Spontaneous Intracranial Hemorrhage with Resulting Intracranial Hypertension in a 3 Month-Old Infant Presenting With Severe Coagulopathy

Moderators: Todd J. Kilbaugh M.D., John McCloskey M.D.

Institution: The Children’s Hospital of Philadelphia

Objectives

- Understand risks of induction in an infant with intracranial hemorrhage and intracranial hypertension
- Understand treatment for intracranial hypertension infants and children
- Understand issues associated with central venous catheter placement and arterial line placement with massive coagulopathy
- Understand advantages and risks of Vitamin K replacement
- Understand the risks and benefits of recombinant factor VIIa therapy in life threatening hemorrhage and intracranial hemorrhage in an infant and child
- Understand the pathophysiology of massive transfusion

Case Description

A 3 month-old female presented to the emergency room with decreased activity and oral intake for the past 8 hours. The infant was previously healthy, except for diagnosis of breast milk jaundice by her primary pediatrician. With attempted placement of an antecubital 24-gauge IV, the patient developed a large hematoma (5 cm x 5 cm) almost immediately. A second IV was placed in the hand and labs were sent for CBC, electrolytes, and a coagulation panel secondary to the hematoma. On re-examination the patient was noted to have a slightly enlarged liver and abnormal coagulation studies (PT>125, PTT 153). 30 minutes after arrival to the emergency room the patient became completely unresponsive with anisocoria and a fixed right pupil unresponsive to light.

Questions:

What are the next steps in this patient's management?

Case Progression:

An emergent Head CT was obtained and was significant for: left parietal hematoma with overlying subarachnoid hemorrhage, and a large overlying left holohemispheric subdural hematoma, life-threatening midline shift and
uncal/transstentorial herniation. The patient was emergently packaged and transported to the operating room for craniotomy and subdural drainage. The patient physical exam is deteriorating: Heart rate of 80, Blood pressure 110/45, obtunded, minimally responsive to painful stimuli.

Pertinent laboratory values revealed: prothrombin time (PT) that was greater than 125 seconds and a partial thromboplastin time (PTT) of 153 seconds. Additionally, an elevated total bilirubin of 9.2 milligrams (mg)/deciliter (dL), a conjugated bilirubin of 4.6 mg/dL, unconjugated bilirubin of 2.1 mg/dL, an elevated gamma-glutyl transferase of 456 units (U)/liter (L), and an alkaline phosphatase of 912 U/L. All other hematologic lab values including hemoglobin, hematocrit and platelet count were initially normal for age.

Additional history revealed a 1 month history of intermittent jaundice that was undergoing work-up by her primary care physician. Labs had been drawn by her pediatrician several days prior to presentation but had clotted. An abdominal ultrasound was completed the day prior and was significant for mild hepatosplenomegaly, a contracted gallbladder without biliary dilatation, and a 2 cm right suprarenal lesion of unknown etiology.

Questions:

On arrival from radiology what would be your initial steps in managing this patient with impending herniation? How would you develop an emergent anesthetic plan? What intraoperative monitoring would you require? How would you place these devices? What blood products would you want available? Would insist on using any hemostatic medications prior to induction and incision? If so what, and what dosing regimen? How would you design your induction and maintenance of your anesthetic?

Intraoperative Progression:

On presentation to the operating room the patient’s vital signs were as followed: HR 100, Blood pressure 105/60. Following induction of anesthesia and intubation, a radial arterial catheter and a femoral central venous catheter was placed under ultrasound guidance. Pre-operatively, she was transfused 15 milliliters (mL)/kilogram (Kg) fresh frozen plasma (FFP) for significant coagulopathy and bleeding as well as 2 grams of mannitol to treat increased intracranial pressure. After placement of the femoral catheter, copious bleeding was noted at the insertion site. Despite pressure applied to the site of bleeding as well as a total of 70 mL/Kg of FFP, 10 mL/Kg packed red blood cells (RBC), and 2mg of intravenous (IV) vitamin K her bleeding still persisted. Due to persistent femoral bleeding and significant concern for uncontrollable bleeding with initiation of the craniotomy, two 40 microgram (mcg)/Kg doses of recombinant factor VII
(rFVIIa) were given 5 minutes apart still without slowing of the hemorrhage. A third dose of rFVIIa of 40 mcg/Kg was given which finally achieved hemostasis. Intraoperative ultrasound showed not intra-abdominal bleeding. Hemoglobin then stabilized at 10 grams (g)/dL, with an international normalized ratio (INR) of 0.67 documented approximately 1 hour after the administration of the last dose recombinant factor VII. A left parietal craniotomy was performed and a large clot was evacuated from her cranial vault, with no further active bleeding visualized by the neurosurgical team. Because hemostasis was achieved, her bone plate was replaced and she was transferred back to the ICU.

Questions:

Would you have placed a central venous catheter? Is hypertonic saline and better choice for intracranial hypertension in this patient? What is the mechanism of rVIIa as a hemostatic agent? What would you choose as starting dose if you were going to choose rVIIa? What is a max dose? Side effects of rVIIa? Should Vitamin K be administered? Can it be administered intravenously/does it make a difference? Would you have been uncomfortable with bone flap replaced?

Post-Operative Course:

She remained hemodynamically stable post-operatively. She continued receiving daily vitamin K for correction of her coagulopathy and was transfused FFP only once more to maintain an INR of less than 1.4. She had no further bleeding and all clinical findings consistent with increased intracranial hypertension resolved. Repeat abdominal ultrasound on post-operative day 2 showed similar findings to her earlier study done prior to admission with resolution of the previously seen suprarenal lesion and no evidence of portal venous thrombosis. However a third sonogram of the abdomen on POD 16 showed concern for portal venous thrombosis that was later confirmed with magnetic resonance venography (MRV) of the abdomen. A liver biopsy was performed, which was consistent with biliary cirrhosis and a diagnosis of biliary atresia.

Discussion:

BA can be a rare, devastating condition resulting in hepatic failure, and ultimately death. In the United States BA is the leading cause of mortality associated with liver failure and is the most common indication for liver transplantation in children. Often presentation occurs early in infancy when there is the best chance for successful therapy. However, when diagnosed after 60 to 70 days of age the likelihood of a successful Kasai portoenterostomy decreases and mortality rates rise. Secondary complications including severe bleeding due to malabsorption of vitamin K are more likely to occur in late-presenting cases.
Our case is unique for several different reasons. First, intracranial hemorrhage (ICH) as a presenting sign of BA is incredibly rare, but potentially fatal. Secondly, we have not identified any cases published to date in which infants have presented with this picture over 80 days of life.

Houwen et. al. in 1987 reported a case series of 4 patients in The Netherlands who presented with bleeding as a first sign of biliary atresia. Of these 4 patients, 1 presented with ICH. Unlike our patient the baby in their case series was not given vitamin K at birth and was only 1 month of age at the time of presentation.

Akiyama et. al. in 2006 published a case series of 15 infants in Japan who presented with ICH as a complication of BA. While none of these 15 patients presented over the age of 79 days the majority of their patients were over 30 days. This is important because we usually think of BA as a disease of the newborn, but atypical presentations can occur even in infants over 2 months of age. A delay in diagnosis can be devastating especially in a condition like BA where early recognition and treatment leads to improved outcomes. Therefore any infant presenting with an unexplained secondary vitamin K deficiency with bleeding should be evaluated for BA.

The third reason that our case is unique is that this is the first time that we are aware of in which a patient with BA complicated by ICH was treated effectively with recombinant factor VIIa in addition to Vitamin K. We used this medication in an attempt to stop the life-threatening bleeding that occurred in our patient. Her evolving ICH prevented definitive intervention by the neurosurgical team and increasing her risk for brain herniation and death. In our case, recombinant factor VIIa was an effective immediate hemostatic agent, stabilizing her impending herniation allowing the craniotomy and evacuation to proceed safely.

Recombinant factor VIIa (rFVIIa) is FDA approved for hemostasis in hemophilia patients with antibodies against factor VIII or IX and patients with congenital factor VII deficiency. However, a recently published retrospective analysis of multiple institutions found that 90% of rFVIIa usage was for off-label conditions. There are several studies that have evaluated off-label use of rFVIIa in the pediatric population, all of which show improvement in bleeding. However these studies are limited to small study populations, retrospective analyses, and widely varying doses.

Jen et al. evaluated 32 non-hemophiliac, critically-ill patients that received rFVIIa in the setting of acute hemorrhage and showed decreased RBC, platelet, and cryoprecipitate requirements. Four patients developed thrombus, however, but the dose and quantity of doses were not related to thrombus formation. Recently, a multicenter cohort study reviewing cases of off-label use of rFVIIa was published by Witmer et al. 3764 patients 18 years and younger were evaluated and they found that thrombotic events occurred in 10.9% of the population, with 45% of these being in patients under 1 years of age. However,
In 2009, a Cochrane review evaluated six randomized control trials in adults with ICH and found rFVIIa did not significantly decrease mortality within 90 days of the ICH.\(^7\)

While data do not consistently show mortality benefit in bleeding patients who receive rFVIIa and there are risks and side-effects to receiving this medication for off-label uses, we maintain that in life-threatening bleeding situations rFVIIa can be successfully used to stop hemorrhage and allow for definitive treatment. Our patient did go on to develop thrombi (at the site of her femoral venous catheter as well as a portal venous thrombus), however it is unclear if the use of fVIIa was related. The portal venous thrombus was not seen until almost 3 weeks after administration despite earlier ultrasound surveillance. Further randomized controlled trials of rFVIIa in pediatrics are needed to evaluate morbidity, mortality, and assess thrombotic risk in the patient with acute hemorrhage.

References:

Figure 1: