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Elevated prothrombin time on routine preoperative laboratory results in a healthy infant undergoing craniosynostosis repair: Diagnosis and perioperative management of congenital factor VII deficiency

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ABSTRACT

INTRODUCTION: Congenital factor VII deficiency is a rare bleeding disorder with high phenotypic variability. It is critical that children with congenital Factor VII deficiency be identified early when high-risk surgery is planned. Cranial vault surgery is common for children with craniosynostosis, and these surgeries are associated with significant morbidity mostly secondary to the risk of massive blood loss.
PRESENTATION OF CASE: A two-month old infant who presented for elective craniosynostosis repair was noted to have an elevated prothrombin time (PT) with a normal activated partial thromboplastin time (aPTT) on preoperative labs. The infant had no clinical history or reported family history of bleeding disorders, therefore a multidisciplinary decision was made to repeat the labs under general anesthesia and await the results prior to incision. The results confirmed the abnormal PT and the case was canceled. Hematologic workup during admission revealed factor VII deficiency. The patient underwent an uneventful endoscopic strip craniectomy with perioperative administration of recombinant Factor VIIa.
DISCUSSION: Important considerations for perioperative laboratory evaluation and management in children with factor VII deficiency are discussed. Anesthetic and surgical management of the child with factor VII deficiency necessitates meticulous planning to prevent life threatening bleeding during the perioperative period.
CONCLUSION: A thorough history and physical examination with a high clinical suspicion are vital in preventing hemorrhage during surgeries in children with coagulopathies. Abnormal preoperative lab values should always be confirmed and addressed before proceeding with high-risk surgery. A multidisciplinary discussion is essential to optimize the risk-benefit ratio during the perioperative period.

1. Introduction

Factor VII deficiency is a rare autosomal recessive disorder, with an incidence of 1:500,000 [1]. Most severe cases of factor VII deficiency are diagnosed during childhood, often during the first 6 months of life. In infants, the most common bleeds occur in the gastrointestinal tract or central nervous system [1]. Postoperative bleeding has been reported in association with 30% of factor VII deficient patients undergoing surgical procedures, even when replacement therapy was prophylactically administered [2]. Anesthetic and surgical management of the child with factor VII deficiency necessitates meticulous planning to prevent life-threatening bleeding during the perioperative period. We present the case of a child with an undiagnosed factor VII deficiency revealed by preoperative laboratory studies collected in preparation for craniosynostosis repair.

2. Presentation of case

An otherwise healthy 2 month old female presented to same-day care for elective sagittal craniosynostosis repair. Her preoperative labs from three days prior included a prolonged prothrombin time (PT) of 27 s with a normal activated partial thromboplastin time (aPTT), hemoglobin, and platelet count. A type and cross for blood was also sent. There was no history of bleeding in the infant and no family history of bleeding disorders. After discussions with neurosurgery, the team decided to repeat the labs

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; CBC, complete blood count; CMP, complete metabolic panel.

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under general anesthesia given the reassuring history and await the results prior to incision.

An inhalation induction and endotracheal intubation was performed uneventfully. A peripheral intravenous catheter was placed and a "superstat" comprehensive metabolic panel (CMP), complete blood count (CBC), PT, aPTT and fibrinogen were sent. The CMP showed no signs of liver dysfunction and the CBC was unchanged from prior results. The repeat value for the PT was 29 s, with an INR of 2.9. aPTT and fibrinogen were normal. The surgery was canceled and the infant was extubated without complications. She was admitted to the pediatric hematology service for further workup and found to have factor VII deficiency, with a factor VII level of 10% (reference range 39–191%).

The infant was rescheduled for endoscopic strip craniectomy during the same admission and recombinant Factor VIIa was administered throughout the case. The surgery was uneventful and she was discharged home four days post-operatively with pediatric hematology follow-up. She had no bleeding complications in the twelve months post-surgery.

3. Discussion

Congenital factor VII deficiencies have a high genotypic and phenotypic variation, and there is no consistent correlation between bleeding symptoms and factor VII levels [3]. Often the patients may be asymptomatic or are diagnosed after surgery related bleeding. Craniosynostosis is the result of premature fusion of one or more cranial sutures and can be classified as non-syndromic or syndromic with an underlying genetic alteration found in some cases. Our patient had sagittal craniosynostosis, or *scaphocephaly*, the most common form of non-syndromic craniosynostosis. The incidence of craniosynostosis is approximately 1 in 2100 children. 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 performed in the first year of life. Because of the nature of the repair, the patient's young age, and new diagnosis of factor VII deficiency, this surgery would be associated with an increased risk of morbidity and mortality secondary to intraoperative blood loss [4,5].

Craniofacial syndromes are typically associated with craniosynostosis and include Apert's and Crouzon's syndrome which are associated with cognitive dysfunction, musculoskeletal deformities, airway abnormalities, and cardiac defects. There has been no report of coagulopathies associated with these syndromes. Another form of craniosynostosis is termed "secondary craniosynostosis" which includes metabolic disorders (ie hypothyroidism), fetal teratogen exposure, and mucopolysaccharidosis all of which are not found to be associated with bleeding disorders (Kohl et al. [4]). In the literature to date, there are several syndromes and genetic mutations associated with craniosynostosis but none with an association with Factor VII deficiency or other coagulation disorders. In 2009, a case report by Maquoi and colleagues described the diagnosis of Von Willebrand's disease as an incidental finding in a child undergoing craniosynostosis repair during the preoperative visit due to a positive family history—no direct association has been reported [6].

Preoperative laboratory evaluation should at minimum include a type and cross to ascertain availability of crossmatched blood prior to incision. Other recommended laboratory evaluation includes a hematocrit, platelet count, and coagulation studies as they can be helpful in establishing a baseline prior to surgery. However, these studies are normal in the vast majority of non-syndromic children [5]. There are no pediatric-specific guidelines for preoperative coagulation testing. Often, testing is performed solely based on clinician-specific practice. A review of the literature demonstrates that routine preoperative coagulation screening may serve as a useful complement to a positive personal or family bleeding history; but may otherwise be futile in identifying occult bleeding disorders in children [4]. However, this child had no clinical bleeding history, therefore a decision not to obtain labs based on a negative history may have contributed to harm in this case. Nevertheless, if preoperative testing is performed, it is imperative that the anesthesiology and surgery teams review this data and proceed systematically to address abnormal values rather than assume they are spurious. Although no bleeding history may seem reassuring, the patient may not be old enough to have a bleeding history [7]. In this patient, the elevated PT and INR warranted further evaluation, and a repeat sample was obtained after the child was anesthetized but before incision given the child's negative bleeding history and to ensure that an adequate and high-quality sample was obtained, minimizing the chance of a false positive result.

Formulation of the differential diagnosis of elevated PT requires a thorough understanding of the extrinsic pathway 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. The differential diagnosis of elevated PT with a normal aPTT includes: tissue factor (extrinsic) deficiency, warfarin or rodenticide ingestion, liver dysfunction, or vitamin K deficiency [4]. Warfarin or rodenticide ingestion was unlikely. The normal comprehensive metabolic panel ruled out liver dysfunction. Although infants are at risk for vitamin K deficiency due to 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. Thus, the patient has an extrinsic deficiency.

Treatment of acute hemorrhage and surgical prophylaxis in patients with factor VII deficiency consists of factor VII replacement therapy. Pediatric hematology should be immediately consulted and dependent on the severity of deficiency, recombinant Factor VIIa (rFVIIa) should be administered at the time of induction and at least 15 min prior to incision. The first dose is 15–30 mcg/kg. Due to its short half-life, it must be re-dosed every 6 h for 24–48 h thereafter at the same dose. Factor VIIa replacement therapy with rFVIIa may also be delivered safely as continuous infusion and this mode of administration is highly cost-effective [8,9] rFVIIa increases the risk of thrombosis and development of new inhibitors, although the incidence of these risks is low in the literature [10].

4. Conclusion

In summary, congenital factor VII deficiency may present without signs of bleeding and pose both diagnostic and management challenges for both the anesthesia and surgical teams. A thorough history and physical examination together with a high clinical suspicion are vital in preventing catastrophic hemorrhage during surgeries in children with coagulopathies. In the setting of abnormal pre-operative coagulation values, a multidisciplinary discussion is essential to optimize the risk-benefit ratio when planning how to move forward.

Conflict of interest

None.

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Ethical approval

N/A.

Consent

Written informed consent was obtained from the patient's parents for the publication of this case report. A copy of the written consent is available for review by the Editor-In-Chief of this journal, upon request.

Author contribution

Jones, K.—case report design, writing the paper.
Greenberg, R.—case report concept, writing the paper.
Ahn, E.—case report concept, writing the paper.
Kudchadkar, S.—case report concept and design, writing the paper.

Guarantor

Jones, K., Greenberg, R., Ahn, E., Kudchadkar, S.

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