Spinal arteriovenous fistulas in children with hereditary hemorrhagic telangiectasia

Report of 2 cases

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Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant angiodysplasia with high penetrance and variable expression. The manifestations of HHT are often age related, and spinal arteriovenous fistula (AVF) may be the initial presentation of HHT in young children. Because spinal AVFs are rarely reported, however, screening is not incorporated into current clinical recommendations for the treatment of patients with HHT. The authors describe 2 cases of children younger than 2 years of age with acute neurological deterioration in the context of a spinal AVF and in whom HHT was subsequently diagnosed. One patient presented with intraventricular and subarachnoid hemorrhage and the other with acute thrombosis of an intramedullary varix. These cases highlight the potential for significant neurological morbidity from a symptomatic AVF in very young children with HHT. Given the lack of data regarding the true incidence and natural history of these lesions, these cases raise the question of whether spinal cord imaging should be incorporated into screening recommendations for patients with HHT.

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Key Words • spinal arteriovenous fistula • hereditary hemorrhagic telangiectasia • vascular disorders

Hereditary hemorrhagic telangiectasia, or Osler-Weber-Rendu syndrome, is an autosomal dominant angiodysplasia with high penetrance.19 The incidence of this disorder is estimated to be 1 case in 5000 persons; however, because of variable expression, this incidence may be an underestimate of its true frequency.16,32 Mutations in at least 3 different genes that encode members of the TGFβ/BMP superfamily have been identified in patients with a clinical diagnosis of HHT. Both ENG and ACVRL1 encode transmembrane TGFβ receptors that are primarily expressed on vascular endothelial cells. SMAD4 encodes an intracellular protein that is a key downstream effector of TGFβ-BMP signaling.39 In addition, a pathogenic mutation has been identified in the BMPR2 gene, which also encodes a receptor in the TGFβ-BMP signaling pathway.39 Linkage analysis in affected kindreds has also identified 2 other loci, indicating additional disease-causing genes.5

The classic presentation of HHT includes recurrent nosebleeds along with multiple telangiectases of the lips, mouth, and fingertips in the context of a family history of similar symptoms.16,31 These common findings form the foundation for consensus diagnostic criteria for HHT, known as the Curaçao criteria (Table 1).32 The diagnosis of HHT is definite if 3 criteria are present, possible if 2 are present, and unlikely if 1 is present. Because of the progressive onset of symptoms with age, however, affected children often may not meet the Curaçao criteria.19 Furthermore, children may have life-threatening complications without any features of the classic presentation.16,20,24
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TABLE 1: Curaçao criteria for diagnosis of HHT*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Type or Description</th>
<th>Characteristic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>epistaxis</td>
<td>spontaneous &amp; recurrent</td>
<td>lips, mouth, nose, fingers</td>
</tr>
<tr>
<td>telangiectases</td>
<td>multiple</td>
<td>gastrointestinal region</td>
</tr>
<tr>
<td>vascular malformation</td>
<td>AVM, AVF</td>
<td>pulmonary region, hepatic region, cerebral region, spinal region</td>
</tr>
<tr>
<td>family history</td>
<td></td>
<td>first-degree relative</td>
</tr>
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* Shovlin et al., 2000.

The initial clinical feature of HHT is typically epistaxis, beginning in childhood and affecting 95%–100% of patients with HHT by late adulthood.4,10-20 The leading cause of morbidity and mortality in HHT is vascular malformation, including pulmonary AVM, which is present in 37%–59% of affected adults.19 Approximately two-thirds of neurological complications in HHT (for example, strokes or brain abscesses) are a result of embolic complications of pulmonary AVMs rather than intrinsic CNS lesions.8 Although patients with HHT have a significantly increased risk of stroke compared with the general population as a consequence of both pulmonary and cerebral AVMs,7 spinal cord infarction in the context of pulmonary AVM has rarely been reported.8

Estimates of the prevalence of intracranial vascular malformations in the CNS among patients with HHT vary widely, ranging from approximately 5% to 23% of patients.10,17,35 Genotype-phenotype correlations suggest that intracranial vascular malformations may be most common in HHT patients harboring ENG mutations.4 A spectrum of intracranial vascular malformations has been observed, including telangiectases, AVFs, and AVMs.15,17,34 In addition, there is an increased incidence of multiple AVMs in patients with HHT as compared with unaffected individuals.27 Despite the rarity of CNS lesions as compared with the incidence of pulmonary lesions, hemorrhage from a CNS vascular malformation is the cause of approximately one-third of neurological complications in patients with HHT and often has a devastating clinical impact.15,16,19,35

Central nervous system vascular malformations can occur in the brain, spinal cord, or both.19 Patients with HHT under the age of 45 years have a 6- to 22-fold increased risk of intracranial hemorrhage as compared with the general population.7 As a result, routine screening for intracranial vascular malformations is recommended by the age of 6 months (or at the time of diagnosis) via MRI of the brain with and without Gd enhancement.9,10 Conversely, spinal AVFs are included in the Curaçao criteria,32 are rarely reported in HHT, and are observed almost exclusively in children.6,12,15,18,22-26,28,33 Routine screening for spinal AVF is not a part of current clinical recommenda-

dations,9 therefore, only symptomatic spinal AVFs are generally detected, and their true prevalence in patients with HHT remains unknown. We present the cases of 2 children with catastrophic acute neurological deterioration in the context of a spinal AVF and in whom HHT was subsequently diagnosed.

Case Reports

Case 1

History and Examination. A previously healthy 2-year-old boy presented to an outside hospital with acute-onset right upper-extremity weakness that rapidly progressed to right hemiparesis. On examination, there were no abnormal bulbar signs, and no cutaneous telangiectases were noted. Computed tomography studies of the head showed no evidence of intracranial disease. The patient rapidly progressed to flaccid quadriparesis with respiratory distress requiring intubation and was transferred to our facility, where MRI studies of the brain and spinal cord were obtained. Magnetic resonance imaging of the brain was normal, but MRI and CTA of the cervical spine revealed a Type IV perimedullary AVF with a large intramedullary aneurysmal varix and severe spinal cord compression (Fig. 1).14 Further studies suggested a second spinal AVF at the thoracolumbar junction.

Operation and Postoperative Course. The patient underwent emergent C3–T1 decompressive laminectomy and duraplasty, but his neurological condition did not improve. Therefore, 36 hours later, the cervical AVF was resected, and dorsal myelotomy was performed, as was complete excision of the intramedullary varix. Persistent suboccipital pseudomeningocele later developed and eventually required permanent CSF diversion via a ventriculoperitoneal shunt. Three months after surgery, the patient recovered antigravity strength in the proximal muscles of both upper and lower extremities. Formal evaluation of the thoracolumbar AVF is pending.

Genetic Evaluation. Medical genetics consultation was obtained. The family history was significant for HHT in the paternal grandfather and several other distant paternal relatives. One affected great-uncle had been shown to have an ENG mutation (c.1A > G). The patient’s father had not been evaluated for HHT, although he had a history of epistaxis. Mutation analysis confirmed the child is heterozygous for the familial mutation in ENG (c.1A > G).

Case 2

History and Examination. A previously healthy 1-month-old girl had sudden-onset cardiorespiratory arrest at home. Bystander cardiopulmonary resuscitation was initiated. The infant was taken to an outside hospital via ambulance and, after resuscitation and intubation, was noted to have seizure activity. A head CT showed intraventricular and subarachnoid hemorrhage (Fig. 2). She was transferred to our facility. There was no history of epistaxis or evidence of telangiectases on examination.
Magnetic resonance imaging and MRA of the brain revealed hypoxic-ischemic injury and vasospasm of both internal carotid and proximal middle cerebral arteries but no evidence of vascular malformation. Spine MRI demonstrated a spinal AVF extending from L-2 to L-3. A spinal angiogram was obtained to further delineate the lesion; it showed a Type IV intradural perimedullary AVF with 2 small pseudoaneurysms feeding a large venous varix from L-1 to L-2 (Fig. 3). \(^{14}\)

**Operation and Postoperative Course.** The AVF was closed by endovascular embolization and subsequently excised by lumbar laminoplasty and microsurgical removal. Intraoperatively, extensive hemosiderin staining of the intradural space in the mid and upper lumbar regions was noted, confirming rupture of the AVF. The patient sustained severe hypoxic-ischemic brain injury. At the most recent follow-up 22 months after surgery, she still suffered from microcephaly, spastic quadriparesis, and severe developmental delay.

**Genetic Evaluation.** On review of the family history, the patient was found to have multiple paternal family members with significant spontaneous epistaxis, including a paternal great-grandfather and a paternal uncle in whom HHT had been diagnosed. According to the family, the paternal uncle died of complications of epistaxis (details unknown). Genetic testing showed that the infant is heterozygous for the previously determined familial mutation (ACVRL1 c.998 G > T), confirming the suspected diagnosis of HHT.
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![A and B](image)

**Fig. 3.** Case 2. Spinal angiograms obtained before (A) and after (B) embolization, showing the large venous varix, which no longer fills with contrast agent after embolization of the fistula.

**Discussion**

We describe 2 very young patients with undiagnosed HHT who presented with acute neurological deterioration in the context of a spinal AVF, including one child with an acute, thrombosed varix due to an AVF (Case 1) and one who presented with intraventricular hemorrhage (Case 2). Although the child in the first case had a history of mild epistaxis, neither child had any significant symptoms prior to neurological deterioration. Both cases highlight the possibility that spinal AVF may be the presenting feature of HHT in very young children.

The neurological presentation in the child in Case 1 was attributable to acute expansion of the intramedullary venous varix as a result of intrapituitary hemorrhage. While endovascular occlusion is usually the therapy of choice for spinal AVF, in this case, the patient’s symptoms were caused by intrinsic cord compression related to this expansion (Fig. 1). We believed that surgical decompression offered the best chance of optimal neurological recovery. The patient in Case 2 experienced sudden cardiopulmonary arrest in the context of acute intraventricular and subarachnoid hemorrhage. Brain MRI and MRA did not demonstrate an intracranial lesion, and at the time of surgery, hemosiderin staining of the thoracolumbar thecal sac was noted, revealing acute rupture of the spinal AVF.

Case 2 is the fourth reported instance of intraventricular hemorrhage resulting from the rupture of a thoracolumbar spinal AVF, and the second case in a patient with HHT. Barzó and colleagues described a 28-year-old man who experienced sudden-onset headache followed by loss of consciousness and cardiopulmonary arrest. After the patient regained consciousness, his neurological examination revealed complete flaccid paraplegia with a T-12 sensory level. Cerebral angiography did not demonstrate an intracranial lesion, but spinal angiography revealed a T10–12 AVF. Kenning et al. described a 14-month-old girl who presented with fever and depressed mental status in the context of subarachnoid and intraventricular hemorrhage with hydrocephalus. Magnetic resonance imaging and MRA of the brain did not reveal a source of the bleed. Acute paraplegia developed 72 hours after admission, and spinal MRI demonstrated subdural hematoma and hematomyelia at T11–12. A diagnosis of HHT was not mentioned in either report. However, Mandzia et al. reported 2 cases of HHT in first-degree cousins who presented with acute paralysis and spinal AVF. One of the patients was an 8-year-old boy who presented with sudden loss of consciousness but no focal deficit along with subarachnoid hemorrhage and blood in the fourth ventricle. Magnetic resonance imaging of the brain and cerebral angiography did not demonstrate an intracranial source, but spinal MRI revealed a perimedullary spinal AVF at T-12.

No prospective studies have documented the prevalence of spinal AVF in patients with HHT, and existing series are very limited. Older reviews have suggested that spinal AVF occurs in 8% of patients with neurological symptoms. Krings and colleagues reported a single-center study of 31 patients with HHT treated for primary CNS vascular malformations; 7 patients (22.5%) had spinal malformations. The mean age of HHT patients presenting with spinal AVFs was 2.2 years (range 1 month–6 years). Five (71%) of 7 patients presented with hematomyelia and acute tetra- or paraplegia. All AVFs were intradural high-flow perimedullary fistulas. Another study documented 2 spinal AVFs (4%) in 50 patients with mutations in ACVR1L, but no fistulas among 61 patients with ENG mutations.

Mei-Zahav and colleagues reviewed the experience of children treated for symptomatic HHT over a 5-year period at a single center. Only 3 (21%) of 14 patients had primary neurovascular lesions, which were spinal AVFs in 2. The high percentage of spinal lesions in this series may reflect elective management of asymptomatic intracranial lesions identified during early radiographic screening. Cullen et al. reported 13 cases of spinal AVF in children younger than 2 years of age; HHT was diagnosed in 6 (46%). Five (83%) of 6 patients with HHT had high-flow perimedullary AVF. Meng et al. described 19 children treated for perimedullary spinal AVF at a single center over 21 years and noted only 2 patients (11%) with HHT. This may reflect the absence of other diagnostic criteria in young children.

Poisson and colleagues documented 2 children with spinal AVF in the context of HHT: one (6 years old) presented with abdominal pain followed by paraplegia 24 hours later, and the other (8 months old) presented with severe back pain followed by subacute paraplegia. These authors discussed the lack of data on the incidence of spinal AVF in children with HHT, as well as the problems...
inherent to radiographic screening via spinal MRI in children under 4 years of age. They recommended thorough neurological examination, noting a generally good outcome in patients with asymptomatic spinal AVFs treated electively compared with patients who presented with acute neurological deterioration.1,11,21,25–28,30,34

The number of reported cases of spinal AVF in children with HHT is small, and the number with detailed information on clinical presentation is smaller. Based on the cases available for our review, including both cases reported here, the majority of patients (14 of 18) presented with acute symptoms due to bleeding rather than progressive myelopathy from venous congestion (Foix-Alajouanine syndrome).11,12,15,18,22,23,26 Therefore, it is possible that physical examination may have low sensitivity in detecting spinal AVFs in children with HHT prior to rupture.

Current recommendations for patients with HHT include radiographic screening for intracranial vascular malformations via MRI by the age of 6 months.8,19 Given that the risk of catastrophic presentation for symptomatic spinal AVF appears to be high,11,12,15,18,22,23,26 consideration should be given to the addition of total spine MRI at the time of the recommended screening brain MRI. In some cases, spinal MRI may allow elective management rather than salvage treatment at the time of rupture. Spinal imaging will also provide important data regarding the true incidence of these lesions in patients with HHT. The spinal evaluation adds approximately 1 hour to the MRI procedure and does not require additional contrast administration.

Because the true incidence and natural history of these lesions are currently unknown, the risk of identifying those that would have remained quiescent is difficult to assess. If the number of spinal AVFs at true risk for rupture is low, early identification could lead to anxiety and unnecessary additional imaging or invasive procedures with their attendant financial costs and medical risks. A quality cost-benefit analysis cannot be performed until better data are obtained.

Although HHT was not diagnosed in either of our patients prior to their presentations, both did have a molecularly proven family history of HHT and would have been candidates for AVM screening. It is likely that screening would establish a better understanding of the true prevalence and allow the treatment of asymptomatic spinal AVF in patients with established HHT. Our review of the limited available data suggests that patients with these lesions are more likely to present with sudden, significant neurological injury rather than with subacute or chronic symptoms, and this may result in worse outcomes. Therefore, the issue of spinal screening needs to be raised and examined further.

Conclusions

We describe 2 young children with previously undiagnosed HHT who presented with paralysis from spinal AVF, one of them the fourth reported case of intraventricular hemorrhage resulting from rupture of a thoracolumbar AVF. These cases highlight the catastrophic acute neurological deterioration seen in the majority of reported cases of children with HHT and spinal AVF. Screening MRI of the spine at the time of recommended screening MRI of the brain may help to understand the true incidence of spinal AVF in HHT and prevent significant morbidity by allowing elective treatment of asymptomatic lesions.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Calhoun, Bollo. Acquisition of data: Calhoun, Bollo. Drafting the article: Calhoun, Bollo. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Walker. Study supervision: Walker, McDonald, Stevenson.

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