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Clinical commentary

Clinical presentation and treatment paradigms in patients with hereditary hemorrhagic telangiectasia and spinal vascular malformations

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ABSTRACT

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder that causes angiodysplasia and results in mucocutaneous telangiectasias and arteriovenous malformations of organs. Although central nervous system vascular malformations can occur anywhere along the neuraxis, spinal vascular malformations are rare. We present our experience with the presentation and management of spinal vascular malformations in patients with HHT. Of the more than 800 patients with the diagnosis of HHT screened at our institution from 1995 through 2017, four patients with spinal vascular malformations (age range 1 month–77 years; 2 male, 2 female) were identified, three of whom came to clinical attention after significant neurological deterioration from previously unknown malformations. A review of the literature including our patients demonstrated 29 total spinal arteriovenous fistulas (AVFs) in 28 HHT patients (69% male). The lesions were located predominantly in the thoracic spine (65.5%). Three lesions were not treated, 17 were treated with embolization, 6 were surgically resected, and 3 were treated with embolization and surgery. In 14 cases, the patients presented with hemorrhage of the AVF. Overall, 79% of patients achieved complete or near-complete occlusion, with 75% reporting improvement in neurological function. Discovery of spinal lesions often occurs after neurological decline because current screening protocols do not include evaluation of the patient for spinal lesions. Most patients benefit from intervention, which is tailored to the characteristics of the patient and their malformation. Given the often-severe neurological deficit encountered at presentation, we favor a protocol that screens HHT patients for spinal vascular malformations.

1. Introduction

Hereditary hemorrhagic telangiectasia (HHT, or Osler-Weber-Rendu syndrome) is a rare autosomal dominant angiodysplastic disorder that affects the vasculature of multiple organ systems throughout the body. It is characterized by mucocutaneous telangiectasias and arteriovenous malformations (AVMs) of the gastrointestinal, pulmonary, and central nervous (CNS) systems. HHT has an estimated prevalence of 1 in 5000–10,000 persons and results from genetic mutations with variable penetrance and expressivity, which drive multisystemic vascular dysplasia [1,2]. These mutations cause altered endothelial cell signaling through modulation of the transforming growth factor-beta (TGF-β)/bone morphogenetic protein superfamily of signaling molecules, leading to dysregulated angiogenesis and the development of fragile, leaky, and tortuous telangiectatic vessels and AVMs.

Commonly mutated genes encode endoglin (*ENG* gene, chromosome 9q34; HHT type 1), activin receptor-like kinase type 1 (*ALK1* or *ACVRL1* gene, chromosome 12q13; HHT type 2), and SMAD4 (chromosome 18q21; HHT in association with juvenile polyposis) proteins [3]. Endoglin and ALK1 proteins act as TGF-β type I and type III receptors, respectively, and are involved in the intracellular phosphorylation of receptor-regulated Smad (R-Smad) proteins [4]. Smad proteins (R-Smads and Smad4) propagate the intracellular signal by forming a heterotrimeric complex before translocating to the nucleus to regulate transcriptional activity of target genes [5]. Expression of these target genes is necessary for angiogenesis,

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blood vessel maturation, stabilization, maintenance, and remodeling. To date, over 750 disease-causing mutations in *ENG* and *ACVRL1* have been described, which collectively comprise over 85% of all mutations in patients with HHT [6].

Symptoms in HHT are highly variable, even among first-degree relatives, and often evolve over time. Clinical manifestations of HHT include recurrent spontaneous epistaxis, gastrointestinal bleeding, and less commonly, hemorrhagic or ischemic stroke of the brain or spinal cord [7,8]. It is estimated that 30% of HHT patients have hepatic involvement, 30% have pulmonary involvement, and 10–20% experience cerebral involvement [9–11]. Spinal vascular lesions comprise 5–9% of all CNS vascular malformations and 3–4% of all intradural spinal lesions [12,13]. Spinal cord AVMs comprise less than 1% of AVMs in HHT patients and most commonly present as intradural perimedullary arteriovenous fistulas (AVFs; also commonly referred to as Type IV spinal AVMs) [14]. Spinal cord vascular malformations can have profound neurological implications and may present with hemorrhage, congestive or compressive myelopathy, or radiculopathy [15]. We describe the clinical presentation, pathogenesis, genetic makeup, treatment, and outcome of 4 cases of patients with HHT and spinal vascular malformation from our institution. We also present a literature review of all other reported cases in the English-language literature.

2. Methods

The cases from our institution were retrospectively identified after the Institutional Review Board (IRB) provided approval for this study. Patients who were diagnosed with HHT and spinal AVF were identified via search of our institutional database. Of over 800 patients screened at the University of Utah HHT Center of Excellence between 1995 and 2017, four patients fit the inclusion criteria.

A literature search was carried out using the PubMed/Medline database from January 1970 to January 2017 for all cases of spinal AVMs and AVFs in patients with HHT. The key words utilized in the search were "spinal arteriovenous fistula," "arteriovenous malformation," "AVM," "AVF," "HHT," "hereditary hemorrhagic telangiectasia," and "Osler-Weber-Rendu." The identified articles were reviewed to discover further relevant publications. Full-text articles were assessed for inclusion and exclusion criteria. Publications were included if they reported a case in the English language of a patient with HHT and spinal AVM/AVF with or without treatment.

Information on baseline characteristics (age, sex, mutation, HHT type, presence of other HHT manifestation, clinical presentation) of each patient was collected. Details about the angiographic characteristics of the AVF were also collected, including location, type of fistula, presence of multiple arterial feeders, arterial supply, and presence of hemorrhage. Treatment details included surgical/endovascular intervention performed and clinical outcome.

3. Current case series

3.1. Case 1

3.1.1. History and examination

A previously healthy 2-year-old boy presented to an outside hospital with acute-onset right upper-extremity weakness, which rapidly progressed to right-sided hemiparesis and eventual flaccid quadriplegia with respiratory distress. The patient required intubation and mechanical ventilation and was transported to our facility. On physical examination, the patient had no grimace to painful stimulus in all extremities and had diminished patellar and Achilles reflexes bilaterally. No mucocutaneous lesions were noted on examination. The results of lumbar puncture, head computed tomography (CT), and brain magnetic resonance imaging (MRI) were normal. Spinal MRI, magnetic resonance angiography (MRA), and computed tomographic angiography demonstrated a Type IV perimedullary AVF and large intramural aneurysmal varix at C5-6 with severe cervical cord compression (Fig. 1).

3.1.2. Operative and postoperative course

The patient underwent emergent C3-T1 decompressive laminectomy with duraplasty. Despite the removal of extrinsic compression, the patient's neurological condition did not improve. Two days later, the decision was made to resect the cervical AVF with dorsal myelotomy and excision of the intramedullary varix. The patient later developed a suboccipital pseudomeningocele that required permanent cerebrospinal fluid diversion via ventriculoperitoneal shunt placement. At 5-year follow up, the patient had recovered antigravity strength of the proximal upper and lower extremities bilaterally but was nonambulatory and had remaining weakness of both hands and decreased sensation below C4.

3.1.3. Genetic evaluation

The patient's family history was significant for HHT in the father, paternal grandfather, and multiple other distant paternal relatives, many of whom had histories of recurrent spontaneous epistaxis. Of note, the patient's paternal great-uncle was known to possess the *ENG* mutation (c.1A>G). Through mutation analysis by the medical genetics team, the patient was found to be heterozygous for the familial mutation of *ENG* (c.1A>G), thus confirming a diagnosis of HHT type 1.

3.2. Case 2

3.2.1. History and examination

A previously healthy 1-month-old girl presented after sudden-onset cardiorespiratory arrest while at home. Cardiopulmonary resuscitation was initiated, and the infant was taken by ambulance to an outside hospital. After resuscitation and intubation, the patient was noted to have seizure-like activity (i.e., conjugate eye-rolling upwards, tonic posturing, and myoclonic movements of the upper and lower extremities) and was transferred to our facility. The patient had no history of epistaxis or mucocutaneous lesions on physical examination. A head CT revealed subarachnoid and intraventricular hemorrhage. Brain MRI and MRA revealed extensive hypoxic-ischemic cortical injury but no evidence of intracranial AVMs. Spinal MRI and angiography demonstrated a Type IV intradural perimedullary AVF spanning L2-3 (Fig. 2).

3.2.2. Operative and postoperative course

The patient was treated with endovascular embolization and subsequent AVF excision by lumbar laminoplasty. Prominent hemosiderin staining was observed intraoperatively within the intradural space of the mid and upper lumbar regions, thereby confirming AVF rupture. The patient developed post-hemorrhagic hydrocephalus that required ventriculoperitoneal shunt placement for two weeks postoperatively. At 13-year follow-up, the patient's sensation was grossly intact, but the patient remained nonambulatory and continued to experience spastic quadriparesis with brisk reflexes and global developmental delay.

3.2.3. Genetic evaluation

The patient's family history was significant for HHT in a paternal great-grandmother and paternal uncle who both had recurrent spontaneous epistaxis. Of note, the paternal uncle was reported to have died from complications related to epistaxis (not further specified). According to the family, multiple other paternal family

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