Novel presentation of factor V Leiden mutation in a neonate with umbilical vein varix

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The case

A small, isolated umbilical vein varix was found on a fetal ultrasound at 27 weeks gestation prompting the obstetrical team to perform weekly monitoring scans. A fetal ultrasound at 32 weeks and 2 days gestation revealed a significant sudden increase in the diameter of the umbilical vein with turbulent and bidirectional flow. Mother was subsequently admitted for continuous fetal heart rate monitoring and a course of betamethasone to enhance fetal lung maturity. Delivery of a male infant was accomplished 2 days later by emergency cesarean delivery for prolonged fetal bradycardia. Apgar scores were 4 and 9 at 1 and 5 minutes respectively with the infant requiring a short interval of positive-pressure ventilation due to apnea and low heart rate. The infant was given vitamin K shortly after delivery and transferred to the neonatal intensive care unit (NICU) for further care. Admission hemoglobin was 25.5 g/dL; white blood cell count (WBC) count was 8.6 x 10^3/µL; mean corpuscular volume (MCV) was 106.4 um^3; and platelet count was 280 x 10^3/µL. Central line access was not required throughout the hospitalization.

An abdominal ultrasound was obtained on day of life (DOL) 3 due to the history of an umbilical vein varix and revealed a thrombosed umbilical vein with extension of the thrombus partially into the left portal vein. An echocardiogram, performed on DOL 4 to rule out emboli, showed only an age-appropriate small patent ductus arteriosus and patent foramen ovale. Based

on the asymptomatic nature of the thrombus and benign echocardiogram, the decision was made to monitor clinically and with periodic abdominal ultrasounds. The baby was not treated with anticoagulation medications.

Family history was notable for a previous early pregnancy loss in the mother. There was no known history of blood clots, pulmonary emboli, early death, or stroke on either parent's side. A pediatric hematologist was consulted and recommended obtaining these basic thrombophilia labs from both the mother and father: factor V Leiden genetic testing, factor II Leiden testing, protein C activity and antigen levels, protein S activity and antigen levels, lupus anticoagulant, and anticardiolipin antibodies. Maternal labs returned normal, but the father was found to be heterozygous for both factor II (prothrombin) gene mutation and factor V Leiden mutation. The baby tested negative for factor II mutation but was found to be heterozygous for factor V Leiden with the same paternal mutation, R506Q.

Head ultrasounds, performed as routine for gestational age, were normal at both DOL 7 and prior to discharge. The abdominal ultrasound was repeated on DOL 10 and showed residual thrombus in the left portal vein with slightly increased flow peripheral to the thrombus. The thrombus within the umbilical vein varix remained stable. Abdominal ultrasound was again obtained 1 month after birth and showed persistent but improved left portal vein and umbilical vein thromboses. At that time, labs showed a hemoglobin of 10.4 g/dL; WBC count of 8.5 x 10^3/µL; MCV of 94.4 um^3; and platelet count of 449 x 10^3/µL. The baby was discharged home on DOL 42 with follow-up appointments arranged with Pediatric Hematology in addition to routine follow-up with primary care and NICU providers.

Background

Factor V Leiden deficiency is a genetic coagulopathic condition that prevents protein C from exerting anticoagulation effects onto the factor V protein of the coagulation cascade.[1,2] Individuals with this condition are at increased risk for venous thromboembolism. Diagnostic clues in the pediatric population include family history of deep vein thrombosis, pulmonary embolism, stroke, miscarriage, and/or early death due to the autosomal dominant inheritance pattern.[3] Factor V Leiden-associated thromboses in neonates are rare, but when they do occur, they most often involve the renal vein or a vessel manipulated by an indwelling catheter.[4-7] We present a case of a neonate with an in utero diagnosis of an umbilical vein varix and subsequent finding of postnatal thromboses of the umbilical and portal veins. Further workup revealed a potentially clinically relevant factor V Leiden mutation abnormality in both a previously undiagnosed parent as well as the newborn infant.

Discussion

The overall incidence of thrombosis in neonates ranges from 3 to 5 cases per 100,000 live births.[5,8,9] Common risk factors for thrombosis in this population include central vascular catheters, infants of diabetic mothers, sepsis, small for gestational age, congenital heart disease, metabolic disorders, nephrotic syndrome, maternal antiphospholipid syndrome, elevated hematocrit, surgery, and prothrombotic disorders.[6,7,10-12] One multicenter study found that 89% of thromboses in neonates were associated with an intravascular catheter.[5] Another study by Morag et al. specifically investigated portal vein thrombosis in neonates and found that 73% of the infants had an umbilical venous catheter which was often not in an optimal position.[13] The neonate described above did not have an intravascular catheter placed during hospitalization nor any other known risk factors at birth. Parental coagulation workup, and the new discovery of

paternal prothrombotic disorder, was accomplished after fetal finding of umbilical varix and subsequent diagnosis of umbilical and portal vein thromboses. Factor V Leiden mutation has reportedly been associated with thromboembolism in newborns and children.[7,10] One study investigating the incidence of prothrombotic risk factors in infancy found that 16% of children with portal vein thrombosis had factor V 1691GA mutation, with one infant also presenting with heterozygous prothrombin G20210A mutation.[14] Despite the later findings of factor V Leiden mutation, portal vein thrombosis diagnosis in the absence of a central venous catheter in newborns is still rare.

Close maternal observation is necessitated when an umbilical vein varix is discovered, and the obstetrical team may elect to induce labor with any increased risk of intrauterine fetal demise.[15] In this case, an umbilical vein varix discovered on fetal ultrasound was the initial presentation of the thrombus, and serial ultrasounds were performed to closely follow the fetal status. Cesarean delivery was accomplished after a significant sudden increase in the diameter of the clot was discovered and fetal distress ensued.

Postnatal follow-up ultrasound should be performed when an umbilical vein varix is noted in utero. Any finding of an anatomical abnormality of umbilical vein anastomosis with the extra-hepatic portal system may place the newborn at increased risk for thrombosis.[16] A previous case report described a neonate with an umbilical vein thrombosis and associated portal vein thrombosis at birth, however, the thrombophilia panel sent from the baby was negative.[17] Neonatal ultrasound in this infant showed no anatomic abnormalities. However, thrombosis of the umbilical vein with extension into the portal venous system was found, and an abnormality was discovered on thrombophilia workup. The treatment team, in this case, decided against anticoagulation therapy due to the asymptomatic nature of the thrombus, thrombus location, and

the risks associated with anticoagulation. Instead, serial ultrasounds were performed and showed no further thrombus extension, an eventual decrease in thrombus size, and significant improvement of blood flow.

Neonates presenting with thrombus formation may be at increased risk for inherited thrombophilia disorders. It is therefore prudent to consider obtaining a thrombophilia panel on both parents as part of the diagnostic work-up. In our case, prior history of fetal demise was obtained, however, neither parent had a history of thrombosis. The father was found to be heterozygous for both factor II (prothrombin) gene mutation and factor V Leiden mutation, and subsequent investigation of the infant discovered the same factor V Leiden R506Q mutation. Close follow-up with a pediatric hematologist was arranged, and discharge parental counseling emphasized the need to properly monitor hydration status as well as observe for any abdominal distension, swelling of extremities, shortness of breath, or neurologic changes.

Discovery of potential sources of clotting abnormalities in a newborn should also necessitate further parental discussion delineating the increased risk of an inherited thrombophilia with future pregnancies. Furthermore, as in this case, workup of unusual presentations of fetal and neonatal thrombosis should trigger investigation of the parents for previously undiagnosed and potentially life-altering findings of their own thrombophilia disorders with appropriate outpatient hematology follow-up.

Conclusions

An abdominal ultrasound should be performed within the first few days of life in any neonate presenting with a fetal diagnosis of umbilical vein varix. Thrombophilia work-up should

be accomplished for both parents and infant to evaluate for the presence of a prothrombotic disorder if a thrombus is found.

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