Intracranial Hemorrhage in Infants and Children With Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

Terry Morgan, MD, PhD*; Jamie McDonald, MS, CGC‡; Christina Anderson, MD§; Magdy Ismail, MD§; Franklin Miller, MD‡; Rong Mao, MD‡; Ashima Madan, MD§; Patrick Barnes, MD∥; Louanne Hudgins, MD¶, and Melanie Manning, MD∥

ABSTRACT. Objective. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia. Most cases are caused by mutations in the endoglin gene on chromosome 9 (HHT type 1) or the activin receptor-like kinase 1 gene on chromosome 12 (HHT type 2), which leads to telangiectases and arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Epistaxis is the most frequent presentation. Visceral involvement includes pulmonary, gastrointestinal, and cerebral AVMs, which have been reported predominantly in adults. The purpose of this article is to describe 9 children who presented with intracranial hemorrhage (ICH) secondary to cerebral AVM. None of these children was suspected of having HHT before the incident, despite family histories of the disease.

Methods. We report the first case of an ICH secondary to a cerebral AVM in a neonate confirmed to have HHT type 1 by molecular analysis. We also describe a series of 8 additional cases of ICH secondary to cerebral AVM in children presumed to have HHT. Examination of multiple affected members from each of these families, using well-accepted published criteria, confirmed the diagnosis of HHT. In addition, genetic linkage studies and/or mutation analysis identified endoglin as the disease-causing gene in 6 of these families. Autopsy, imaging studies, and/or surgery confirmed the presence of cerebral AVMs and ICH in all 9 cases.

Conclusion. Our report shows that infants and children with a family history of HHT are at risk for sudden and catastrophic ICH. A preemptive diagnosis may potentially identify and prevent more serious sequelae.

Abbreviations. HHT, hereditary hemorrhagic telangiectasia; ALK-1, activin receptor-like kinase 1; AVM, arteriovenous malformation; ICH, intracranial hemorrhage; MRI, magnetic resonance imaging; TGF-β, transforming growth factor-β.

From the *Department of Pathology, Stanford University, Stanford, California; ‡Hereditary Hemorrhagic Telangiectasia Clinic, Department of Radiology, University of Utah Health Sciences Center, Salt Lake City, Utah; §Department of Pediatrics, Division of Neonatology, Stanford University, Stanford, California; ¶Department of Radiology, Stanford University, Stanford, California; and ∥Department of Pediatrics, Division of Medical Genetics, Stanford University, Stanford, California. Received for publication Jul 31, 2001; accepted Sep 25, 2001. Reprint requests to (T.M.) Department of Pathology, Stanford University Medical Center, Stanford, CA 94305. E-mail: terrymorgan@sisna.com

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TABLE 1. Summary of Children Who Presented With ICH and a Family History of HHT*

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Gender</th>
<th>AVM Confirmation</th>
<th>Family History</th>
<th>Linkage to Endoglin Gene</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Newborn</td>
<td>Male</td>
<td>Autopsy</td>
<td>Mother, uncle, maternal grandmother, maternal great-grandmother</td>
<td>Yes</td>
<td>Death</td>
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<tr>
<td>2</td>
<td>4 wk</td>
<td>Female</td>
<td>Autopsy</td>
<td>Father, 2 aunts, uncle, paternal grandfather</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>6 y</td>
<td>Female</td>
<td>MRI</td>
<td>Mother, 2 aunts, uncle, maternal grandmother, cousins</td>
<td>Yes</td>
<td>Significant cognitive and motor impairment</td>
</tr>
<tr>
<td>4</td>
<td>7 y</td>
<td>Male</td>
<td>Autopsy</td>
<td>Mother, 2 aunts, uncle, maternal grandfather</td>
<td>Not tested</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>10 y</td>
<td>Female</td>
<td>Autopsy</td>
<td>Father, brother, 2 aunts, paternal grandmother</td>
<td>Not tested</td>
<td>Death</td>
</tr>
<tr>
<td>6</td>
<td>10 y</td>
<td>Male</td>
<td>Surgery</td>
<td>Mother, paternal grandfather</td>
<td>Yes</td>
<td>Hemiparesis</td>
</tr>
<tr>
<td>7</td>
<td>11 y</td>
<td>Male</td>
<td>Surgery</td>
<td>Father, brother, 2 sisters, paternal grandfather</td>
<td>Yes</td>
<td>Significant cognitive and motor impairment</td>
</tr>
<tr>
<td>8</td>
<td>16 y</td>
<td>Male</td>
<td>Autopsy</td>
<td>Mother, maternal grandmother, 2 aunts</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>9</td>
<td>16 y</td>
<td>Male</td>
<td>CT scan</td>
<td>Mother, aunt, maternal grandmother</td>
<td>Not tested</td>
<td>Significant cognitive and motor impairment</td>
</tr>
</tbody>
</table>

* Six boys and 3 girls with ICH at an average age of 8.5 years, standard deviation is 5.5 years.

CASE REPORTS

Case 1
A male neonate was born at 38.5 weeks’ gestation to a primiparous 34-year-old woman with good prenatal care. He was delivered by cesarean section because of fetal bradycardia and loss of beat-to-beat fetal heart rate variability. At birth, he was pale without muscle tone or respiratory effort. He was intubated with an endotracheal tube and received cardiopulmonary resuscitation with epinephrine, normal saline, and sodium bicarbonate. Apgar scores were 2 and 4 at 1 and 10 minutes, respectively. On examination, a full fontanelle and asymmetric pupils were noted.

The neonate was transported to a local tertiary care center. Both pupils were noted to be fixed and dilated. In addition, several small telangiectases were identified on the forehead and nape of the neck. A small telangiectasia was noted on the mucosa of the left nare. He had spontaneous respirations on the ventilator but no other spontaneous movements.

Head ultrasound showed a massive left parietal occipital hemorrhage (Fig 1A and 1B). A noncontrast head computed tomographic scan revealed a massive subdural and subarachnoid hemorrhage in the left hemisphere with extensive mass effect. A dumbbell-shaped ring enhancing lesion in the left parietal/occipital region, suspicious for an AVM, was identified (Figs 1C and 1D). An enlarging dumbbell-shaped ring enhancing lesion in the right parietal area associated with acute subarachnoid, intraventricular, and subdural hemorrhage (Figs 2A–2C). Secondary Duret hemorrhages were identified in the brainstem, consistent with increased mass effect. In addition, multiple remote and subacute hemorrhages were identified in both lungs and at the gastroesophageal junction (Figs 2D–2G). The neonate died shortly thereafter.

Family history was significant for the patient’s mother, who had a diagnosis of HHT, presenting with occasional epistaxis, migraine headaches, and telangiectases. Other family members with HHT included her brother, mother, and maternal grandfather (Fig 3).

Molecular analysis was performed to confirm HHT in the neonate. With the family’s consent, a postmortem tissue sample was taken from the proband for DNA analysis. In addition, blood samples were obtained from 4 affected and 2 unaffected family members. These samples were sent to the University of Utah DNA Diagnostic Laboratory for DNA extraction and linkage analysis.

Linkage analysis was performed on the neonate and his parents, uncle, maternal grandparents, and maternal great grandparents. Four of the 5 probes used (D9S660, D9S515, ENG-CA, and D9S61) were found to be fully informative. Linkage was established to the endoglin gene on chromosome 9, confirming the diagnosis of HHT type 1 (Fig 3). Risk calculations showed this prediction to be 99% accurate using current recombination estimation.

In addition to the markers examined for HHT type 1, 6 polymorphic markers were analyzed for the ALK-1 gene (HHT type 2) on chromosome 12. There was no evidence for linkage to the ALK-1 gene.

Case 2
A female neonate was born after an unremarkable pregnancy and delivery. Her medical history was unremarkable. In particular, there was no history of seizures, abnormal posturing, or increased fussiness. At 4 weeks of age, however, she began “screaming” while breastfeeding and turned blue. Emergency transport was called, and her mother administered cardiopulmonary resuscitation until their arrival. Emergency personnel could not revive the neonate. Autopsy attributed her death to an ICH secondary to an AVM. Her father’s family had multiple members with HHT type 1 (her father, paternal grandfather, 2 aunts, and an uncle) confirmed by molecular analysis.

Case 3
A 6-year-old girl with no significant medical history presented with an ICH secondary to cerebral AVM, which was confirmed by magnetic resonance imaging (MRI). She now has significant cognitive and motor impairment.

Despite a strong family history of HHT type 1, this diagnosis previously had not been suspected in this child. Her mother, maternal grandfather, 2 aunts, 1 uncle, 4 cousins, and many additional relatives had a diagnosis of HHT with molecular confirmation of an endoglin mutation.

Case 4
A 7-year-old boy died from an ICH secondary to a cerebral AVM, which was confirmed at autopsy. He had a history of nosebleeds but no history of significant headaches, seizures, or other central nervous system manifestations. His family history included a mother, maternal grandfather, 2 aunts, and an uncle with a clinical diagnosis of HHT. Molecular analysis has not been performed.

Case 5
A 10-year-old girl with a medical history remarkable for rare episodes of epistaxis experienced an ICH secondary to an AVM, which was confirmed at autopsy. There were 4 episodes of unexplained emesis in the month before her fatal hemorrhage. She also complained of a headache the day of her death.

Despite a strong family history of HHT, this diagnosis previously had not been suspected in this child. Her brother, father, paternal grandmother, 2 aunts, and multiple extended family members on her father’s side had a clinical diagnosis of HHT. Molecular analysis has not been performed.
Case 6

A 10-year-old boy with a history of occasional nosebleeds suddenly developed left hemiparesis. He was transported to a hospital, where an ICH secondary to an AVM was identified and subsequently resected. He has residual left hemiparesis.

HHT previously had not been considered for this boy. His mother had received a diagnosis of HHT type 1 and died at 24 years of age from a brain abscess secondary to a pulmonary AVM. In addition, his maternal grandfather, an uncle, and multiple extended family members have a confirmed endoglin mutation.

Case 7

An 11-year-old boy presented with sudden onset ataxia while playing at the beach. He was comatose on arrival at the emergency department. An ICH secondary to an AVM was diagnosed and resected. He remained comatose for 3 months and in a rehabilitation hospital for 2 years. He currently has significant brain damage; recurrent, spontaneous epistaxis; multiple skin telangiectases; and left hemiparesis. He lives in a state institution for the handicapped and is capable of only the most basic self-care activities.

Despite a family history of HHT, this diagnosis previously had not been suspected in this child. His brother, 2 sisters, father, and paternal grandfather have HHT type 1 confirmed by molecular analysis.

Case 8

A 16-year-old boy presented with headache, vomiting, lethargy, slurred speech, and partial right-sided paralysis. He died from an ICH secondary to a cerebral AVM, which was confirmed at autopsy. His medical history was significant for spontaneous nosebleeds since early childhood and headaches beginning in elementary school. He had been described as a clumsy child and accident prone.

Despite a strong family history of HHT, this diagnosis previously had not been suspected in this child. His mother, maternal grandmother, 2 aunts, and multiple extended family members had HHT type 1, confirmed by molecular analysis. In fact, physicians had told the family that HHT was unlikely in this boy because he had a “negative physical examination.”

Case 9

A 16-year-old boy with a history of intermittent epistaxis and mild headaches presented with an ICH secondary to an AVM, which was subsequently resected. He currently has significant cognitive and motor impairment.

Before the ICH, a diagnosis of HHT was not suspected in this child despite his history of nosebleeds, headaches, and a family history of HHT. HHT had been diagnosed in his mother, maternal grandmother, and an aunt. Molecular analysis has not been done.
DISCUSSION

We report the first case of an ICH secondary to a cerebral AVM in a neonate confirmed to have HHT by molecular analysis. In addition, we report a series of 8 infants and children, 5 boys and 3 girls ages 4 weeks to 16 years (average age: 8.5 years; standard
type 2), and there was no evidence for linkage (data not shown). Notably, markers containing the endoglin locus (boxed) in HHT-affected family members (blackened, including the proband). Fig 3. Linkage is established to the endoglin gene on chromosome 9 (HHT type 1) in case 1. Molecular analysis using short tandem repeat polymorphic markers D9S60, D9S315, ENG-CA, STPAN-CA, and D9S61 shows inheritance of the same haplotype containing the endoglin locus (boxed) in HHT-affected family members (blackened, including the proband). Notably, markers were also analyzed for the ALK-1 gene on chromosome 12 (HHT type 2), and there was no evidence for linkage (data not shown).

deviation: 5.5 years), who also presented with ICH secondary to cerebral AVMs. Before these hemorrhages, none of the children was suspected of having HHT, despite a family history of the disease. Our report demonstrates that infants and children with a family history of HHT are at risk for sudden and catastrophic ICH. Therefore, a preemptive diagnosis of HHT and screening for cerebral AVMs may potentially identify and prevent more serious sequelae.

Unfortunately, HHT is often difficult to diagnose on the basis of history and physical examination alone, especially in infants and children. The signs and symptoms of HHT are nonspecific and even within families are extremely variable. The most common feature and typical presenting sign of HHT is recurrent epistaxis. Nosebleeds are common in childhood, however, and family members with recurrent epistaxis may also discount them as being normal. Although 80% to 90% of patients with HHT will demonstrate recurrent epistaxis by 21 years of age,9,15 most do not have nosebleeds in the first decade of life.9

Cutaneous manifestations, in the form of telangiectases of the lips, palms, nail beds, tongue, ears, or face, are the next most common disease manifestation. Cutaneous manifestations are unusual in children. They typically present later than epistaxis, in the second or third decade of life.3 By age 40, most individuals will have visible telangiectases.15

Visceral involvement, specifically gastrointestinal, does not usually manifest until the fifth or sixth decade.15 Although rare, there have been reports of infants and children with HHT presenting with visceral involvement more commonly seen in adults. Cases involving the lungs, gastrointestinal tract, and urinary tract have been described, which predated epistaxis or cutaneous lesions in these children.16–21

Patients with HHT have an increased risk of having AVMs compared with the general population. The prevalence of cerebrovascular malformations in adults with HHT is approximately 23%,13 Fulbright et al13 reviewed brain MRI scans of 184 consecutive patients with HHT. They found 63 vascular malformations in 42 patients, a prevalence of 23% (42 of 184) but concluded that MRI may underestimate the prevalence of cerebrovascular malformations in these patients. True AVMs were identified in 5% of the patients studied. The prevalence of cerebrovascular malformations in children is unknown, but there are a number of case reports in the literature (Table 2).22–39 Human and animal studies suggest that these vascular malformations are a consequence of abnormal arteriovenous connections that fail to differentiate properly.40–42 Therefore, if cerebrovascular malformations are a congenital malformation in children with HHT, then the prevalence may approximate that of adults (23%).

The risk of ICH in infants and children with HHT is uncertain. A recent study by Maher et al43 showed that only 7 of 321 patients who had HHT and were seen at the Mayo Clinic during a 20-year period presented with ICH (2.1%). Their data suggest that the risk of ICH is low. Therefore, they suggest that routine screening imaging studies of asymptomatic HHT patients is probably not indicated. However, other studies have shown that the risk of ICH from unruptured AVMs is 2% to 4% per year.44–46 The prevalence of AVMs in patients with HHT is between 5% and 11%,13,33 and the annual risk of ICH in these patients is also 2% to 4%, then the anticipated risk of hemorrhage during a 20-year period (2%–8%) may be greater than that reported by Maher et al. In light of the dire consequences of ICH in infants and children with HHT, as shown by our study and those of others, compared with the “good functional outcome after hemorrhage” reported for adults in the study by Maher et al, the application of these estimates to infants and children with HHT is unclear. Until more data are collected about the prevalence of AVMs and the risk of ICH in this pediatric population, we recommend screening all children who are considered to be at high risk for HHT.

Our report also highlights the risk of ICH in neonates with a family history of HHT. We describe 2 neonates who died because of massive ICH secondary to cerebral AVMs (cases 1 and 2). There are also a few case reports in the literature.22,30,47 These case
studies suggest that prenatal diagnosis may be a consideration in families with HHT. Prenatal imaging studies, including sonography and MRI, may assist in ruling out large internal AVMs or detecting vascular dysplasias that may suggest the diagnosis of HHT. Similar to our case 1, however, definitive diagnosis depends on molecular analysis. Amniocentesis or chorionic villous sampling may obtain tissue for DNA extraction. Unfortunately, because of the genetic heterogeneity of HHT and the lack of common mutations, diagnostic DNA testing is limited to linkage analysis, which requires multiple affected family members from at least 2 generations.

The genetic heterogeneity of this disease was shown by several groups, which have demonstrated that at least 2 genes and many different mutations can cause HHT.5,6,8,48,49 Linkage was originally established in some families to markers on chromosome 9 (9q33–q34).6,7 Subsequent investigation by McAllister et al5 led to the identification of "endoglin" as the causative gene. Endoglin is a transforming growth factor-β (TGF-β) binding protein, which plays an important role in the TGF-β receptor complex. These factors regulate differentiation, growth, tissue remodeling, motility, wound repair, and programmed cell death.50

Some families have mutations in a different gene. This second locus for HHT is located on chromosome 12 (12q13) and is named ALK-1.4,8,51 This form of the disease, HHT type 2, is suspected to have a dominant inheritance; therefore, 50% risk of having HHT be in a child. A detailed and targeted family history may be required. The family history should include questions about recurrent epistaxis, telangiectases, migraines, seizures, internal bleeding, and surgery for vascular malformations. A family history of HHT, especially if a parent is affected, should raise the suspicion of HHT in the child (autosomal dominant inheritance; therefore, 50% risk of having HHT for each child).

CONCLUSION

Our report and review of the literature shows that infants and children with a family history of HHT are at risk for sudden and catastrophic ICH. A preemptive diagnosis of HHT in childhood may potentially identify and prevent more serious sequelae. Screening for cerebrovascular malformations should be performed in all children who are considered to be at high risk for HHT. In addition, DNA diagnosis should be recommended to all at-risk family members when testing becomes more practical and widely available.

ACKNOWLEDGMENTS

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REFERENCES


TABLE 2. Summary of Reported Children With Cerebral AVMs and a Family History of HHT*

<table>
<thead>
<tr>
<th>Report</th>
<th>Age</th>
<th>Gender</th>
<th>AVM Confirmation</th>
<th>Family History</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Quickel and Whatey57</td>
<td>17 y</td>
<td>Male</td>
<td>Angiography</td>
<td>Mother, siblings</td>
<td>Recovered</td>
</tr>
<tr>
<td>Boynton and Morgan22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacques et al4</td>
<td>8 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
</tr>
<tr>
<td>Waller et al46</td>
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<td>Female</td>
<td>Angiography</td>
<td>Father</td>
<td>Asymptomatic</td>
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<tr>
<td>Adams et al15</td>
<td>14 y</td>
<td>Male</td>
<td>Angiography</td>
<td>Positive</td>
<td>Hemiplegia, global aphasia</td>
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<tr>
<td>Reddy et al39</td>
<td>16 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
</tr>
<tr>
<td>Roy et al23</td>
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<td>Surgery</td>
<td>Mother, sister</td>
<td>Death</td>
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<td>Willinsky et al55</td>
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<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Unknown</td>
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<td>John24</td>
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<td>Female</td>
<td>Angiography</td>
<td>Mother, sibling</td>
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<td>Iizuka et al31</td>
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<td>Jessurum et al38</td>
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<td>Angiography</td>
<td>Positive</td>
<td>Death</td>
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<td>Kadoya et al35</td>
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<td>Angiography</td>
<td>Father, uncle</td>
<td>Recovered</td>
</tr>
<tr>
<td>Kikuchi et al26</td>
<td>2 y</td>
<td>Female</td>
<td>CT</td>
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<td>Angiography</td>
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<tr>
<td>Kikuchi et al26</td>
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<tr>
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<td>Putman et al27</td>
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<tr>
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<td>MRI</td>
<td>Mother</td>
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<td>Autopsy</td>
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</tbody>
</table>

* In many of these papers, a “positive” family history of HHT was reported, but relatives were not specified. The average age of AVM confirmation was 8.5 years, standard deviation is 5.5 years, in 11 boys and 13 girls.


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