Unexpected coagulopathy in a 2 month old undergoing elective craniosynostosis repair
“Fact or Fiction”?

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Goals
1. To identify a rational “routine” pre-operative evaluation for the infant undergoing craniosynostosis repair
2. To describe the differential diagnosis of abnormal coagulation studies and what further workup may be needed
3. To identify the key peri-operative anesthetic considerations in the pediatric patient with congenital coagulopathy

Case
An otherwise healthy 2 month old, full-term female presents to same-day care on a Monday for elective sagittal strip craniectomy for craniosynostosis repair. The case has been moved to your room secondary to a Level 1 trauma. As you review her history, you observe her pre-operative labs from three days prior (Friday) include a prothrombin time of 29.3 seconds, International Normalized Ratio (INR) of 2.6, normal activated partial thromboplastin time (aPTT), hemoglobin of 10.3, and a platelet count of 358,000. A type and cross for 2 units of blood was also sent at that time. On careful history, there is no family history of bleeding disorders and no clinical signs of bleeding in the infant since birth. The family has traveled a significant distance and made special arrangements to have the surgery done on this specific date. The pediatric neurosurgical team asks you for your recommendation about whether or not to proceed with the case and how to manage the elevated PT and INR.

Questions:
1. What is craniosynostosis? What are the most common forms and the associated morbidities associated with these various forms?
2. What is a “routine” pre-operative evaluation in a healthy infant undergoing sagittal craniosynostosis repair? Should labs be drawn? What labs should be included?
3. How are the PT and INR measured in the laboratory? What are the chances this is an isolated, spurious lab value given this is an apparently healthy child with no bleeding history?

4. What are normal values for coagulation studies in a 2 month old infant? At what age after birth are values expected to be the same as in an adult?

5. What is the differential diagnosis of elevated PT and INR? What further laboratory studies are needed?

6. How should this case be managed knowing that the patient has no history of bleeding but has an isolated abnormal lab value? Cancel the case and follow-up? Anesthetize and repeat lab prior to incision? Proceed with surgery and have blood products readily available?

7. If this child does have a coagulopathy without clinical signs or symptoms, what are the important anesthetic considerations for surgery in this patient? What blood products would correct this abnormality?

**Discussion**

Craniosynostosis is the result of premature fusion of one or more cranial sutures in an infant. The incidence of craniosynostosis is approximately 1 in 2100 children, and a proportion of these are associated with craniofacial syndromes. The most common syndromes include Apert’s and Crouzon’s syndrome. The most common form of non-syndromic craniosynostosis is sagittal craniosynostosis or scaphocephaly. Unrepaired craniosynostosis can lead to impaired brain growth, increased intracranial pressure, and severe craniofacial deformities. In order to achieve optimal surgical results, craniosynostosis repairs are done in the first year of life. Because of the nature of the repair, the patient’s young age and associated syndromes, these surgeries are associated with significant morbidity (8%) and mortality (1%) mostly secondary to the risk of massive blood loss. The most common is a sagittal strip craniectomy where the fused sagittal suture is resected. More recently the developments of the endoscopic techniques have minimized blood loss by avoiding significant surgical dissection and exposure.

The pre-operative assessment, as with any surgery, is crucial to safe anesthetic care of the child undergoing cranial vault surgery. In addition to a thorough evaluation by the surgical team, the pediatric anesthesiologist should evaluate the patient for important factors that may affect the patient during anesthesia and surgery. Patients with syndromic craniosynostosis can have abnormal airway anatomy and require a formulation of a detailed airway plan prior to induction should intubation issues arise. They are also associated with congenital heart disease.

Laboratory evaluation should at minimum include a preoperative type and cross in order to ascertain availability of crossmatched blood prior to incision. A pre-operative hematocrit, platelet count, and coagulation studies can be helpful in establishing a baseline prior to surgery, although these studies are normal in the vast majority of non-syndromic children undergoing repair. These labs are often difficult to obtain in young, chubby, awake and wriggling children. Regardless, the guardians should be counseled about the likelihood of transfusion during and/or after the surgery.

Unexpected abnormal laboratory results in the healthy infant prior to craniosynostosis repair pose an interesting dilemma. The likelihood of a falsely elevated prothrombin (PT)
or partial thromboplastin time (PTT) are no higher than the general population secondary to lab or collection error, when the initial sample is drawn through a fresh venous cannulation. Newborns, because of decreased liver function at birth and an intrinsic vitamin K deficiency, are known to have PT, PTT, and fibrinogen levels above the adult reference range, although the PT and fibrinogen has been demonstrated to return to normal levels within 7 days of life and the fibrinogen within 4 days of life. The PTT, however, can remain elevated beyond 20 days of life in some healthy infants. In addition, the high hematocrit of newborns can contribute to falsely elevated values secondary to a decreased anti-coagulant to blood ratio. In this patient, the significantly elevated PT and INR warrants further evaluation and follow-up, as this is an older infant with a low-normal hemoglobin, approaching her nadir. Although no bleeding history may seem reassuring, the patient may not be old enough to have a bleeding history.

The prothrombin time is most commonly measured using blood plasma. The blood is drawn into a test tube containing citrate, which acts as an anticoagulant by binding the calcium in the sample. The blood is mixed, and then centrifuged to separate blood cells from plasma. In newborns, whole blood is used. At 37 degrees Celsius, excess calcium is added to the plasma sample to reverse the effects of the citrate. An underfilled sample tube can result in excess citrate and lead to an incorrect value. Similarly, an overfilled tube can have the same result, which is why the amount of citrate in the tube needs to be fixed.

The prothrombin time is the time in seconds it takes this plasma to clot after addition of tissue factor (obtained from animals). Because different laboratories use tissue factors with differing sensitivities, the calculation of the INR was designed to create an international standard taking this into account.

Formulation of the differential diagnosis of elevated prothrombin time (PT) and INR requires a through understanding of the coagulation cascade.
Abnormalities in the tissue factor, or extrinsic pathway, affect the PT, whereas the contact activation, or intrinsic pathway, affects the aPTT. Any abnormalities in the common pathway will affect both the aPTT and PT. It should be noted that the strategy of workup for a prolonged PT and/or PTT in children is not the same as in adult patients because the quantity of the specimen is usually limited, and the prevalence of the lupus anticoagulant among children is lower than in adults.

The differential diagnosis of elevated PT/INR with a normal aPTT includes:

- Tissue factor (Extrinsic) Deficiency
  - Factor VII
- Warfarin or Rodenticide Ingestion
- Liver Dysfunction
- Vitamin K Deficiency

It is unlikely that this infant is taking warfarin or recently ingested rodenticide. This leaves extrinsic factor deficiency, liver dysfunction resulting in acquired factor deficiency or Vitamin K deficiency. Although infants are at risk for Vitamin K deficiency because a lack of gut flora resulting in intestinal malabsorption, this infant was born in a hospital and received routine Vitamin K prophylaxis at birth. Also, Vitamin K deficiency would result in deficiency in the other Vitamin K dependent factors, namely factors II, IX, and X. Further workup for these diagnoses is as follows:

**Extrinsic Factor Deficiency:** Factor VII activity level (resulted as a percentage)
Liver dysfunction: Comprehensive metabolic panel—evaluate for transaminase elevation, evidence of synthetic dysfunction (low albumin), increased bilirubin.

The complicating factor in this case is that factor levels are not immediately resulted, and require special handling in the hematology lab. On the other hand, the comprehensive metabolic panel is resulted immediately, and can be used to rule out any obvious liver dysfunction quickly.

Where to go from here?

This infant and her family have traveled a significant distance in order to have this surgery done on this specific day. The parents have made arrangements for childcare for their other children for the week that the patient is anticipated to be in the hospital. Delaying or canceling the surgery would be of significant monetary cost to the family and make it very difficult for the family to reschedule surgery for a future date. Unfortunately, there are no operating room times available for this lengthy elective surgery in the next four days.

Option 1 - Proceed: In proceeding with high-risk surgery, you are assuming that the PT and INR are spurious. As discussed above, this infant should have PT and INR levels within the normal adult reference range. We do not have details about the manner in which the blood was collected. Therefore, proceeding with the surgery could result in life-threatening bleeding that would be very difficult to control without knowing the specific cause. We cannot rule out liver dysfunction with the laboratories that were drawn in pre-op, or severe factor deficiency. For an elective surgery it is not prudent to proceed without confirmation of a normal PT value.

Option 2 - Draw labs in the same day care area: Repeating the coagulation profile with a fibrinogen as well as a comprehensive metabolic panel is an option, and awaiting the results prior to proceeding to the operating room. The challenge with this is performing a valid blood draw in an awake infant, which can be stressful for the infant and parents and difficult for the phlebotomist.

Option 3 - Anesthetize the patient and draw labs and await result prior to incision: Because of the likelihood that this is a spurious value, in a busy operating room environment, it might be beneficial to do the inhalational induction and initial preparation for surgery. Once the infant is induced, IV access is obtained assuming the surgery will be performed and a repeat coagulation profile and comprehensive metabolic panel are sent at that time. While the team awaits the result, the surgeons, scrub nurse, and anesthesiologists can proceed with preparation so that incision can be made upon receipt of a normal result. This option is not without risks—if the repeat value is still abnormal, then the child has undergone an anesthetic without any intervention (other than the lab draw), and as we know anesthesia is not without risk.

Option 4 - Cancel the case: The patient can be admitted to the floor for further evaluation and workup or sent home for further evaluation since she has no clinical signs. This has obvious downsides, since the family has traveled a significant distance and will have to return another day for the surgery and if there is an abnormality, it is in the patient’s best interest to identify it.
In our case we chose option 3 after discussion with the pediatric neurosurgeons. A mask inhalation induction was performed without event, and the infant was intubated. A peripheral IV catheter was placed and a “superstat” comprehensive metabolic panel (CMP), complete blood count (CBC) and PT, PTT and fibrinogen were sent. The CMP showed no signs of liver dysfunction and the CBC was unchanged from three days prior. The repeat value for the PT was 29 seconds, with an INR of 2.9. PTT and fibrinogen were normal. The surgery was canceled and the infant was extubated without any complication. She was admitted to the pediatric hematology service for further workup.

The hematology service workup included Factor II, V, VII, and X activity. After 12 hours the Factor VII activity level was reported as 5% (reference range 70-130%). A mixing study was negative for inhibitors. The infant was diagnosed with Factor VII deficiency.

**Factor VII Deficiency**

Inherited Factor VII deficiency is a rare autosomal recessive disorder, with an incidence of 1:500,000. Factor VII has a short half-life and is synthesized in the liver as one of the vitamin K-dependent coagulation factors. Activation of Factor VII (FVIIa) initiates coagulation in vivo, and binds with cofactor tissue factor (TF) in response to inflammation or injury. This bound complex then activates clotting factors VII, IX and X to begin the coagulation cascade.

Congenital factor VII deficiencies have a very high phenotypic variation, and there is an absence of clear-cut and consistent correlation between bleeding symptoms and factor VII levels. Often the patients may be asymptomatic or get diagnosed after surgery-related bleeding which is a possibility in this patient. Over 100 mutations, mostly missense mutations, have been identified in the Factor VII gene located on chromosome 13.

Most severe cases of factor VII deficiency are diagnosed during childhood, often during the first 6 months of life. In the infant, the most common bleeds occur in the gastrointestinal tract or CNS. Children under 5 years old present more frequently with spontaneous hemarthrosis. These children usually have FVII levels of more than 2%. The most common bleeding presentation in older children and adults involve easy bruising and mucosal bleeding, particularly epistaxis. Postoperative bleeding has been reported in association with 30% of Factor VII deficient patients undergoing surgical procedures, including procedures for which replacement therapy was administered. In addition, treatment with replacement therapy is associated with increased risk for thrombosis.

**Diagnosis**

As described above, the PT and INR are elevated, while the aPTT is always normal. A specific Factor VII assay is required for definitive diagnosis. To distinguish between factor VII deficiency and the presence of an inhibitor to factor VII, mixing studies are useful. PT testing is repeated using a 1:1 mixture of the patient's plasma and normal plasma. Normal plasma is a source of factor VII; therefore, when such a mixture
normalizes the prolonged PT, the patient likely has a deficiency of factor VII. When the mixture still results in a prolonged PT, an inhibitor to factor VII is probably present.

**Treatment**

Acute bleeding: Treatment of acute hemorrhage primarily consists of factor VII (FVII) replacement therapy. A level of more than 10% activity is usually hemostatic, but higher levels may be advisable in the event of a severe bleeding episode. Because of the short half-life of 3-4 hours, repeat treatment is usually necessary. Treatment alternatives include the following:

**Fresh frozen plasma** although inexpensive and readily available, requires large volumes to provide adequate Factor VII replacement and risks circulatory overload.

**Prothrombin complex concentrates** contain factors II, IX, and X in addition to FVII, and carries a risk of thrombogenic complications. These concentrates have undergone viral attenuation during manufacturing. Determining the appropriate dosage for treatment of FVII deficiency can be difficult.

**Factor VII concentrates** are purified plasma–derived preparations that have undergone a vapor-heat viral-inactivation process. At high doses, these concentrates carry a risk of thrombosis, likely because of other vitamin K-dependent factors (II, IX and X) that are present in significant concentrations.

**Recombinant activated FVII (rFVIIa)**, originally developed to treat patients with hemophilia and inhibitors, can be used at lower doses for patients with congenital FVII deficiency. Although very expensive, with increasing experience and evaluation of rFVIIa for treatment and prophylaxis in FVII deficiency, the benefits and safety profile in this setting are becoming clearer, particularly in the operating room setting.

<table>
<thead>
<tr>
<th>Materials</th>
<th>Potency (IU mL(^{-1}))</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP (VI)</td>
<td>1</td>
<td>Cheap; easily available</td>
<td>Limited effectiveness: unsuitable for surgery because of circulatory overload</td>
</tr>
<tr>
<td>PCC (VI)</td>
<td>5–10</td>
<td>Suitable for surgery</td>
<td>Conc. vit. K-dep. factors &gt; FVII and activated. Risk of thrombosis</td>
</tr>
<tr>
<td>pdFVII (VI)</td>
<td>20–40</td>
<td>Effective; suitable for surgery</td>
<td>Other vit. K-dep. Factors concentrations higher &gt; than FVII</td>
</tr>
</tbody>
</table>
rFVIIa >25 000 Effective; no risk of Cost per treatment: demanding
(Novoseven®) viral transmission

FFP, fresh frozen plasma; FVII, factor VII; PCC, prothrombin complex concentrates; pdFVII, plasma-derived factor VII; rFVIIa, recombinant activated factor VII; VI, virus inactivated.

**Peri-operative management of the infant with Factor VII deficiency**

After consultation with the hematology service, the infant was rescheduled for surgery and arrangements were made for administration of recombinant Factor VIIa (Novoseven®) at the time of induction and at least 15 minutes prior to incision. After discussion with the family, the pediatric neurosurgery team opted to pursue an endoscopic strip craniectomy to minimize blood loss given the congenital coagulopathy. The dosing for the first Novoseven® administration is 30 mcg/kg. Because of the known short half-life of Factor VII in vivo, the recombinant Factor VIIa must be redosed every 6 hours for 24-48 hours thereafter at the same dose. If there are any bleeding complications during the surgery despite pre-surgical prophylaxis, FFP would be the next intervention.

As with any child undergoing craniosynostosis repair, it is imperative that a type and cross for a minimum of 2 units be available for transfusion prior to incision so that it is available immediately when needed.

Our patient did well during the surgery, and received packed red cell transfusion of 10 cc/kg with an estimated blood loss of only 150 cc. No FFP was given, and her hemoglobin was stable intra-operatively. She was extubated in the operating room and transferred to the PICU where she continued to receive the Novoseven® per the hematology team’s recommendations. Her drain output from the surgical site was minimal, and she was discharged to the floor on post-op day #1. She was discharged to home with pediatric hematolgy follow-up and has had no bleeding complications four months post-surgery.

**References:**


