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Significant Hematochezia and Intracranial Bleeding in Neonatal Hereditary Hemorrhagic Telangiectasia

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is an underreported autosomal dominant vascular dysplasia. Neonatal presentations of HHT are rare, as this disorder typically presents in adolescence or beyond with epistaxis. We report a female neonate with hematochezia on the 1st day of life secondary to multiple gastrointestinal arteriovenous malformations (AVMs) along with intracranial hemorrhage. We describe her clinical course and management, as well as her novel family mutation in *ENG*. This is the first reported HHT case with significant gastrointestinal bleeding in the newborn. We review neonatal HHT and raise the consideration for more directed prenatal imaging and delivery options for fetuses at high risk of HHT.

Keywords

- hereditary hemorrhagic telangiectasia
- Osler–Weber–Rendu syndrome
- hematochezia
- intracranial bleeding
- neonate

Hereditary hemorrhagic telangiectasia (HHT), also called Osler–Weber–Rendu syndrome, is an underreported autosomal dominant vascular dysplasia affecting multiple organ systems. It is characterized by mucocutaneous telangiectasias and arteriovenous malformations (AVMs) most often found in the cerebral, pulmonary, hepatic, and gastrointestinal circulations. While symptoms are rare in early childhood and typically present in adolescence or beyond with epistaxis, case reports in neonates highlight intracranial and pulmonary hemorrhages as well as hepatic AVMs, resulting in high-output congestive heart failure.[1–5] However, to the authors' knowledge, there is no literature to date describing significant gastrointestinal bleeding secondary to multiple AVMs during the neonatal period due to HHT.

Case Report

A term female was delivered via cesarean section after failure to progress in the setting of maternal chorioamnionitis. Poor tone and respiratory effort were noted at delivery. After initial resuscitation, including tracheal suctioning for thick meconium, she was brought to the neonatal intensive care unit (NICU) on room air but was intubated shortly thereafter for recurrent apneas. Apgar scores of 1, 4, and 6 were assigned at 1, 5, and 10 minutes, respectively. In the absence of convincing physiologic evidence and clinical history, no therapeutic hypothermia was offered. Within 24 hours of birth, she was noted to have significant hematochezia. Her hematocrit declined from 63% on admission to 37% on postnatal day 5. Imaging, including abdominal and cranial ultrasounds were obtained during this interval, with the former study not revealing any abnormalities and the latter showing a 1.5 cm rounded echogenic lesion in her left posterior fossa. After pertinent history including paternal HHT was discovered, she was transferred to a regional center for further evaluation and management.

Shortly after transfer, magnetic resonance imaging (MRI) of her brain/spine revealed an intracranial hemorrhage within the left midbrain/pons and left middle cerebellar

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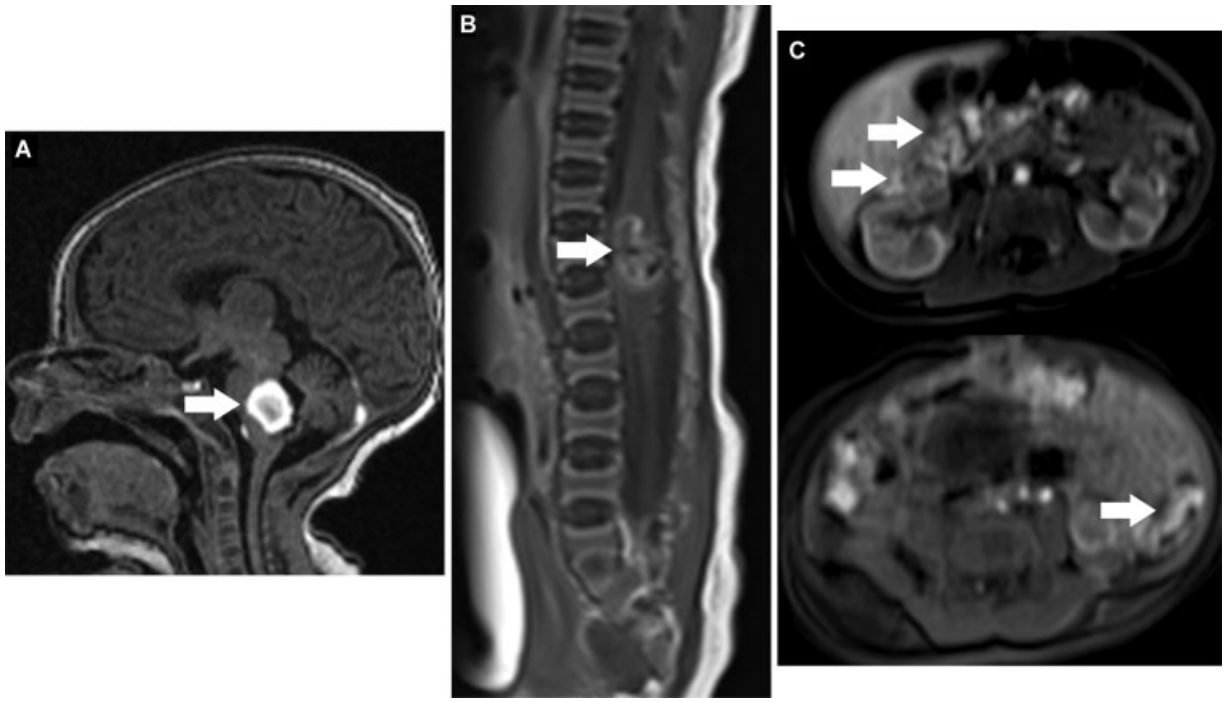

Fig. 1 Initial MRI findings on admission. (**A**) T1 sagittal MRI without contrast demonstrates hyperintense hemorrhagic focus in the midbrain (arrow). (**B**) T1 post gadolinium with peripherally enhancing hypointense focus in the distal spinal cord (arrow). (**C**) T1 post contrast arterial enhancing serpiginous structures in the hepatorenal space (arrows) and associated with the descending colon (arrow). MRI, magnetic resonance imaging.

peduncle (►**Fig. 1A**). A probable intramedullary AVM within the conus medullaris without findings of hemorrhage was also identified (►**Fig. 1B**). MRI of her abdomen showed multiple tortuous AVMs within the transverse and descending colon which appeared to communicate with the superior mesenteric artery and vein, as well as a large AVM in the hepatorenal space (►**Fig. 1C**). No pulmonary AVMs were seen. Targeted mutation analysis of her DNA (deoxyribonucleic acid) detected the heterozygous novel familial mutation c.1687–1G > T in *ENG* and confirmed her diagnosis of HHT. Given parents' desire to continue aggressive management in the setting of recurrent hematochezia requiring multiple transfusions, she was taken to the operating room for exploration at 6 weeks of age. Initially, a diagnostic laparoscopy was performed with the hope of finding enlarged AVMs in the bowel mesentery which could allow for individual ligation and/or cauterization, and potentially avoid a bowel resection. As seen in ►**Fig. 2**, the AVMs were found to be encasing the colonic wall, invading through the serosa, and into the lumen. The vast majority of these appeared to be confined to the transverse and descending colon. A subtotal colectomy was performed and at this point the ascending colon was anastomosed to the sigmoid colon. A gastrostomy tube (GT) was also placed due to her neurologic impairment and a central line was inserted for blood draws and potential transfusions.

Following surgery, hematochezia initially resolved but returned within a week. Oral aminocaproic acid (Amicar, Akorn, Inc., Lake Forest, IL) was started in an attempt to decrease the bleeding. Due to continued bleeding and it's large oral volume, the medication was changed to intravenous form (initially bolus dosing and then continuous infusion). Aminocaproic acid was discontinued after a 3-week trial without any abatement of the bleeding. She had a colonoscopy toward the end of this period at 12 weeks of age that demonstrated small telangiectasias in the rectum and large AVMs in the ascending colon that were not visualized on the external surface of the bowel during her initial surgery (►**Fig. 3**). Angiogram and intralesional bevacizumab (Avastin, Genentech, Inc., San Francisco, CA) were strongly considered but due to her history of intracranial bleeding and the potential systemic effects, it was decided that the risks outweighed the benefits. At 13 weeks of age, 8 weeks after her initial operation, the patient returned to the operating room for a complete colectomy and ileorectal anastomosis. No lesions were seen in the terminal ileum. The patient received one transfusion on day 1 after surgery. Despite intermittent small bleeds, she has not received any transfusions since. During her entire hospital course, she received 25 packed red blood cell transfusions with a lowest hematocrit of 16.4%.

The patient was cautiously advanced on GT feeds of an elemental formula. She did not tolerate fortification to 24 Kcal with increased bleeding noted, so she was decreased back to 20 Kcal formula with addition of safflower oil. The patient was discharged at 4.5 months of age (26 days after the second surgery) at a weight of 6.48 kg and hematocrit of 34.5% with a reticulocyte count of 4.4%. Upon discharge, she was tolerating bolus GT feeds during the day with continuous feeds at night.

The patient has continued with close outpatient follow-up in multiple subspecialty clinics. Repeat MRI studies at

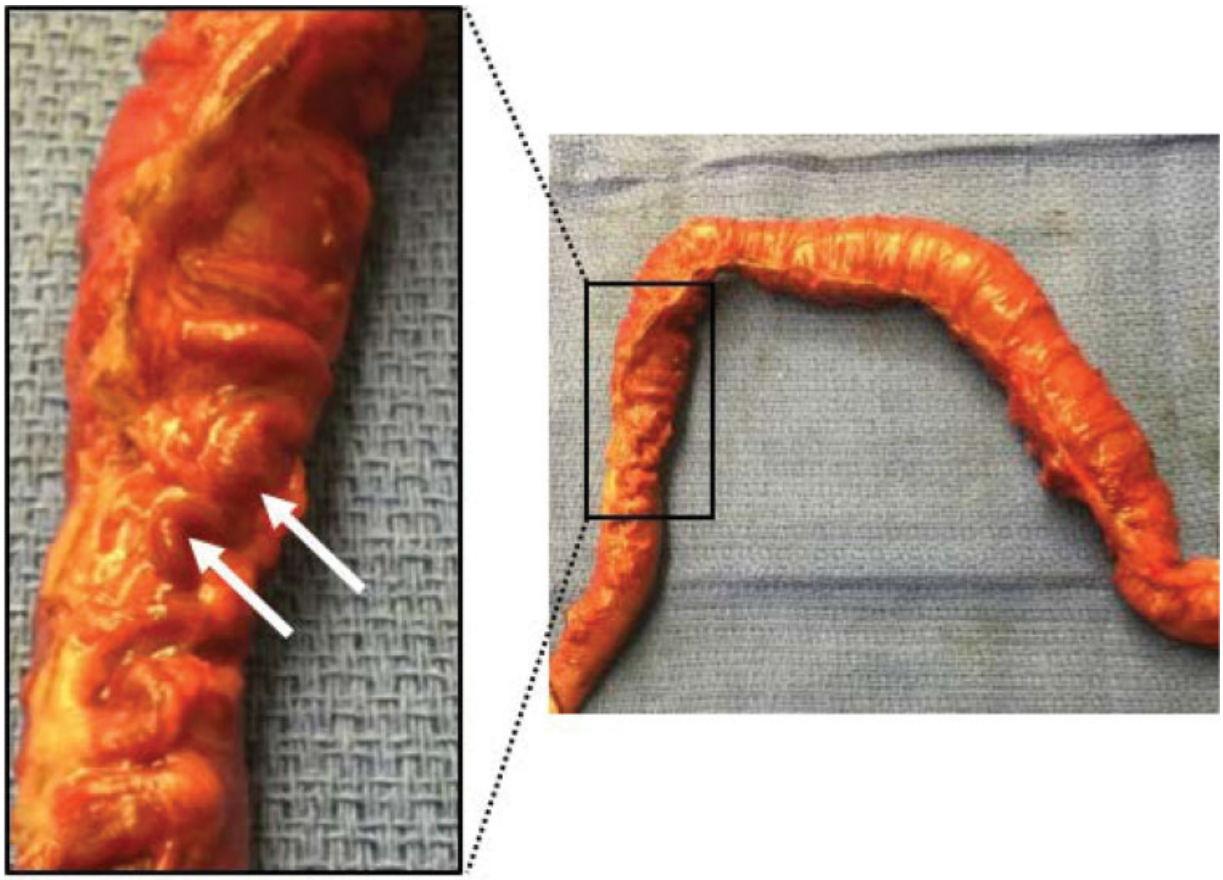

Fig. 2 Gross resection of patient's ascending and transverse colon with multiple, large AVMs (arrows). AVMs, arteriovenous malformations.

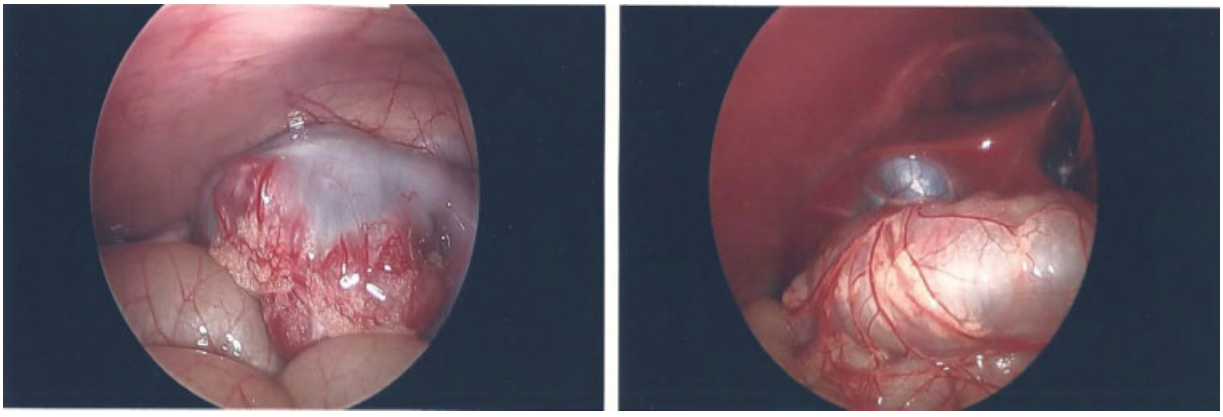

Fig. 3 Endoscopic images revealing multiple telangiectasias in ascending colon/rectum.

approximately 1 year of life demonstrated a stable spinal AVM without signs of bleeding, ongoing evolution of her intracranial hemorrhage without any additional lesions, and no visible abdominal AVMs. At 2 years of age, she continues to have normal growth on gastrostomy tube feeds and is at approximately the 25th percentile for length and the 10th percentile for weight. There has been no additional gastrointestinal bleeding that has required endoscopy. She continues to be seen by speech, occupational, and physical therapies with neurodevelopmental milestones approximated most closely to 6 months of age.

Discussion

HHT rarely presents in the newborn period but is likely also significantly underreported due to variable penetrance and many patients with only minor symptoms until later ages.[6] International consensus diagnostic criteria have been developed based on the following four findings:

1. Spontaneous and recurrent epistaxis
2. Multiple mucocutaneous telangiectasia
3. Visceral involvement with AVM
4. Family history of HHT

Patients can be classified as 'definite', 'suspected,' or 'unlikely' when more than two, two, or less than two diagnostic criteria are present, respectively.[7] Given that symptoms tend to develop with age, current clinical diagnostic criteria likely underestimate the presence of HHT in children which can have grave consequences if AVMs go untreated.[8] Thus, it is important to consider HHT in children, even newborns, with any significant bleeding of unclear etiology.

This is the first case report detailing significant gastrointestinal bleeding in the newborn period due to HHT. An extensive literature search demonstrated that prior to this report, the earliest mention of this manifestation was noted in a patient with severe HHT phenotype at 10 months of age.[2] While complications from HHT in adults have been extensively reported, neonatal complications remain limited to case reports. These include cerebral and pulmonary hemorrhages, hepatic AVMs resulting in high-output congestive heart failure, and a case describing a 1-month-old with catastrophic acute neurological deterioration in the context of a spinal arteriovenous fistula.[1,3–5,9]

Pathogenesis of HHT is incompletely understood as to whether the lesions are congenital or acquired with time. For example, traditional dogma teaches cerebral AVMs likely form during weeks 4 to 8 of embryonic development secondary to trauma, infection, radiation therapy, or congenital malformation. However, recent advancements in diagnostic techniques, such as MRI, have led to reports of de novo cerebral AVMs postnatally.[10,11] Given that gastrointestinal manifestations of HHT develop with increasing age,[12] one might conclude that these lesions are acquired due to genetic susceptibility and environmental triggering factors throughout life. However, our patient's hematochezia beginning one day after birth would suggest otherwise.

HHT is an autosomal dominant, genetically heterogeneous disorder caused by mutations in one of multiple genes in the TGF-signaling pathway, including *ENG*, *ACVRL1*, *SMAD4*, *and GDF2* to date. Mutations in *ENG* and *ACVRL1* cause HHT1 (OMIM 187300) and HHT2 (OMIM 600376), respectively, which are detected in approximately 85% of cases of clinically suspected HHT. *SMAD4* mutations cause the combined juvenile polyposis/HHT (JP/HHT) syndrome (OMIM 175050) and *GDF2* mutations recently have been described in three individuals with HHT-like presentation. HHT displays age-related penetrance with increased manifestations developing over a lifetime which makes early recognition and diagnosis difficult, especially in neonates and young children without recognizable symptoms. Molecular testing should be recommended to all at-risk family members. Appropriate screening and surveillance should be provided to the asymptomatic patient, even during the pre-/perinatal period to potentially improve the outcome.

HHT has significant phenotypic variability, wherein the number and location of telangiectasias and AVMs vary widely between individuals even within the same family. By reviewing the reported symptomatic neonatal HHT cases, intracerebral and pulmonary AVMs are mostly attributed to ENG mutations and *ACVRL1* mutations account for most symptomatic hepatic AVMs. However, data suggest that no absolute genotype–phenotype correlations exist between clinical phenotypes and specific pathogenic variants.[13] In our case here, multiple family members are variably affected by HHT but none of them had manifestations in the neonatal period. The considerable intrafamilial variability suggests effects of genetic or environmental modifiers on the HHT phenotype.

This case highlights prenatal and perinatal considerations for parents with personal or family history of HHT given its varying degree of penetrance. With advances in prenatal imaging, including sonography and MRI, detection of vascular dysplasia in utero may suggest the diagnosis of HHT. Amniocentesis or chorionic villous sampling could yield a definitive genetic diagnosis. Knowledge of such while in utero could have implications for delivery. Given the accumulating case reports of neonatal complications from HHT, consideration for delivery near a more tertiary neonatal center should be discussed. Avoidance of a prolonged or difficult labor, as occurred in this case, should also be considered if significant fetal AVMs are suspected. While incidence of birth defects, prematurity, low birthweight, or miscarriage do not seem to be increased above the general population, prenatal anomaly scanning focusing on the detection of AVMs with special emphasis to crucial organs, such as the lungs, liver, or brain, should be considered as the first step toward managing improved neonatal outcome for HHT.[3,14]

Contributors' Statement Page

Drs. M.M. and H.L. initially managed the care of the patient and began a thorough literature review, drafted the initial manuscript, and reviewed and revisited the manuscript.

Drs. K.P. C.S. managed care of the patient for a significant portion of her hospital stay in the NICU and contributed to the clinical course section of the manuscript.

Dr. A.A. reviewed the patient's radiographs and provided key images in addition to review of the manuscript.

Dr. J.M. managed the patient's surgical care and contributed to the clinical course section of the manuscript.

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Conflict of Interest

None of the authors have conflicts of interest to disclose.

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