Symptomatic Liver Involvement in Neonatal Hereditary Hemorrhagic Telangiectasia

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KEY WORDS

hereditary hemorrhagic telangiectasia, HHT, genetics, Rendu-Osler-Weber, arteriovenous malformations, visceral, liver, children

ABBREVIATIONS

HHT—hereditary hemorrhagic telangiectasia

CHF—congestive heart failure

AVM—arteriovenous malformation

ALK1—activin receptor-like kinase 1

Dr Al-Saleh contributed as a first author by performing a detailed review of the cases and writing the manuscript; Dr John contributed as a co-author by reviewing the images and interventions for the cases and reviewing the manuscript; Dr Letarte contributed as a co-author by reviewing the genetic tests and the cases and reviewing the manuscript; Dr Faughnan contributed as a co-author by reviewing the families of these case-patients and reviewing the manuscript; Dr Belik contributed as a co-author by reviewing the neonatal history of the case-patients and reviewing the manuscript; and Dr Ratjen contributed as a senior author by performing a detailed review of the cases and drafting the manuscript.

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abstract

High-flow hepatic vascular anomalies with arteriovenous shunting commonly manifest during the neonatal period with signs and symptoms of congestive heart failure, but to our knowledge, they have never been described in patients with hereditary hemorrhagic telangiectasia (HHT). We report here our experience with 3 patients with hepatic arteriovenous malformations (AVMs) who presented with symptoms of high-output congestive heart failure during the neonatal period and were subsequently diagnosed with HHT. Imaging showed large hyper-vascular lesions and multiple hepatic arteriovenous shunts that differentiated these lesions from liver hemangiomas. Transcatheter embolization was performed in all cases. One infant died of sepsis shortly after embolization; follow-up at the age of 2.5 years of the surviving infants revealed involution of the vascular lesions and no evidence of symptom recurrence. We conclude that severe symptoms related to hepatic AVMs in HHT can occur in the neonatal period and that HHT should therefore be included in the differential diagnosis of symptomatic neonatal hepatic vascular malformations. Imaging plays a key role in differentiating hepatic AVMs from hemangiomas, because the latter require additional pharmacologic treatments. Early transcatheter embolization seems to be effective, but long-term outcomes still need to be assessed. *Pediatrics* 2011;127:e1615–e1620

Hepatic vascular malformations can manifest during the neonatal period,¹ and high-output congestive heart failure (CHF) is a commonly reported clinical presentation. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder associated with vascular malformations of the liver, but there have been no reported pediatric cases of HHT with liver involvement presenting with CHF. Therefore, HHT is usually not considered a part of the differential diagnosis of symptomatic neonatal hepatic vascular malformations.

The aim of this case series is to review our experience of pediatric patients with HHT who presented with symptomatic hepatic arteriovenous malformations (AVMs) at the Hospital for Sick Children in Toronto, Ontario, Canada.

CASE REPORTS

Case 1

A term male infant was intubated shortly after birth because of respiratory distress, CHF, and hypoxemia that required ventilatory and inotropic support. Echocardiography on day 1 of life revealed normal cardiac anatomy but dilatation of the inferior vena cava, right atrium, and right ventricle, right-ventricular hypertrophy, and elevated right-atrial pressure. An abdominal ultrasound revealed a large hypervascular area in the right lobe of the liver ($7.0 \times 3.3 \times 5.0$ cm) with arteriovenous shunting between branches of the right hepatic artery and hepatic veins, both of which were dilated (Fig 1 A and B). MRI of the liver confirmed these findings (Fig 1C). Angiography on day 7 revealed large hepatic AVMs with numerous shunts draining into hepatic veins (Fig 2 A and B) and systemic arterial supply from hepatic and extra-hepatic arteries (right-lumbar, gastroduodenal, right-phrenic, superior mesenteric, and left gastric arteries).

FIGURE 1

Imaging at presentation before embolization. A and B, Ultrasound. An enlarged hepatic artery (open arrow) arising from the aorta (asterisk) is shown; multiple intrahepatic vascular channels (single arrows) represent the arteriovenous shunts draining into enlarged hepatic veins (arrowheads). The liver parenchyma is otherwise normal. C, MRI. A T1-weighted sequence (no contrast) reveals abnormal vascularity in the liver with enlarged right and middle hepatic veins (asterisk). The region of reduced signal in the right liver (arrow) is caused by abnormal perfusion as a result of the AV shunting. There was no enhancement of this region after contrast.

FIGURE 2

Catheter angiogram. A, The catheter was placed in the aorta from the left brachial artery (arrow). The preembolization angiogram shows rapid shunting through the liver from an enlarged hepatic artery into an enlarged hepatic vein (asterisk). The aorta above the hepatic artery is significantly larger than the one below the hepatic artery because of the high flow through the intrahepatic shunts. B, Reduced flow through the shunts on a repeat aortogram after embolization.

Transcatheter embolization was performed during the same procedure by using a co-axial technique. Cyanoacry-

late glue mixed with lipiodol was used as the embolic agent and delivered as close to the arteriovenous shunts as

FIGURE 3

Catheter embolization. A coaxial catheter system was used with an outer 4F catheter advanced into the hepatic artery from the left brachial artery. An inner microcatheter was advanced through the outer catheter and used for embolization. A, Contrast injection via the inner microcatheter into the shunts. B, The “glue cast” throughout the shunts after injection of cyanoacrylate glue plus lipiodol via the microcatheter.

possible by using a microcatheter placed into the right-hepatic, gastroduodenal, right-lumbar, left gastric, and peripheral branches of the superior mesenteric arteries (Fig 3 A and B). After embolization, there was excellent response, and inotropic support was quickly weaned; there was no further CHF. As a result of embolization of a small superior mesenteric artery branch, the course was complicated by perforation of the terminal ileum and sepsis. The patient improved after

ileal resection, ileostomy, and broad-spectrum antibiotics, and ventilatory support was weaned. After embolization, a liver ultrasound revealed marked decrease in both lesions' size and vascularity and no shunting, and echocardiography revealed normalization of cardiac dilatation. Ultrasound of the liver at the age of 2.5 years revealed no evidence of liver AVMs (Fig 4). Genetic testing confirmed that the patient is heterozygous for a previously reported disease-causing muta-

FIGURE 4

Liver ultrasound 2.5 years after embolization. No evidence of hepatic shunts can be seen. No abnormal liver vascularity is evident, and the hepatic veins are normal.

tion (exon 3:c.101G→A;p.Cys34Tyr) in the activin receptor-like kinase 1 (*ALK1*) gene.³ The infant had no history of cutaneous telangiectasia or epistaxis. Screening tests for other visceral AVMs resulted in normal chest computed tomography, contrast echocardiography, and cerebral MRI. Exploration of the family history revealed that the mother had recurrent epistaxis, cutaneous telangiectasia, and small pulmonary AVMs; genetic testing confirmed that she carried the same *ALK1* mutation.

Case 2

A term male infant was transferred to the NICU on day 2 of life because of poor feeding and irregular heart rate. Echocardiography revealed normal cardiac anatomy but evidence of dilated hepatic veins, right atrium, left atrium, and right ventricle and elevated right-ventricular pressures. Ultrasound, computed tomography, and MRI of the liver revealed a large hypervascular area in the right lobe of the liver ($4.6 \times 3.4 \times 3.0$ cm) with dilatation of hepatic and extrahepatic vessels. The course was complicated by thrombocytopenia and acute renal failure that improved after 48 hours. Doppler ultrasound revealed poor arterial flow to both kidneys and increased aortic blood flow into the celiac axis. Angiography on day 8 of life revealed large liver AVMs with multiple shunts from branches of both the common hepatic artery and pancreaticoduodenal branches of the superior mesenteric artery shunting into draining hepatic veins. Transcatheter embolization was performed by using cyanoacrylate glue mixed with lipiodol delivered into the feeding vessels of the hepatic AVMs. There was slight improvement in his cardiac status. However, 36 hours after embolization, the infant's condition deteriorated, and he showed signs of sepsis, coagulopathy, and lactic acidosis. Results of a blood

culture were positive for *Escherichia coli*. Despite maximal cardiorespiratory support and broad-spectrum antibiotics, the patient died on day 10 of life.

Further investigations of the family history revealed that the mother had recurrent epistaxis, cutaneous telangiectasia, and small pulmonary AVMs. The maternal grandmother had recurrent epistaxis, cutaneous telangiectases, and bleeding from gastrointestinal telangiectasia. The mother's genetic testing revealed that she is heterozygous for a previously unreported *ALK1* missense mutation (exon 3: c.136T→G;p.Cys46Gly).

Case 3

A female term infant, the sibling of the boy in case 2, was diagnosed with a hepatic vascular anomaly and cardiomegaly by antenatal ultrasound. She was intubated after birth for respiratory distress and required inotropic support. Echocardiography on day 1 of life revealed normal cardiac anatomy but a dilated right atrium, right-ventricular hypertrophy, and elevated right-ventricular pressures. Postnatal ultrasound and computed tomography revealed a large hypervascular area, mainly in the right liver ($3.1 \times 4.1 \times 2.7$ cm), with arteriovenous shunting between dilated hepatic arteries and veins. Angiography on day 9 revealed a large hepatic AVM with multiple arteriovenous shunts (similar to those in cases 1 and 2). Transcatheter embolization was performed during the same procedure by using a co-axial technique, and the embolic agent was delivered into the feeding vessels of the hepatic AVM (similar to case 1). Inotropes were weaned during the procedure and stopped soon afterward along with weaning of the ventilatory support. A postembolization liver ultrasound revealed a decrease in AVM size, and echocardiography revealed

normalization of cardiac size. A liver ultrasound at the age of 2.5 years revealed no evidence of hepatic AVMs. Genetic testing of the patient confirmed heterozygosity for the same familial *ALK1* mutation. She showed no evidence of telangiectasia or epistaxis, and the results of screening tests for other visceral AVMs were normal.

DISCUSSION

To our knowledge, this is the first report of neonatal presentation of HHT-related hepatic AVMs. These cases were associated with missense mutations in the *ALK1* gene (one of which was novel), which are associated more commonly with liver AVMs.² The infants in all of these cases presented during the first 24 hours of life with high-output CHF caused by intrahepatic arteriovenous shunting similar to that reported for symptomatic adult patients.^{4,5} The aim of the embolization procedure was to close a significant number of the shunts to improve cardiac status without necessarily closing all shunts. These single-embolization procedures resulted in significant and immediate improvement in the condition of the 2 surviving infants; it was surprising that the AVMs demonstrated involution over time in both cases.

HHT is characterized by mucocutaneous telangiectases, recurrent epistaxis, and visceral AVMs.⁶ Hepatic vascular malformations have been reported for 32% to 78% of adult patients with HHT^{7–13} and 47% of pediatric patients with HHT¹⁴ when screened systematically. Symptoms occur in only 8% of adult patients with HHT with hepatic vascular malformations^{9,15} and include high-output CHF, portal hypertension, or biliary necrosis.^{4,16–18} Reports of symptomatic hepatic vascular malformations in pediatric patients with HHT are scarce; to date, only 2 cases have been reported.^{19,20} The chil-

dren in both of these cases were older and differed in presentation. The first case involved a 15-year-old boy with hepatic AVMs complicated by portal hypertension without CHF.²¹ The second case involved a 21-month-old child who presented with gastrointestinal bleeding thought to be secondary to hemorrhage from the hepatic vascular malformation into the biliary tract.²² This child's symptoms resolved spontaneously without intervention.

Pediatric hepatic vascular anomalies are categorized as vascular tumors (mainly hemangiomas) or high- and low-flow vascular malformations. The majority of symptomatic pediatric hepatic vascular anomalies manifest during the neonatal period and early infancy^{1,21–23}; liver hemangiomas are the predominant type. Commonly reported clinical presentations include CHF, coagulopathy, and/or hepatomegaly.^{1,21–29} Our cases indicate that HHT-related hepatic vascular malformations can occur in the neonatal period contrary to recently published guidelines that suggest presentation only in late adulthood.³⁰ It is interesting to note that involvement of lung vasculature in infants with hepatic vascular anomalies has been reported previously,^{21,24,27,29} and hepatic AVMs have been described in neonates with liver vascular anomalies.^{24,28,31–34} This raises the suspicion that HHT may actually be underdiagnosed and missed in some cases. Detailed family history and genetic testing should be considered for any infant or child with hepatic vascular malformations (specifically AVMs). However, we did not assess an unselected series of neonatal hepatic AVM cases; therefore, we cannot estimate the overall prevalence of HHT.

Treatment options for liver involvement in adult HHT include surgical arterial ligation, arterial embolization, and liver transplantation. Although he-

patic embolization is effective in improving CHF, the effect is transient, symptoms generally recur,¹⁶ and the mortality rate from embolization has been high. It is unclear whether the death in our small series of patients was related to the embolization procedure secondary to intestinal perforation, but the 2 surviving patients rapidly improved after the embolization procedure. To our knowledge, single-embolization procedures that rescue

infants from life-threatening hepatic AVMs have not been described previously. Factors that potentially affect survival could include differences in embolization technique, use of prophylactic antibiotics, and timing of the intervention. The 2 surviving patients were followed for more than 2 years. There has been no recurrence of their symptoms but, rather, a progressive involution of the hepatic AVM; therefore, repeated interventions were not

required. Longer-term follow-up will clarify the effect of early therapy in this age group.

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