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

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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.

PEDIATRICS 2002;109(1). URL: http://www.pediatrics.org/cgi/content/full/109/1/e12; hereditary hemorrhagic telangiectasia, intracranial hemorrhage, neonates, infants, children, linkage analysis.

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.

H ereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia with a high degree of penetrance but extremely variable expression. It occurs in approximately 1 in 10 000 individuals.1–4 Most cases of HHT are caused by mutations in the endoglin gene on chromosome 95–7 or the activin receptor-like kinase-1 (ALK-1) gene on chromosome 12,8 which can lead to telangiectases and arteriovenous malformations (AVM) of the skin, mucosa, and viscera.

Epistaxis is the most frequent presentation; >90% of cases manifest by the age of 21.9 Telangiectases of the tongue, lips, and skin are also common. Gastrointestinal involvement presenting as hemorrhage occurs in approximately 16% of patients; half of these require transfusion.10 Additional visceral involvement includes pulmonary, hepatic, and cerebral AVMs, which have been reported predominantly in adults.3,10–13

Approximately 20% of adults with HHT have cerebrovascular malformations.15 Most are asymptomatic, but some present with acute headache associated with intracranial hemorrhage (ICH). The prevalence of cerebrovascular malformations among children with HHT is unknown.

The purpose of this article was to describe the first molecularly confirmed case of HHT presenting with ICH secondary to a cerebral AVM in a neonate (case 1). Eight additional cases of infants and children who had a family history of HHT and presented with ICH are also described (cases 2–9).

CLINICAL REPORT

Examination of multiple affected members, using accepted published criteria,14 confirmed the diagnosis of HHT in these families. The diagnosis was made if the patient met at least 3 of the following 4 criteria: epistaxis, telangiectases, visceral lesions, and an appropriate family history. Before the ICH, none of the infants or children described in this report was suspected of having HHT.

In all, there were 6 boys and 3 girls (newborn to 16 years). Their clinical features are summarized in Table 1. Notably cases 2 to 9 were identified from a total of 106 families being treated by the HHT clinic at the University of Utah Health Sciences Center.
INTRACRANIAL HEMORRHAGE IN CHILDREN WITH OSLER-WEBER-RENDU

Given the extent of ICH and poor neurologic status of the infant, a diagnosis of HHT was suspected. A systemic review of the neonate’s medical record revealed a history of epistaxis. Her mother, who had a clinical diagnosis of HHT, was noted to have an enlarged left carotid artery on magnetic resonance imaging (MRI). In addition, several small telangiectases were identified on the forehead and nape of the neck. A small telangiectasia was noted in 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 hemmorhage (Fig 1A and 1B). A noncontrast head computed tomographic scan revealed a massive subdural and subarachnoid hemorrhage (Fig 1A and 1B). A noncontrast head computed tomographic scan revealed a massive subdural and subarachnoid hemorrhage (Fig 1A and 1B). A noncontrast head computed tomographic scan revealed a massive subdural and subarachnoid hemorrhage (Fig 1A and 1B).

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 with no 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 in 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). A dumbbell-shaped ring enhancing lesion in the left parietal/occipital region, suspicious for an AVM, was identified (Figs 1C and 1D).

A 10-year-old girl with a medical history remarkable for rare episodes of epistaxis, migraine headaches, and telangiectases. Other family members with HHT included her brother, mother, and maternal grandmother (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-grandmother. Four of the 5 probes used (D9S60, D9S315, 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 estimates. 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 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 with no 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 in the mucosa of the left nare. He had spontaneous respirations on the ventilator but no other spontaneous movements.

### TABLE 1.

<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>
</tr>
<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, paternal grandmother</td>
<td>Not tested</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 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 deviation: 1.5 years). The series includes 1 infant, 1 girl, and 1 boy with HHT confirmed by molecular analysis and 7 older children, 4 boys and 3 girls, confirmed to have HHT via clinical criteria.

Fig 2. Autopsy of the neonate in case 1 confirms massive ICH (A) emerging from an arteriovenous malformation (B and C) in the left temporal-parietal lobe. Calcification is noted in the abnormal vessel wall. Elastin and Van Gieson stain highlights discontinuity of internal elastica (arrow). The lungs exhibit multifocal brown discoloration (D), which microscopic examination reveals as multiple subacute microhemorrhages with hemosiderin-laden macrophages (E). Gross examination of the esophagus shows multiple subacute and remote mucosal hemorrhages near the gastroesophageal junction. F, Microscopic examination confirms that the hemorrhages are associated with angiodysplasias, including capillary telangiectases (inset). G, Elastin and Van Gieson stain highlights several back-to-back blood vessels with and without an internal elastica, consistent with an arteriovenous malformation.
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. 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.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 If the prevalence of AVMs in patients with HHT is between 5% and 11%,13,23 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
Can cause HHT. That at least 2 genes and many different mutations have been shown by several groups, which have demonstrated affected family members from at least 2 generations. Related to linkage analysis, which requires multiple affected family members before prenatal diagnosis may be considered.

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. Linkage was originally established in some families to markers on chromosome 9 (9q33–q34). Subsequent investigation by McAllister et al 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.

Some families have mutations in a different gene. This second locus for HHT is located on chromosome 12 (12q13) and is named ALK-1. This form of the disease, HHT type 2, is suspected to have a decreased incidence of pulmonary AVMs but has been shown to be associated with the same visceral AVMs as HHT type 1. ALK-1 is also part of the TGF-β complex. Because molecular analysis is not available on a routine clinical basis, the diagnosis in most families relies on physical examination and history. As we have shown, a routine physical examination and family history may not be sufficient to diagnose HHT 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

We gratefully acknowledge the families reported in these cases for their cooperation. We also thank Dr Kenneth Ward and the University of Utah DNA diagnostic laboratory for performing the genetic analysis.

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>
</tr>
</thead>
<tbody>
<tr>
<td>Quickel and Whatey</td>
<td>17 y</td>
<td>Male</td>
<td>Angiography</td>
<td>Mother, siblings</td>
<td>Recovered</td>
</tr>
<tr>
<td>Boynton and Morgan</td>
<td>Newborn</td>
<td>Female</td>
<td>Angiography</td>
<td>Father</td>
<td>Death</td>
</tr>
<tr>
<td>Jacques et al</td>
<td>8 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
</tr>
<tr>
<td>Waller et al</td>
<td>12 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Father</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Adams et al</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 al</td>
<td>16 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
</tr>
<tr>
<td>Roy et al</td>
<td>6 wk</td>
<td>Male</td>
<td>Surgery</td>
<td>Mother, sister</td>
<td>Death</td>
</tr>
<tr>
<td>Willinsky et al</td>
<td>7 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Unknown</td>
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<tr>
<td>John</td>
<td>7 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
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<tr>
<td>Iizuka et al</td>
<td>6 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
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<tr>
<td>Jessurum et al</td>
<td>13 y</td>
<td>Male</td>
<td>Angiography</td>
<td>Positive</td>
<td>Death</td>
</tr>
<tr>
<td>Kadoya et al</td>
<td>9 y</td>
<td>Male</td>
<td>Angiography</td>
<td>Father, uncle</td>
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<tr>
<td>Kikuchi et al</td>
<td>2 y</td>
<td>Female</td>
<td>CT</td>
<td>Mother</td>
<td>Recovered</td>
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<td>Kikuchi et al</td>
<td>7 y</td>
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<td>Angiography</td>
<td>Mother</td>
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<tr>
<td>Kikuchi et al</td>
<td>16 y</td>
<td>Female</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
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<td>Garcia-Monaco et al</td>
<td>6 y</td>
<td>Female</td>
<td>Angiography</td>
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<td>Garcia-Monaco et al</td>
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<td>Female</td>
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<tr>
<td>Garcia-Monaco et al</td>
<td>9 y</td>
<td>Male</td>
<td>Angiography</td>
<td>Positive</td>
<td>Death</td>
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<tr>
<td>Putman et al</td>
<td>6 wk</td>
<td>Female</td>
<td>MRI</td>
<td>Positive</td>
<td>Visual field defect</td>
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<tr>
<td>Putman et al</td>
<td>9 y</td>
<td>Male</td>
<td>MRI</td>
<td>Positive</td>
<td>No impairment</td>
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<tr>
<td>Coubles et al</td>
<td>13 y</td>
<td>Female</td>
<td>MRI</td>
<td>Positive</td>
<td>Recovered</td>
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<td>Bourdeau et al</td>
<td>Newborn</td>
<td>Male</td>
<td>Autopsy</td>
<td>Father</td>
<td>Death</td>
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<tr>
<td>Willemse et al</td>
<td>14 y</td>
<td>Male</td>
<td>Angiography</td>
<td>Positive</td>
<td>Recovered</td>
</tr>
</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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_Pediatrics_ 2002;109;e12
DOI: 10.1542/peds.109.1.e12

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