 children from a family with HHT2. Spinal AVMs have rarely been described in patients with HHT2.²⁴ Mutation analysis thus provides an important tool in the diagnosis of HHT, particularly in children because of variation in the age at onset and clinical manifestations even within a single family.

This study illustrates the heterogeneity of presentation of severe cases of HHT in children at a tertiary specialized pediatric center. However, there are limitations to this study. First, the study group is too small to represent the full clinical spectrum of HHT in childhood. Second, these children probably represent the more severe cases because only children presenting with symptoms were included. To ascertain the whole spectrum of pediatric HHT, a disorder with an autosomal mode of inheritance, large prospective studies should be conducted. The inclusion of mutation analysis in the diagnostic criteria will increase the probability of detecting children early in life and determine the prevalence of AVMs in children with both types of HHT.

In summary, pulmonary and cerebral AVMs are found in children with HHT and can lead to life-threatening complications, often as the first presentation of HHT. The clinical diagnostic criteria for HHT likely underestimate the prevalence of this disease in children. Screening for visceral AVMs in asymptomatic children with a family history of HHT is under way in our centers to evaluate their prevalence and to determine whether screening can prevent serious complications associated with pulmonary and cerebral AVMs.

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REFERENCES


