CLINICAL VIGNETTE

Prekallikrein Deficiency

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Case Report

A 75-year-old Caucasian female with a past medical history including rheumatoid arthritis and hypertension presented to hematology for evaluation of a prolonged activated partial thromboplastin time (aPTT). She was in her usual state of health and was planning to undergo an elective blepharoplasty procedure. She was evaluated by her primary care physician who ordered preoperative blood tests including a complete blood count (CBC), complete metabolic panel (CMP) and coagulation tests including prothrombin time (PT) and activated partial thromboplastin time (aPTT). Her CBC, CMP, and PT were all within the normal limit, but her aPTT was prolonged at 41 seconds with a normal reference range of 22 to 34 seconds. Repeat aPTT remained prolonged at 40 seconds. Her blepharoplasty was delayed, and she was referred for further evaluation. She complained of having easy bruising for many years but denied any personal history of significant bleeding. Prior to menopause, she did not have menorrhagia. She had intermittent nose bleeds in her teenage years, but none since then. She had several procedures in the past including tonsillectomy and excisions of skin cancers without any bleeding complication. She did not have any preoperative blood tests before those procedures. She also denied having any prior pregnancy-related complication nor any family history of bleeding or clotting disorder. She was not on any anticoagulation medications. On physical exam, she did not have any bruises nor rashes. An aPTT-based mixing study was done, and her prolonged aPTT corrected with donor plasma, consistent with clotting factor deficiency. There was no immediate, nor late acting inhibitors noted. Additional testing for intrinsic pathway defects including von Willebrand factor antigen, coagulation factors VIII, IX, XI, and XII activities were all within normal limits. Interestingly, her prekallikrein factor activity was low at 48%, with a normal reference range of 55-207%. Because prekallikrein deficiency is not a bleeding disorder and she did not appear to have any other major medical problem, the patient was cleared for the procedure and had the blepharoplasty without any perioperative bleeding complication.

Discussion

An abnormal coagulation test is a relatively common finding during the preoperative medical evaluation. Although routine preoperative testing of hemostasis is generally not recommended in patients without a personal history, family history and physical examination suggestive of a bleeding disorder, it is still a common practice in the community.[1] Primary care physicians and hematologists are frequently asked to perform additional work up to further risk stratify these patients before the planned surgery. aPTT and PT are screening coagulation tests that measure the time for patient's plasma to clot when exposed to activating substances or some source of tissue factor. aPTT assesses the intrinsic and common pathways of coagulation including coagulation factors I (fibrinogen), II (prothrombin), V, VIII, IX, X, XI, XII as well as prekallikrein (PK) and high-molecular-weight kininogen (HK). PT assesses the extrinsic and common pathways of coagulation including coagulation factors I, II, V, VII, and X. When an abnormal aPTT or PT is noted, a detailed history and physical exam is required to find out whether the patient has a history of bleeding diathesis or thrombosis. Repeating the abnormal test is also recommended to rule out laboratory error due to improper blood sample handling. In the case mentioned above, she had a normal PT but a prolonged aPTT. The prolonged aPTT suggested an abnormality in the intrinsic or the common pathways of coagulation. Because she had a normal PT, it narrowed the abnormality to the intrinsic pathways. An aPTT-based mixing study was then carried out to determine whether she had a factor deficiency or a presence of an immediate or delayed factor inhibitor. Mixing study is performed by mixing a patient's plasma with normal plasma in a 1:1 ratio and then remeasuring the aPTT or PT. Because aPTT and PT are expected to be normal when there is at least 50% activity of any factor required for the test, the mixing of 1:1 dilution should normalize the abnormal test in the setting of a pure factor deficiency. However, if a factor inhibitor is present, the added clotting factors from the normal plasma would be affected by the inhibitor leading to a persistent prolonged aPTT or PT. This patient, had a normal aPTT after the mixture of normal plasma to her plasma, suggesting a potential factor deficiency in the intrinsic pathway, i.e., factor VIII, IX, XI, XII, prekallikrein (PK) and high-molecular-weight kininogen (HK). Factor VIII, IX and XI deficiencies are associated with excessive bleeding. Inherited deficiency of factor VIII is hemophilia A and inherited deficiency of factor IX is hemophilia B. Inherited factor XI deficiency, also known as hemophilia C, is a very rare bleeding disorder with a prevalence of 1 in a million.[2] In this case, further workup revealed normal factor VIII, IX, XI, XII activities. However, her prekallikrein factor activity was low. At this point, she was diagnosed with PK deficiency and had the proposed surgery without further testing because PK deficiency is not associated with any significant clinical bleeding.[3-5]

Prekallikrein is known as the *Fletcher factor*, a serine protease that complexes with the high-molecular-weight kininogen (HMWK). It is synthesized in the liver and circulates mostly in the blood as a complex with HMWK. In the coagulation system, it is a precursor to kallikrein and is cleaved by the activated factor XII to form kallikrein. Formed kallikrein can then activate other factor XII to factor XIIa which further speeds up the coagulation process. It also has non-coagulation related actions. Kallikrein is involved in fibrinolysis by converting plasminogen to plasmin. It can also increase vascular permeability and decrease blood pressure by cleaving HMWK into bradykinin, which is a vasodilator. In vitro, PK is required for the normal factor XI activation in the aPTT assay, so PK deficiency leads to aPTT prolongation. However, PK deficiency is not associated with clinical bleeding.[4] This may partially be due to the fact that factor XI can be activated directly by thrombin in vivo.[6] The exact role of PK in vivo is not fully understood at this time.

Hathaway et al. first described the congenital deficiency of PK in 1965.[7] An 11-year-old female was being evaluated for possible adenoidectomy but was noted to have a prolonged clotting time without a history of bleeding diathesis. This finding led to a study of 14 of her family members. Three siblings were found to have similar coagulation deficits, and none of them had a history of abnormal bleeding. The missing plasma component was initially called the *Fletcher factor* after the family name of this index case. *Fletcher factor* was later determined to be the PK. Based on the family studies, it was noted that the deficiency has an autosomal recessive inheritance pattern.[8] Homozygous individuals typically have <1% PK activity and heterozygous individuals have 20-60% of normal activity.[9] The exact prevalence of congenital PK deficiency is unknown because this deficiency does not cause any symptoms, so most people with this diagnosis are probably never diagnosed.[4] Moreover, PK is synthesized in the liver, so acquired deficiency of PK can be seen in patients with liver disease and disseminated intravascular coagulation (DIC).[4,10] It is important to note that a patient with low PK level may present with bleeding due to underlying liver disease or DIC. Currently, a commercially available PK assay can be performed to diagnose PK deficiency. If needed, molecular testing can be sent to identify specific inherited PK mutation.

Because of kallikrein's involvement in fibrinolysis, there is also concern that PK deficiency may influence thrombosis risk. There are a few reported cases of thrombotic manifestations in patients with severe PK deficiency.[11,12] A 2010 review of 75 previously reported cases of PK deficiency noted that there had been 9 patients with either arterial or venous thrombosis. Of note, 6 of them had acquired thrombosis risk factors at the time of the event. The review concluded that PK deficiency does not protect the patients from arterial and venous thrombosis.[13]

Conclusion

An abnormal coagulation test is a relatively common problem encountered during preoperative medical evaluations. Evaluation for the prolonged aPTT or PT requires a good basic understanding of the underlying coagulation pathways. Repeating the test is the first step to exclude inadvertent mishandling of the initial blood sample. If the problem persists, a mixing study is then indicated to narrow the problem down to a factor deficiency or the presence of a factor inhibitor. This is often a frustrating exercise because the mixing study can be ambiguous, e.g., PTT corrects several seconds but is at or slightly above the upper limit of normal. However, normal factor VIII, IX, and XI levels allow the patient to proceed with the proposed surgery if the patient does not have a personal history of bleeding diathesis. In the case mentioned above, our patient was diagnosed with PK deficiency, a rare cause of prolonged aPTT with normal PT. Both congenital and acquired deficiencies of PK have been reported. Congenital PK deficiency is not associated with bleeding and does not protect the patient from thrombosis. Both arterial or venous thromboses may still occur. On the other hand, acquired PK deficiency can be seen in patients with severe liver disease or DIC. Similar to the general population with these disease states, bleeding risk is increased so precaution should be taken.

REFERENCES

1. **Chee YL, Crawford JC, Watson HG, Greaves M**. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. *Br J Haematol*. 2008 Mar;140(5):496-504. doi: 10.1111/j.1365-2141.2007.06968.x. Review. PubMed PMID: 18275427.
2. **Mumford AD, Ackroyd S, Alikhan R, Bowles L, Chowdary P, Grainger J, Mainwaring J, Mathias M, O'Connell N; BCSH Committee**. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2014 Nov;167(3):304-26. doi: 10.1111/bjh.13058. Epub 2014 Aug 6. PubMed PMID: 25100430.
3. Factor XII Deficiency [Internet]. NORD (National Organization for Rare Disorders). [cited 2019 Feb 28]. Available from: https://rarediseases.org/rare-diseases/factor-xii-deficiency/
4. **Girolami A, Scarparo P, Candeo N, Lombardi AM**. Congenital prekallikrein deficiency. *Expert Rev Hematol*. 2010 Dec;3(6):685-95. doi: 10.1586/ehm.10.69. Review. PubMed PMID: 21091145.
5. High molecular weight kininogen deficiency - Conditions - GTR - NCBI [Internet]. [cited 2019 Mar 1]. Available from: https://www.ncbi.nlm.nih.gov/gtr/conditions/C0272340
6. **Naito K, Fujikawa K**. Activation of human blood coagulation factor XI independent of factor XII. Factor XI is activated by thrombin and factor XIa in the presence of negatively charged surfaces. *J Biol Chem*. 1991 Apr 25;266(12):7353-8. PubMed PMID: 2019570.

7. Prekallikrein deficiency [Internet]. Genetics Home Reference. [cited 2019 Mar 1]. Available from: https://ghr.nlm.nih.gov/condition/prekallikrein-deficiency
8. **Hathaway WE, Belhasen LP, Hathaway HS**. Evidence for a New Plasma Thromboplastin Factor I. Case Report, Coagulation Studies and Physicochemical Properties | *Blood Journal* [Internet]. [cited 2019 Mar 12]. Available from: http://www.bloodjournal.org/content/26/5/521.long?sso-checked=true
9. Prekallikrein deficiency [Internet]. [cited 2019 May 13]. Available from: https://www.pathologyoutlines.com/topic/coagulationprekallikreindef.html
10. **Ragni MV, Lewis JH, Hasiba U, Spero JA**. Prekallikrein (Fletcher factor) deficiency in clinical disease states. *Thromb Res*. 1980 Apr 1-15;18(1-2):45-54. PubMed PMID: 6902559.
11. **Hess DC, Krauss JS, Rardin D**. Stroke in a young adult with Fletcher trait. *South Med J*. 1991 Apr;84(4):507-8. Review. PubMed PMID: 2014441.
12. **Currimbhoy Z, Vinciguerra V, Palakavongs P, Kuslansky P, Degnan TJ**. Fletcher factor deficiency and myocardial infarction. *Am J Clin Pathol*. 1976 Jun;65(6):970-4. PubMed PMID: 937251.
13. **Girolami A, Allemand E, Bertozzi I, Candeo N, Marun S, Girolami B**. Thrombotic events in patients with congenital prekallikrein deficiency: a critical evaluation of all reported cases. *Acta Haematol*. 2010;123(4):210-4. doi: 10.1159/000313361. Epub 2010 Apr 27. PubMed PMID: 20424433.