CLINICAL VIGNETTE

Congenital Factor XIII Deficiency

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Clinical Case

A 36-year-old female presented to the Obstetrics Gynecology at 34 weeks of gestation for evaluation of a possible bleeding disorder. Patient reported previous mild oral mucosal bleeding after tooth extraction. Otherwise, menstrual periods were regular and not heavy, and there was no history of spontaneous bleeding. Her brother, sister and parents, had no history of bleeding related complications. Obstetric plan was for conventional vaginal delivery with consideration for Caesarean section. Patient was otherwise healthy and the only active medication was a prenatal multivitamin supplement.

Initial laboratory evaluation included CBC with differential and normal platelet count of 266 x 10E3/uL, with no morphologic platelet abnormalities on peripheral smear. Coagulation test included, normal prothrombin time (PT) of 13s and activated partial thromboplastin time (aPTT) of 25.3 s. Von Willebrand factor (vWF) panel testing showed antigen (Ag) level 215 % (normal 52-214%), wWf:Ristocetin Co-factor activity level 198% (normal 51-215%), and normal vWF multimeric distribution pattern. Further testing showed a normal fibrinogen level 451 mg/dL (normal 235-490 mg/dL) and a normal platelet aggregation pattern to all platelet agonists. Testing of individual coagulation factor activity levels was obtained. Levels were normal for extrinsic pathway factor VII, intrinsic pathway factors VIII, IX, XI, XII, as well as common pathway factors II, V, X. Patient was noted to have a mild decrease of factor XIII activity level at 50% (normal 69-143%) consistent with a new diagnosis of factor XIII deficiency.

Discussion

Under normal physiologic conditions, there exists a balanced interaction between pro- and anti-coagulant forces. This equilibrium enables the normal flow of blood without the formation of pathologic thrombosis or excessive bleeding. This process constitutes normal body hemostasis, and it is understood as a two-component pathway of “primary” and “secondary” hemostasis.[1] The end result of primary hemostasis is the formation of a platelet plug at a site of blood vessel endothelial injury. Simultaneously through a highly intertwined process, secondary hemostasis leads to the formation of a crosslinked fibrin mesh at the same site of injury. Secondary hemostasis consists of the activation of multiple coagulation factors that ultimately lead to downstream formation of a stable blood clot in order to allow for the process of blood vessel repair and healing.

Congenital or acquired coagulation factor deficiencies are not uncommonly encountered in day-to-day clinical practice. More common congenital factor deficiencies associated with clinically significant bleeding include Hemophilia A and B, which are associated with relative deficiencies of factor VIII and IX, respectively.[2] Other less commonly encountered factor deficiencies include congenital factor XIII deficiency. This particular bleeding disorder is often challenging to recognize clinically as initial screening coagulation tests, PT and aPTT are within the normal range. This is because factor XIII is not directly involved in the formation of fibrin. Rather the main function of factor XIII is to introduce covalent bonds between different subtypes of fibrin chains, leading to a stiff and compact fibrin clot mesh.[3]

One of the first cases of factor XIII deficiency was reported in 1961 in a pediatric patient who exhibited some classic clinical features of this disorder, impaired wound healing with abnormal scar formation and an associated severe bleeding diathesis. Congenital factor XIII deficiency is inherited in an autosomal recessive mode. The estimated frequency is 1 in 2-3 million live births, and it is more common in areas of the world where consanguineous marriage is still practiced. Factor XIII is composed of A and B subunits and circulates as a zymogen tetramer consisting of 2 A subunits with 2 B subunits. The B subunit serves a dual function as a regulatory and carrier protein.

In clinical practice, patients with severe congenital factor XIII deficiency are identified as neonates. Umbilical cord bleeding is reported in up to 80% of affected neonates. There is also a significant incidence of neonatal spontaneous and post-traumatic intracranial hemorrhage. In the adult population, affected individuals may report a history of ecchymosis and hematomas. In addition, significant and prolonged bleeding is common after surgery or trauma-related hemostatic challenges. Women, may report menorrhagia and recurrent early spontaneous abortions early in pregnancy may be noted.

In the setting of a clinically significant bleeding diathesis, the diagnosis of congenital factor XIII deficiency is established by demonstration of reduced factor XIII activity using quantitative assay. Various in vitro assays are available to confirm factor XIII deficiency.[4] These include: (1) clot solubility test, (2) factor XIII activity assay, (3) factor XIII antigen assay, as well as molecular diagnostic testing. In general, first-line testing

involves the use of factor XIII activity assay, which can be performed using three different methods. Each method has its intrinsic technical advantages and disadvantages along with different limits of detection expressed as a percentage of residual factor XIII activity. For example, the amine incorporation assay has a reference range of activity of 70 to 140 U/dL with a detection limit of 0.1 to 1%.

In general, the management of congenital factor XIII deficiency is dependent on baseline activity level and associated individual bleeding phenotype. Another factor considered, is the intrinsic long plasma half-life of factor XIII, which is in the order of 7 to 12 days.[5] It has long been recognized that there is an apparent discrepancy between factor XIII activity level and bleeding tendency. This is illustrated by the fact that even factor activity levels less than 5% are sufficient to control bleeding.[6] Therapy for individuals with factor XIII deficiency is administered both as prophylaxis, and on-demand needs due to spontaneous or surgical bleeding.[7] In the United States, the FXIII human concentrate Corifact™ is available for use in both clinical scenarios. Typical initial dose for routine prophylaxis is 40 international units (IU)/ kilogram (kg) of body weight every 28 days.[8] Maintenance dose adjustments are made based on FXIII trough levels. For peri-operative management, dose is determined based on baseline FXIII activity level, type of surgery, and clinical response. As it is true with other congenital severe bleeding disorders, management of factor XIII deficiency in surgical setting requires a multidisciplinary approach involving Surgeon, Anesthesiologist, and Hematologist.

Conclusion

In general, congenital bleeding disorders are not uncommonly encountered in quotidian clinical practice. Medical practitioners should maintain a high degree of awareness, and have the insight to be able to clinically distinguish congenital from acquired bleeding diathesis. In these cases, prompt referral to a Hematologist is warranted. Our understanding of the basic pathophysiology of congenital bleeding disorders continues to expand, leading to newer and safer treatment options. This is illustrated by the recent FDA approval of catridecacog (Tretten®), the first recombinant factor XIII replacement product.[9] Tretten is a recombinant analog of the Factor XIII A subunit, a deficiency of which accounts for about 95% of all cases of congenital factor XIII deficiency.

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