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Enoxaparin Failure in Patient With Cerebral Venous Sinus Thrombosis and Prothrombin G20210A Mutation

Case Report

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Introduction: Cerebral venous sinus thrombosis (CVST) is a rare, serious, and complex cerebrovascular disease. The prothrombin G20210A mutation is the second most common inherited thrombophilia and is considered to be one of the etiologies of CVST. The optimal heparinoid medication for treatment remains a topic of debate.

Case Report: This case report describes a young woman with CVST who did not respond to low–molecular-weight heparin (LMWH). The patient was initially treated with LMWH; however, her symptoms and clot burden in the sagittal sinus worsened, and coagulation studies showed no evidence of therapeutic anticoagulation despite good compliance. Unfractionated heparin was then initiated, and the patient's symptoms improved dramatically within 24 hours, along with the recanalization of the cerebral venous sinuses. Genetic testing revealed a heterozygous mutation in the prothrombin gene (G20210A). This mutation is a known risk factor for CVST. However, it is unclear why the patient did not respond to LMWH but responded appropriately to unfractionated heparin.

Conclusion: This case report highlights the potential for LMWH resistance in patients with CVST and prothrombin gene mutations. These findings also emphasize the importance of close monitoring of coagulation parameters and clinical response in patients with CVST receiving LMWH.

Key Words: anticoagulants, cerebrovascular disorders, enoxaparin, low–molecularweight heparin, prothrombin G20210A thrombophilia, sinus thrombosis, treatment failure

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Cerebral venous sinus thrombosis (CVST) is an uncommon but serious and complex cerebrovascular disease that affects 5 per million adults annually and accounts for 0.5% to 1% of all strokes.[1,2] CVSTs are more frequent in women, with an estimated female-to-male ratio of 3:1,[3] and the majority of patients develop identifiable predisposing factors. Studies have shown that hereditary thrombophilias may cause CVST in 12% to 18% of patients.[4,5]

The prothrombin G20210A mutation exhibits an autosomal dominant inheritance pattern and is the second most prevalent inherited thrombophilia after the Factor V Leiden mutation. This mutation leads to elevated prothrombin production without altering its structure. Compared with individuals in the noncarrier population, individuals with the prothrombin G20210A mutation exhibit a 10-fold increased risk of venous thromboembolism.[6] This mutation is more common in South European & Middle Eastern populations.[7]

Apart from the debate regarding the best heparinoid medication for CVST, no study has investigated the impact of inherited thrombophilia on treatment protocols.

CASE DESCRIPTION

A 19-year-old White woman with no significant past medical history visited the University Medical Center Emergency Department (ED) after 5 days of new-onset headache. The onset was acute and localized to the right frontal and retroorbital areas. The pain was moderate, 4/10 in intensity, nonradiating, and aggravated with cough and sneezing. The patient also had photophobia. The pain did not respond to the over-the-counter medications.

The headache fluctuated in intensity over the next few days, between moderate and severe, and has never disappeared since its onset. Two days before admission, the patient developed nausea and vomiting. She noted intermittent numbness in the left fourth and fifth fingers. One day before her admission, the headache became so intense that she decided to visit the local ED. She was diagnosed with migraine and received intravenous (IV) pain medications, which partially helped with the pain, and was subsequently discharged.

As her headache recurred, she decided to visit our facility. On history taking and physical examination, she denied recent head trauma, fever, upper respiratory tract infections, or a history of meningitis. There was no family history of migraine. She denied any history of smoking or drug abuse.

Significantly, she had an uneventful delivery 6 months before her visit to the ED and had been using a weekly

contraceptive transdermal patch (norelgestromin and ethinyl estradiol).

On admission, her blood pressure was slightly elevated (156/90 mm Hg). Her body mass index (BMI) was 35 kg/m^2 (86 kg). Physical examination revealed an alert and fully oriented patient with no focal neurological deficits, normal pupils, and no papilledema. The patient's visual acuity was normal. The patient tested negative for meningeal signs.

Laboratory findings and computed tomography (CT) of the head were unremarkable. Subsequent magnetic resonance imaging (MRI) (Fig. 1) and magnetic resonance venogram (MRV) (Fig. 2) of the brain revealed a thrombus in the superior sagittal sinus, right transverse sinus, right sigmoid sinus, right internal jugular vein, and great cerebral vein. It also revealed a small area of restricted diffusion in the left parietal subcortical region, which was compatible with a venous infarct.

After being diagnosed with extensive CVST, she was started on subcutaneous enoxaparin at a therapeutic dose of 1 mg/kg every 12 hours. A hypercoagulable panel was sent and the transdermal contraceptive patch was discontinued. The hematology team recommended enoxaparin for 14 days, followed by oral rivaroxaban.

The patient's headaches improved during admission. She was hospitalized for 4 days. At discharge, she was sent home with acetaminophen codeine and enoxaparin at the recommended therapeutic dose. She was advised to undergo hematology and neurology follow-up for further treatment and review of the hypercoagulable panel results.

The patient returned to the ED the day after discharge. This time, she complained of new-onset double vision that started a few hours before her visit. Headache and photophobia persisted. The patient was compliant with enoxaparin.

Neurological examination revealed a new left sixth cranial nerve palsy. Her partial thromboplastin time (PTT) was normal, indicating possible enoxaparin failure. A repeat MRI (Fig. 3) of the brain revealed a subarachnoid hemorrhage in both frontoparietal lobes. Contrast-enhanced MRI (Fig. 4A) and repeat MRV (Fig. 4B) showed a slight increase in thrombus size within the superior sagittal sinus. The ophthalmological evaluation revealed mild papilledema as indicated by elevated intracranial pressure. The patient continued on the same therapeutic dose of enoxaparin and started oral acetazolamide 500 mg twice daily.

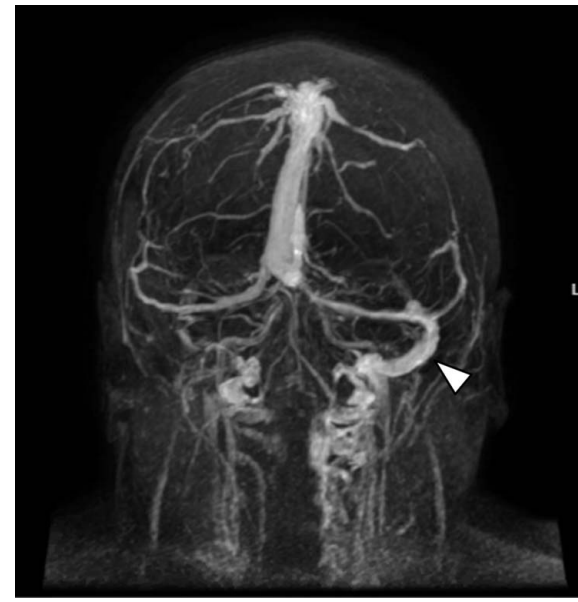

FIGURE 2. MR venogram of the brain with contrast agent (reconstruction, coronal view) showing the right transverse sinus (distal portion), right sigmoid sinus, right internal jugular vein, and great cerebral vein. Note the asymmetry of the veins compared with that of the normal left venous sinuses (arrowhead).

Her double vision remained stable, her headache was intermittent and fluctuating, and was managed with intravenous (IV) pain medications.

The day after her readmission, the patient experienced worsening headache, double vision, and nausea. MRI of the patient's brain revealed worsening of subarachnoid hemorrhage. Enoxaparin was discontinued. The patient was switched to unfractionated heparin (UFH) infusion with close observation of activated partial thromboplastin time (aPTT). IV levetiracetam (500 mg every 12 h) was initiated as seizure prophylaxis.

At that point, the hypercoagulable panel showed elevated factor 8, elevated vWF activity/antigenic, normal levels of protein C antigenic (130%) and protein S antigenic (81%), but decreased protein C activity (30%) and free

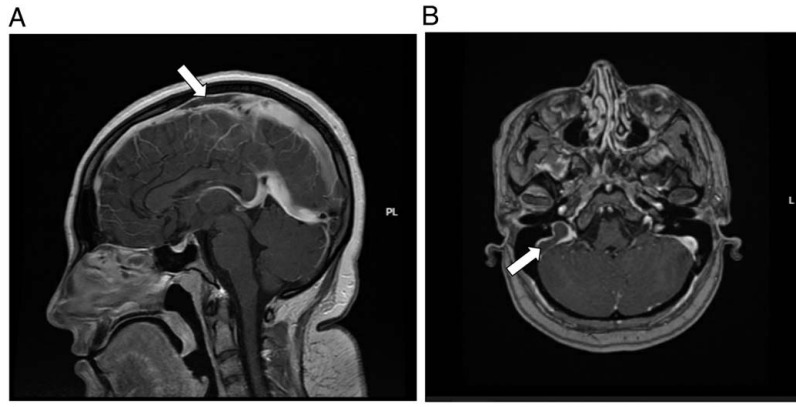

FIGURE 1. MRI of the brain with contrast: (A) sagittal view showing a thrombus in the superior sagittal sinus (arrow). (B) Axial view showing a thrombus in the right sigmoid sinus (arrow).

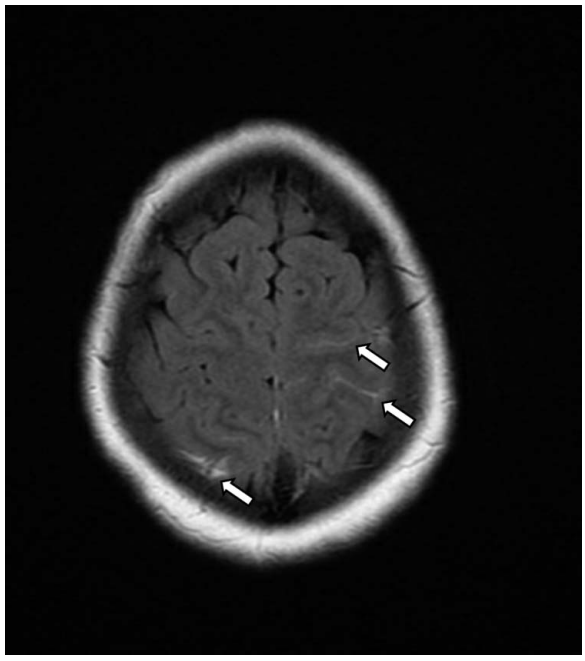

FIGURE 3. MRI brain FLAIR: subarachnoid hemorrhage noted in bilateral frontoparietal regions (arrows).

protein S (35%). The antithrombin III concentration was within the normal range. Studies were inconclusive because they were conducted during the acute phase of thrombosis.

Given the rapid progression of the patient's symptoms despite the use of anticoagulation for 6 days and the worsening of CVST and subarachnoid hemorrhage, the patient was referred to another facility (Covenant Medical Center) with interventional radiology capabilities.

Approximately 18 hours after UFH, her symptoms stabilized, and she underwent digital subtraction angiography (DSA) and possible venous thrombectomy (Fig. 5).

Surprisingly, the images revealed a significant decrease in the venous thrombus with the re-establishment of straight-line flow through the transverse and sigmoid sinuses on the right side. The thrombectomy was discontinued. The patient was monitored clinically and continued on UFH with anti-Xa levels between 0.4 and 0.8.

Finally, further serological studies revealed that the patient had a positive factor II mutation for one copy (heterogeneous) of G20210A.

The remaining tests were negative, including JAK2 V617F mutation, Factor V Leiden variant, P190 and P210 BCR-ABL1, hexagonal phospholipid neutralization qualitative test for lupus, kaolin clotting time, anticardiolipin antibody IgG and IgM, beta 2 glycoprotein I IgG, beta 2 glycoprotein I IgM and beta 2 glycoprotein I IgA, antiphosphatidylserine (APTS) IgG, and APTS IgM.

Symptoms improved over the next 24 hours. Her headache improved significantly compared with the previous days (2/10 in intensity) and finally resolved completely over the next few days. Further neurological examination revealed a mild left sixth cranial nerve palsy. No other focal neurological deficits were noted.

She was started on warfarin with a goal international normalized ratio (INR) of 2 to 3. Heparin was bridged with warfarin. She was discharged in a stable condition.

DISCUSSION

We present the case of a young female with a new diagnosis of prothrombin G20210A mutation who developed a new-onset headache with extensive CVST and signs of elevated intracranial hypertension. Most patients with CVSTs respond appropriately to anticoagulation therapy if promptly administered. This patient, even though she was rapidly diagnosed and treated for LMWH, developed thrombus progression complicated by subarachnoid hemorrhage.

Inherited thrombophilia increases the risk of venous thrombosis. The prothrombin G20210A mutation is the second most common inherited thrombophilia after the Factor V Leiden mutation. This autosomal dominant mutation increases prothrombin function. Most individuals are heterozygous. Although the risk of developing CVST secondary to this mutation is not well established, it is known that this inherited thrombophilia increases venous thromboembolism by 10 times in patients with the prothrombin G20210A mutation compared with the population without this mutation.[6] Studies have shown that inherited thrombophilia has a synergistic effect on the risk of CSVT in women taking oral contraceptives.[8]

The patient failed to provide information regarding her ethnicity, but multiple studies have shown a correlation

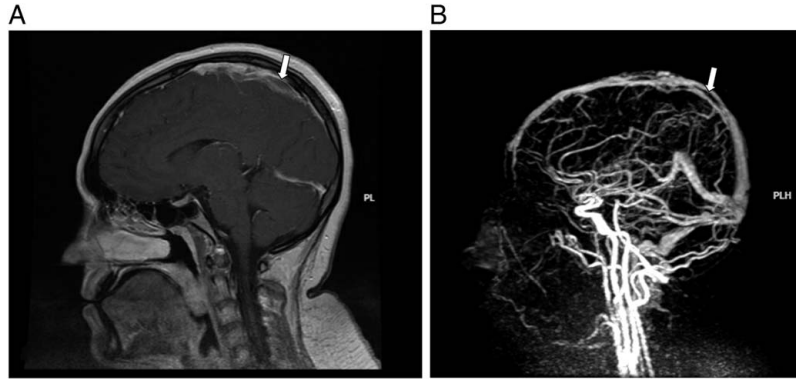

FIGURE 4. (A) Brain MRI with contrast and (B) MRV (both sagittal views): extension of the thrombus noted in the superior sagittal sinus (arrow).

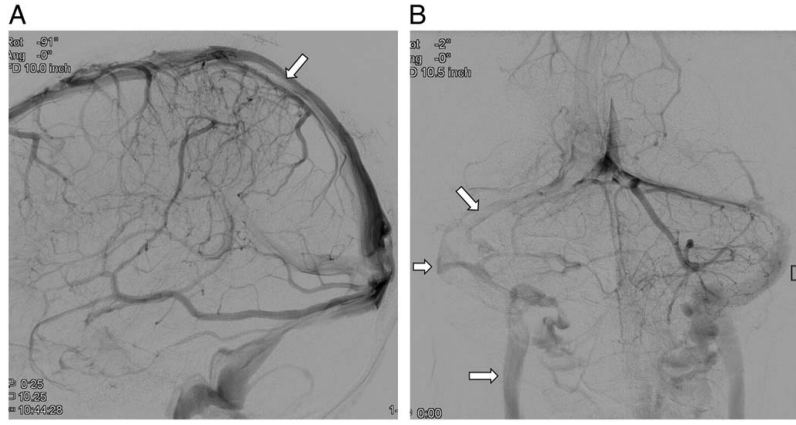

FIGURE 5. Digital subtraction angiography: (A) sagittal view, right internal carotid artery (ICA) injection. Minimal filling defect noted in the superior sagittal sinus (arrow); (B) coronal view, left vertebral artery injection, spontaneous flow through the previously obstructed right transverse sinus, sigmoid sinus, and internal jugular vein (arrows).

between ethnicity and prevalence to this mutation. According to Dziadosz and Baxi's 2016 meta-analysis, the prevalence of polymorphisms varies significantly based on geographic location and ethnicity, with a higher frequency observed in South European and Middle-Eastern populations.[7] Southern European populations had a carrier rate of 3% (2.2% to 9.1%), which was higher than the rate of 1.7% (0 to 2.7%) in Northern European populations. In Middle Eastern populations, the carrier rates ranged from 2.5% to 12.5%, which was notably higher than the rate of 0% in East Asian populations (Japan, Singapore, China, Oman, South Korea, and India). The carrier rates in North African populations closer to Europe, such as Morocco, Tunisia, and Algeria, ranged from 2.4% to 3.9%, whereas those in Egypt were 1.43%, and all other West African and South African populations, including Ethiopian Jews, showed a 0% prevalence. South American populations have moderate carrier rates, with variations between countries ranging from 2% to 5%. In North America, carrier rates varied by ethnicity, with higher rates among Whites and Hispanics (3.6% and 3.5%, respectively) than among African Americans (0% to 1.7%) and American Indians (0% to 0.6%). No evidence of polymorphism was found in the Australian Aboriginal population. Given the geographical variations, a recent study by Fan in 2023 hypothesized that the Prothrombin mutation, similar to the Factor V Leiden mutation, could have been caused by pathogenic selective pressure from the Black Death (bubonic plague), which ravaged Europe in the 14th century.[9]

The main goals of CVST treatment are recanalization of occluded veins, prevention of thrombus propagation, and prevention of further episodes of thrombosis. This goal is achieved with anticoagulation, and only a small percentage of patients will require endovascular thrombolysis of the affected vessels (2.1%)[10] or other invasive measures.

The 2017 European Stroke Organization guidelines for the diagnosis and treatment of CVST endorsed by the European Academy of Neurology recommend anticoagulation therapy for CVST. They recommended UFH or LMWH followed by oral anticoagulation, emphasizing 6 to 12 months of treatment for patients with the G20210A mutation.[11]

The guidelines also favor the treatment of acute CVST with LMWH over UFH. This recommendation does not apply to patients with a contraindication for LMWH, such as renal failure, or situations where fast reversal of the anticoagulant effect is needed, such as a large intracranial hemorrhage.[1]

A randomized controlled trial by Misra et al,[12] one observational study by Coutinho et al,[13] and 2 meta-analyses by Qureshi et al,[14] and Al Rawahi et al[15] showed a trend in favor of LMWH in mortality and functional outcomes.

The reasons behind the preference for LMWH in the above studies are that it is a more stable anticoagulant, does not require adjustments based on aPTT levels, and has a decreased frequency of ICH compared with the heparin group.

Moreover, a study by Afshari et al[16] revealed that LMWH and UFH were equally effective in reducing neurological deficits and functional disability in patients with CVST, with no significant differences in hemorrhagic or thrombotic events.

Although both American and European guidelines[1,11] rely on the study by Misra et al[12] to support the recommendation of LMWH over UFH, it has several methodological limitations, as detailed in a subsequent editorial by Davie CA[17], who reported that the treatment effect of LMWH could have been overestimated.

Importantly, apart from the abovementioned findings, a significant yet easily overlooked fact is that the clinical profile of any given LMWH cannot be extrapolated to another or generalized to the entire LMWH family because of the differences among LMWHs.[18] This fact becomes crucial, especially when various trials arrive at different conclusions while using LMWH molecules at opposite ends of the spectrum, as in Dalteparin and Enoxaparin, with anti-factor Xa/anti-IIa ratios of 2.5 and 3.9, respectively.[18]

The decreased inhibition of prothrombin by heparinoid products is evident in the in vitro potencies of the anti-factor Xa and anti-IIa levels of enoxaparin and UFH, which are 98:25 and 193:193, respectively.[18]

Commercially used LMWHs have anti-factor Xa/anti-IIa ratios between 2:1 and 4:1, depending on their molecular size distribution.[19]

In our specific case, the challenges of controlling the patient's symptoms, thrombus progression, and new signs of elevated intracranial hypertension prompted us to explore

other treatment options. In addition, the fact that the aPPT was within the normal range after 4 days of LMWH raised concerns about possible LMWH resistance or failure. We hypothesized that the likelihood of enoxaparin failure would be high based on the normal PTT level at readmission. Unfortunately, the anti-Xa level was not measured at that point, which could have helped support this hypothesis.

Finally, considering all these factors and the evidence of SAH, the decision to transfer the patient to another facility (Covenant Medical Center) for the interventional procedure was made. In preparation for the scheduled procedure, the patient's anticoagulant regimen was changed from LMWH to IV UFH. The abnormalities in other coagulation factors, including protein C and S activity, were not reliable because they could not be interpreted during the period of acute thrombosis. The dramatic and rapid response of the patient's coagulation studies and cerebral venograms to UFH, but not LMWH, was surprising and unexpected. The planned thrombectomy procedure was aborted, and the patient's symptoms improved dramatically after 24 hours of IV heparin administration.

The differential response of the patient to UFH compared with that to LMWH is a striking finding that prompted us to further investigate the literature, which led us to hypothesize that the genetic mutation in this patient could have played a role in the lack of response to LMWH but not UFH. Figure 6 shows the process of gain-of-function mutations via the G-to-A transition at nucleotide 20210 in the 3'-UTR of the promoter of the prothrombin gene located on chromosome 11p11.2 (G20210A mutation), which enhances the stability of messenger RNA, thus increasing plasma levels of prothrombin by 30%, resulting in a greater risk for venous or arterial thrombosis because of its potential to form thrombin and excessive growth of fibrin clots.[20]

It is known that LMWH is not as effective at inhibiting factor IIa (thrombin) as UFH.[19,21]

The popularity of LMWHs stems from their peculiar property of minimal prolongation of aPTT and negligible thrombin inhibition while retaining their ability to inhibit factor Xa. This dissociation of antithrombotic and anticoagulant properties allows LMWHs to be used as effective anticoagulants with a reduced risk of bleeding than UFH. LMWHs have a reduced ability to inactivate thrombin because smaller fragments cannot simultaneously bind to AT III and thrombin.

Despite having a profound effect on FXa, LMWH has a progressively weaker effect on aPTT, reflecting less marked inhibition of thrombin (FIIa). This is because, rather than FXa, FVa is the rate-limiting component of the prothrombinase complex (ie, FXa and FVa are adsorbed on the membrane surface), which converts prothrombin to thrombin. Studies on Factor V Leiden strongly support this concept[21] (Fig. 7).

Recent studies have shown that patients with the G20210A prothrombin mutation display remarkably similar characteristics to those of patients with the Factor V Leiden mutation.[22]

Unfortunately, no large amount of data are available regarding treatment failure in patients with this mutation (G20210A prothrombin mutation), the type of anticoagulant used, or studies regarding the progression and extension of thrombosis. However, few case reports have shown the therapeutic success of UFH in patients with the prothrombin G20210A mutation without any complications.[23]

Other case reports of CVST patients with prothrombin mutations have been published; however, these patients had fewer complications following treatment, in contrast to our patients. One patient was treated with LMWH for a short period and then transitioned to warfarin. The other 2 patients were treated with IV UFH but not LMWH.[23–25]

LMWH resistance has also been observed in patients with Factor V Leiden mutation, which could support its common characteristics to G20210A prothrombin mutation.[26,27]

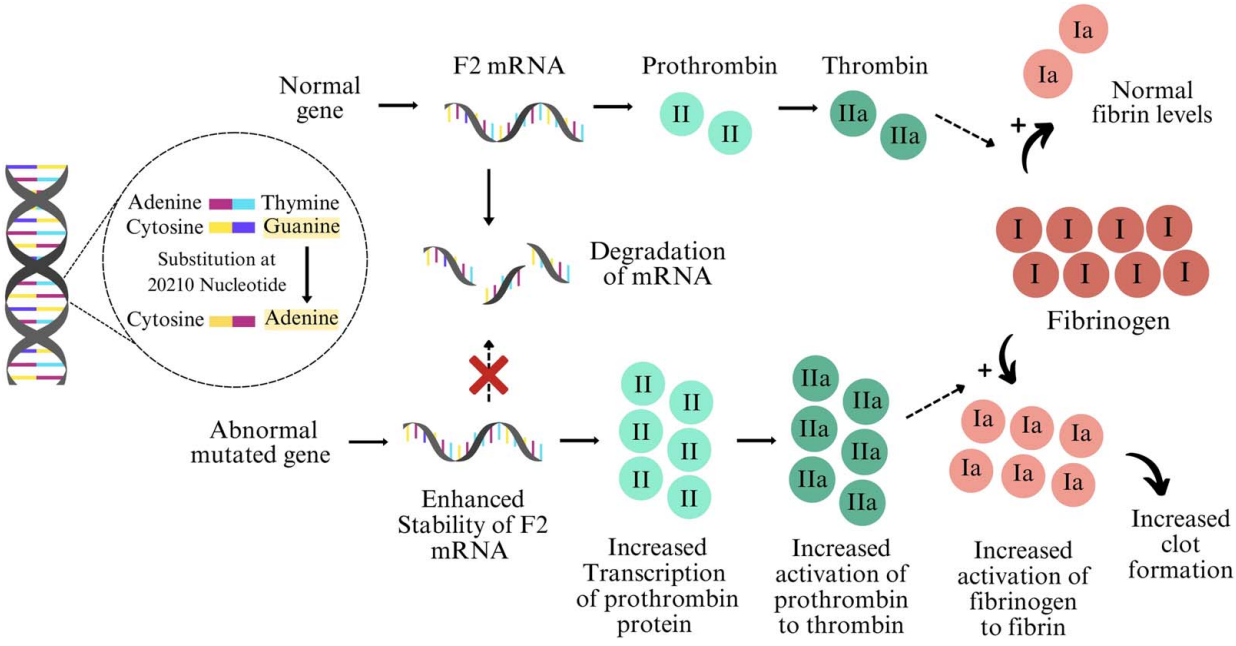

FIGURE 6. Pathogenesis of prothrombin G20210A mutation. There is increased prothrombin without structural changes via increased expression of factor 2 mRNA, thus increasing the risk of clot formation.

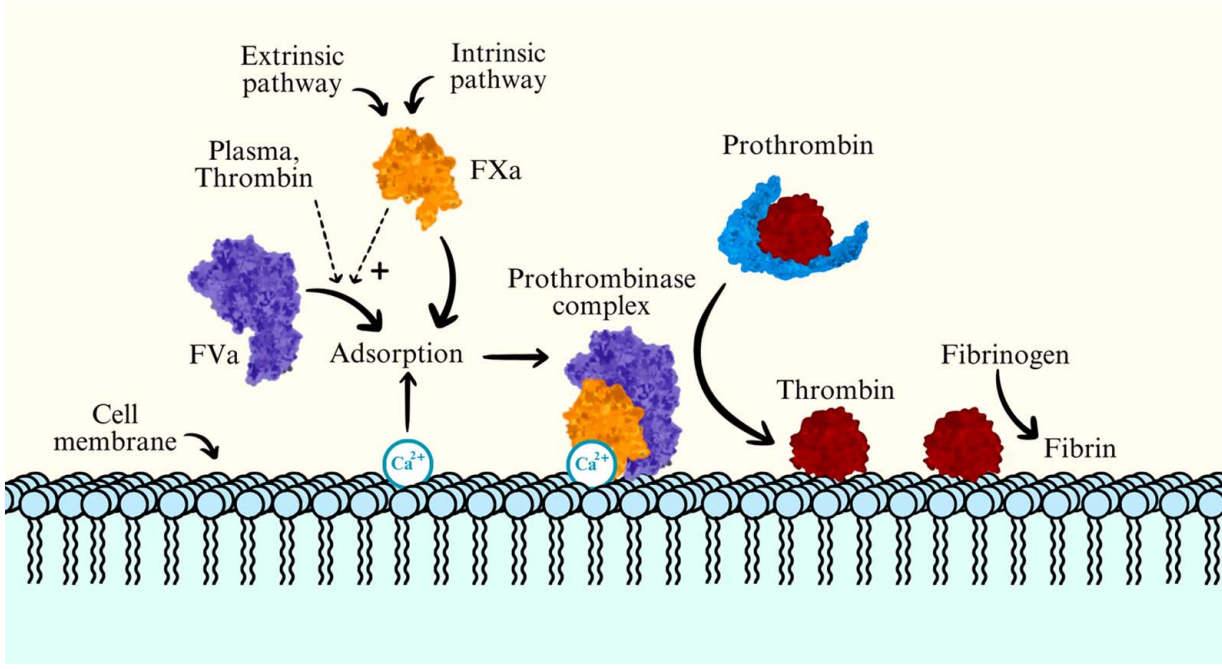

FIGURE 7. Role of the prothrombinase complex in the activation of prothrombin to thrombin. Note that the rate-limiting factor in the formation of the thrombinase complex is Factor Va.

Although no randomized controlled trials have reached a significant conclusion, experts prefer LMWH to UFH for the treatment of CVST. However, further studies are needed to characterize the response of patients with CVST and prothrombin G20210A mutation to LMWH. More controlled anticoagulation with UFH and closer attention to aPTT or anti-Xa therapy may be required for this mutation.

CONCLUSIONS

Caution and closer monitoring of the anticoagulation response may be needed when using LMWH in CVST patients with the prothrombin G20210A mutation. Further research on LMWH resistance or failure in patients with hereditary thrombophilia, exclusively in those with prothrombin mutations, is needed.

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