Cerebral hemorrhage in monozygotic twins with hereditary hemorrhagic telangiectasia: case report and hemorrhagic risk evaluation

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The authors present a case of monozygotic twins with hereditary hemorrhagic telangiectasia (HHT) who experienced cerebral arteriovenous malformation (AVM) hemorrhage at a very young age. The clinical variables influencing HHT-related AVM rupture are discussed, and questions surrounding the timing of screening and intervention are explored. This is only the second known case of monozygotic HHT twins published in the medical literature, and the youngest pair of first-degree relatives to experience AVM-related cerebral hemorrhage. Evidence guiding the screening and management of familial HHT is lacking, and cases such as this underscore the need for objective and validated protocols.

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of epistaxis and facial telangiectasias rendered the clinical diagnosis of HHT, which was confirmed when genetic workup identified the endoglin (ENG) mutation in Twin A and presumed in Twin B, the mother, maternal half-brother, and maternal grandmother, given symptom constellation (Fig. 2). Given the monozygotic relationship between twins, Twin B was presumed to harbor the mutation, and therefore underwent comprehensive screening for associated pathology at 5 months of age. Indeed, MRI of his brain revealed a posterior fossa vascular malformation (Fig. 3A and B), and the patient was referred to the emergency department. MR angiography sequences revealed a left cerebellar vascular malformation, which was thought to most likely represent an arteriovenous fistula (AVF) supplied by a prominent left anterior inferior cerebellar artery (AICA) and posterior inferior cerebellar artery (PICA), and drained by multiple cortical veins emptying into an enlarged left transverse sinus. The lesion also contained what appeared to be a large bi-lobed feeding aneurysm arising from the distal branch vessels of the left AICA-PICA. The patient was asymptomatic and therefore was discharged the next day; elective cerebral angiography for AVM characterization was scheduled for the following week. On the evening prior to the elective angiography session, the patient presented to the emergency department with vomiting and lethargy, and a CT scan without contrast revealed a posterior fossa hemorrhage and obstructive hydrocephalus (Fig. 3C).

Following emergency placement of an external ventricular drain, a suboccipital craniectomy and C-1 laminectomy were performed. The posterior fossa contents were under significant pressure, and immediately on opening the dura, a large blood clot spontaneously extruded from the cortical surface. With gentle suction and irrigation, the remaining blood products were evacuated. On exploration, the medial and lateral arterial feeders were identified and ligated with aneurysm clips. The large dilated vein draining directly into the tentorium was then ligated, and the entire lesion was removed. After inspecting the entire hemorrhage cavity and ensuring hemostasis, the dura and incision were closed, and the patient was taken to the ICU. An estimated blood loss of 150 ml was noted. Pathologic examination demonstrated thick-walled vessels, some with marked luminal hemorrhagic distention consistent with an AVM.
Despite prolonged external ventricular drain weaning and ICU course, the patient was eventually discharged home without neurological deficits or the need for permanent CSF diversion. Like his brother, Twin B has made a full neurological recovery, remains neurologically intact, and has regained lost milestones.

Discussion

To our knowledge, this is only the second known case of monozygotic HHT twins published in the medical literature, and the youngest pair of first-degree relatives to experience AVM-related cerebral hemorrhage. Evidence guiding the screening and management of familial HHT is lacking, and cases such as this underscore the need for objective and validated protocols. Through multiinstitutional collaboration and data aggregation, the HHT consortium represents the best effort yet to better quantify the rates and risk factors for HHT-related cerebral AVM hemorrhage. These risk factors are explored below and related to the present cases to offer a unique window into the relationship between genetic makeup and clinical manifestations in HHT.

Risk Factors for HHT-Related Cerebral Hemorrhage

Patient Age

Infants and children are at risk for sudden, serious hemorrhage if a cerebral AVM is present; therefore, if there is a family history of HHT in a first-degree relative, evaluation for HHT in childhood has been suggested to limit potential catastrophic sequelae. Moreover, in a study of 50 individuals with HHT, 75 vascular lesions were noted in the CNS, 90% of which were AVFs that were diagnosed by the age of 6 years, with 53% being infratentorial.

![Pedigree](image)

**FIG. 2.** Pedigree. The proband (Twin B) is indicated by the arrow. The twin brother (Twin A) and half-sister were the only ones to undergo DNA testing. The ENG mutation was presumed in the proband, mother, maternal half-brother, and maternal grandmother given the severity of symptomology. All have had screening MRI of the brain with and without contrast and other screening tests per the international HHT guidelines. The squares represent males and the circles, females. The diagonal lines indicate that the individual is deceased. *Confirmed cerebral AVM; †ENG mutation.

![Images](image)

**FIG. 3.** Twin B. Images obtained in the 5-month-old proband. A and B: Postcontrast axial (A) and sagittal (B) T1-weighted MR images demonstrating a bi-lobed vascular lesion in the left cerebellar hemisphere. A prominent and tortuous AICA-PICA complex is seen along with an engorged ipsilateral transverse sinus. C: Noncontrast axial CT scan demonstrating an acute posterior fossa hemorrhage causing complete effacement of the fourth ventricle and ventriculomegaly. D: Postoperative postcontrast axial T1-weighted MR image demonstrating hemorrhage evacuation and complete resection of the vascular lesion.
A correlation between genotypic and phenotypic manifestations is currently being explored for HHT; the evolution of vascular phenotype varies across patients with identical mutations. HHT pathophysiology is associated with mutations in the transforming growth factor–β signaling cascade, and most cases of HHT are due to a lack of sufficient ENG or activin receptor–like kinase (ALK)–1 protein function, both necessary for vascular integrity and vasculogenesis. Mutations tend to be found across all coding regions; no common mutation targets have been associated with either ENG or ALK-1.

The ENG gene, located on the long arm of chromosome 9 at position 34.11 (9q34.11), encodes for a protein that exists as covalently linked homodimer composed of inter- and intrachain bonds; thus, ENG mutations are linked to structural instability and protein function loss. Abdalla and Letarte noted that 80% of ENG gene mutations identified in HHT1 cases led to “stop codons and truncated polypeptides,” further concluding that ENG mutations result in decreased levels of functional endoglin on endothelial cells and peripheral blood monocytes, thus leading to the clinical manifestations of HHT1. The lack of vascular integrity leads to a wide variation in angioarchitecture, thus giving rise to phenotypically different AVMs, most commonly AVFs, shunting “nidus-type” AVMs, and nonshunting capillary vascular malformations (CVMs).

A genotype-phenotype relationship has been noted between certain genetic mutations and resulting phenotype. ENG mutations are diagnostic for HHT1, with pulmonary and cerebral AVMs (some have reported a variable association of cerebral AVMs to HHT1) being more common in this population, while ALK-1 mutations are diagnostic for HHT2, with hepatic AVMs being more common. Others have noted that while diagnostic mutations have been described for particular HHT genotypes, no definitive relationship can be concluded between genotype and phenotypic manifestation of HHT. Krings et al. purported that the phenotypic differences in terms of blood vessel capacity and strength observed among HHT patients were age dependent. Hypoxia, presumably over time, has been considered as a potential environmental candidate for triggering vascular remodeling in HHT AVM development.

Family History

There seems to be an increased risk for cerebral AVMs in individuals with HHT who have a first-degree relative with a cerebral AVM, although the risk of rupture in HHT patients with first-degree relatives is unclear. In a systematic review of familial occurrence of sporadic cerebral AVMs unrelated to HHT, van Beijnum et al. noted that 79% of familial relationships of patients with cerebral AVMs were first-degree relatives. Additionally, they reported that in families with at least 2 successive generations of cerebral AVMs, the child at the time of diagnosis was younger than the parent, suggesting possible anticipation of a cerebral AVM. Such a pattern is supported for HHT—though hardly confirmed—by our case, wherein presentation occurred at a much earlier age after skipping a generation. In a review of 9 patients, Morgan et al. reported a higher and notably severe AVM rupture risk among children and infants with a family history of HHT. It is clear that further research is needed to clarify the relationship between first-degree relatives and AVM rupture risk, especially among the HHT population.

Vascular Phenotype

Rupture risk of cerebral AVMs increases based on lesion type, with AVFs posing the most serious and devastating consequences. Multiple cerebral AVMs have a 10%–20% incidence rate of rupture in HHT cases. Interestingly, Willemse et al. noted that while HHT patients have a higher risk of harboring a cerebral AVM, especially if a history of pulmonary AVM is noted, the bleeding risk of the cerebral AVM in HHT may be less than that in patients with sporadic AVMs.

Cerebral AVMs can be categorized into 3 types: nonshunting CVMs with characteristic enhancing vessel conglomeration feeding into arteries or veins, shunting “nidus-type” AVMs, and single-hole pial (brain) AVFs. HHT-related CVMs are usually smaller than 1 cm, superficial, supratentorial lesions with a suspected low risk of rupture, multiplicity, and no dilated arterial feeder or draining vein; these constitute 61% of all vascular malformations. Nidus-type AVMs occur with a frequency of 40% among aneurysms with characteristic features of early venous drainage, compact/discrete nidi, and flow-voids, occurring in settings of prior hemorrhage; these AVMs have a low-to-moderate risk of rupture. AVFs occur with a frequency of 12% and are primarily found in children. Multiple vascular lesions are observed in 36%–44% of patients. Features of AVFs include an enlarged arterial feeder, early venous drainage, a large venous pouch, venous congestion/reflux, associated aneurysms, and a relatively higher rupture risk.

Both of our twins had experienced cerebral AVM rupture before catheter angiography was performed; thus, thorough angioarchitecture evaluation and subtype classification were not performed. Nonetheless, CT angiography findings were most consistent with AVF (Figs. 1 and 2), and therefore carried a higher rupture risk. Summarily, based purely on radiographic features of the posterior fossa lesion, Twin B harbored a higher-risk lesion, and he was being evaluated for possible early (prophylactic) surgical intervention.

Other Factors

Prior history of hemorrhage has been reported as a risk factor in HHT patients harboring a cerebral AVM. Gross and Du noted prior hemorrhage risk with a hazard ratio of 3.2 (95% CI 2.1–4.3). Kim et al. reported that HHT patients with cerebral AVMs presenting with rupture have higher rerupture rates (10.1%; 95% CI 3.3%–31.2%) than patients with unruptured cerebral AVMs at presentation (0.4%, 95% CI 0.1%–1.7%); rerupture rates were comparable to patients with sporadic cerebral AVMs. Other
major high-risk features for cerebral AVM rupture include associated aneurysms (HR 1.8, 95% CI 1.6–2.0), deep AVM location (HR 2.4, 95% CI 1.4–3.4), and exclusively deep venous drainage (HR 2.4, 95% CI 1.1–3.8). 14

Timing of Screening and/or Intervention

Per HHT international guidelines, for children with possible or definite HHT, screening for cerebral vascular malformations with unenhanced MRI is recommended in the first 6 months of life or at the time of clinical diagnosis. 9 The timing of treatment remains an ongoing debate, as rupture rates are of relevant concern in terms of pursuing interventions sooner than later. Brinjikji et al. noted that despite the international guidelines, there is less consensus about screening children with HHT for cerebral AVMs (64%) compared with the adult population (77%). 6 Moreover, they argued that treatment for AVMs should be evaluated on a case-by-case basis with evaluation of AVM anatomic distribution and prevalence. 16

In this case, the patient’s twin history of early rupture combined with the high-risk fistulous appearance of the lesion may indicate a greater risk of rupture and therefore the need for early intervention. If early CNS hemorrhagic sequelae of HHT are identified in a first-degree relative, we advocate for early, prophylactic surgery. A devastating outcome was narrowly avoided in this case, but could have been prevented altogether if swift action was taken as soon as the posterior fossa pathology was identified in Twin B. In such cases, even vigilant observation may be too conservative a treatment strategy.

On the other hand, one may reasonably argue that the body of literature indicates low overall rupture rates. This final point is of particular importance as one considers the risks assumed when pursuing a prophylactic craniotomy for AVM resection, particularly in a young, developing brain. This disparity between innumerable clinical variables and the limited clinical evidence underscore the importance of evaluating patients and family members with HHT on a case-by-case basis until better evidence exists to support a definitive screening and treatment algorithm. As the HHT guidelines suggest, when a cerebral AVM is found, individuals should be referred to a center with neurovascular expertise for further evaluation and management; specific pediatric neurovascular expertise is advisable in young children. 20

In sum, we advocate for the following: 1) comprehensive genetic workup in patients and family members with suspected disease; 2) early imaging; 3) early and collaborative consultation with both neurology and neurosurgery teams if neuroimaging demonstrates a malformation; and 4) early neurosurgical intervention if there is evidence of cerebral hemorrhagic complications in first-degree relatives.

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