CASE REPORT

# Two cases of Factor XI deficiency: Use of Thrombin Generation Assays (TGA) to detect a non-bleeding phenotype

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**ABSTRACT**

Factor XI deficiency is a rare disorder of hemostasis. Previously also known as "hemophilia C", this defect has been regarded as a risk factor for bleeding. However, it has been known for long that bleeding tendency and severity of bleeding are not related to the residual factor XI activity in symptomatic patients. Moreover, a large proportion of patients with even severe factor XI deficiency are clinically unremarkable and do not show any signs of abnormal bleeding. Here, we present two cases of factor XI deficiency with a non-bleeding phenotype. Adequate diagnostic work-up and evaluation of the bleeding risk are reported and discussed with focus on thrombin generation assays (TGA) for the prediction of bleeding in affected patients. This is of high relevance in affected patients, particularly in the context of surgery.

**KEYWORDS:** Factor XI deficiency; thrombin generation assays; TGA

## INTRODUCTION

Factor XI deficiency is a rare disorder of hemostasis. Previously also known as "hemophilia C", this defect has been regarded as a risk factor for bleeding. However, it has been known for long that bleeding tendency and severity of bleeding are not related to the residual factor XI activity in symptomatic patients. Moreover, a large proportion of patients with even severe factor XI deficiency are clinically unremarkable and do not show any signs of abnormal bleeding. Here, we present two cases of factor XI deficiency with a non-bleeding phenotype, focusing on the potential use of thrombin generation assays (TGA) for stratification of the bleeding risk.

## CASE REPORTS

### First Case

The first patient was a 57-year-old woman who presented to our department for hemostasis work-up and consultation due to a family history of thrombophilia, the sister had been diagnosed for heterozygous factor V Leiden mutation elsewhere and the patient now presented to estimate her thrombotic risk. Diagnostic work-up led to the diagnosis of heterozygous factor V Leiden mutation which was also present in the sister of the patient. Other relevant inherited thrombophilic risk factors, in particular prothrombin mutation G20210A, protein C, protein S, and antithrombin deficiency, were excluded. In addition, a remarkable prolongation of the activated partial thromboplastin time (aPTT) up to 73 seconds (normal range 25-27 seconds) was observed, but prothrombin time was normal. The result was confirmed in a control examination and further diagnostic work-up was initiated: As a correlate of prolonged aPTT, a factor XI activity of only 1% was detected. The activity of other coagulation factors influencing aPTT but not the prothrombin time (factors XII, IX and VIII, precallicrein, high-molecular weight kininogen [HMWK]) was within normal range, and the lupus anticoagulant was also negative. Thus, the diagnosis of severe factor XI deficiency was established. Molecular genetic analysis was initiated showing the heterozygous mutation c.1775T>C, p.(Ile592Thr) in exon 15 of the factor XI gene (NM_000128.3). This mutation has previously been described to be causal for factor XI deficiency. Thus, the diagnosis of genetically determined severe factor XI deficiency was established. However, it should be noted that the severity of factor XI reduction is not explained fully by the only heterozygous mutation and additional genetic factors leading to the severe reduction of factor XI activity cannot be excluded. To evaluate the impact of factor XI deficiency on thrombin formation, a thrombin generation assay (TGA) was performed. Interestingly, thrombin generation was normal despite the severe

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reduction of factor XI activity, suggesting a non-bleeding phenotype (Table 1).

### Second Case

The second patient was a 56-year-old woman who presented to our department for hemostasis work-up and consultation due to a family history of bleeding. The father of the patient suffered from factor XI deficiency with a bleeding phenotype. However, the patient was free of any bleeding symptoms. In addition, she did not suffer any thrombotic or thromboembolic events. She received primary prophylaxis with acetylsalicylic acid (ASS) 100 mg daily due to increased cardiovascular risk profile with arterial hypertension, diabetes mellitus type 2, and severe obesity (1,58m, 120 kg; BMI 48 kg/m$^2$). In addition, she had medication for arterial hypertension, metformin for diabetes mellitus and a HMG-CoA reductase inhibitor for hyperlipemia. Also, was treated with duloxetine, a SSNRI (selective serotonin noradrenalin reuptake inhibitor), for depression. In the diagnostic work-up, aPTT was prolonged to 83 seconds, but the prothrombin time was not prolonged. Further diagnostic work-up revealed a factor XI activity of less than 1%. Other factor deficiencies that potentially prolong the aPTT but do not affect the prothrombin time (coagulation factors XII, IX, and VIII, precallicrein, high-molecular weight kininogen [HMWK] were within normal range. Furthermore, a lupus anticoagulant as additional cause of aPTT prolongation was ruled out. Furthermore, there was no evidence for an additional defect of plasmatic hemostasis or for von-Willebrand-disease. Platelet aggregation was typically altered with reduction of aggregation upon stimulation with arachidonic acid due to the intake of ASS medication.

Due to family history and results of the diagnostic work-up, genetically determined factor XI deficiency was suspected. Genetic testing was performed showing the homozygous mutation c.623C > A, p.(Thr208Lys) in exon 15 of the factor XI gene (NM_000128.3). Although this mutation has not yet been previously described, the mutation can be assumed to be causative for factor XI deficiency according to prediction analysis with the software polyphen-2 (polymorphism phenotyping, http://genetics.bwh.harvard.edu/pph/). Thus, the diagnosis of genetically determined or inherited factor XI deficiency was established. Again, the thrombin generation assay TGA) revealed normal results, indicating normal thrombin generation despite the very low factor XI activity. This was also compatible with a non-bleeding clinical phenotype of the defect (Table 1).

## DISCUSSION

Factor XI deficiency, also called hemophilia C or Rosenthal syndrome, was first reported in 1953 in a patient with severe bleeding after dental extractions. The general incidence is estimated at 1:100.000, but it is found in up to 8-10% of Ashkenazi Jews because of intermarriage [1,2]. Factor XI deficiency follows an autosomal inheritance, mostly recessive, in some cases dominant; thus, woman and men are equally affected. Patients with factor XI deficiency may suffer from epistaxis, hypermenorrhea, peripartum and periinterventional bleeding, whilst joint and muscle bleeds are uncommon. The low bleeding risk in patients with factor XI deficiency also promoted the development of factor XI pathway inhibitors (e. g., fesomersen, osocimab, abelacimab, milvexian, asundexian) for "safe anticoagulation", the prophylaxis of thrombosis without inducing bleeding [3].

In the laboratory, factor XI deficiency leads to a prolongation of the aPTT while prothrombin time (PT) is unremarkable. The diagnosis is established by determination of factor XI activity using factor XI deficient plasma. In case of aPTT prolongation, other defects leading to a prolonged aPTT have to be excluded; among these, hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are associated with bleeding, whilst patients with factor XII deficiency, prekallikrein deficiency, HMWK (high-molecular weight kininogen) deficiency or lupus anticoagulant do not exhibit any bleeding symptoms. Once factor XI deficiency is detected, mixing studies should eventually be performed to exclude an underlying factor XI inhibitor. Genetic testing can be performed to identify the genetic defect leading to factor XI deficiency. So far, more than 250 defects causative for this disorder have been identified [4]. Since there is no clear association between factor XI activity and bleeding, risk stratification of affected patients is challenging.

Factor XI deficient patients without spontaneous bleeding symptoms do not need any treatment. If bleeding symptoms are provoked by intake of platelet-inhibitory agents, such as agents containing acetylsalicylic acid, these agents should not be used. Spontaneous nosebleeds could be prevented by antifibrinolytic agents, hypermenorrhea by use of antifibrinolytic agents and/or hormonal contraception. Since clotting factor concentrates for substitution are not available in all countries, such as in Germany, and the application of these concentrates bears a considerable risk for thrombotic complications, the management of severely factor XI deficient patients undergoing interventions and surgery remains a challenge. Thrombotic complications such as pulmonary embolism and transient ischemic attack (TIA) have been reported in patients receiving factor XI concentrates [5,6]. As an alternative, therapeutic plasma can be used to substitute lacking factor XI, but high volumes are needed since 1 ml plasma per kg bodyweight may only lead to an increase of 1-2% in factor XI activity. Thus, plasma application in this setting bears a considerable risk for transfusion associated circulatory overload (TACO) or

**Table 1.** Relevant laboratory results of the presented cases: remarkably, thrombin generation is not altered at all despite severe reduction of factor XI activity.

| Parameter | Case 1 | Case 2 | Normal Range |
|---|---|---|---|
| **Coagulation Assays** | | | |
| aPTT | 70 sec | 83 sec | 25-37 sec |
| Factor XI activity | 1% | < 1% | 65-150% |
| **Thrombin Generation Assay (TGA)** | | | |
| Peak thrombin | 63 nM | 65 nM | 43-368 nM |
| Total thrombin | 1435 nM | 1561 nM | 1.236-2.945 nM |

pulmonary edema. Years ago, one of the authors reported on the off-label use of recombinant activated factor VII (rFVIIa) in a patient with congenital factor XI deficiency during brain tumor neurosurgery [7]. It must be stressed that rFVIIa has not been approved for this indication.

The main problem with factor XI deficiency is the lacking association of residual factor XI activity with presence and severity of bleeding symptoms. Even more, it is known that the majority of affected patients does not show any signs of abnormal bleeding and does even not have an increased bleeding risk during surgery. In support of this, Wheeler et al. (2020) reported that only 20% of factor XI deficient women will develop pregnancy-related bleeding with missing association of factor XI activity and bleeding risk [8].

Due to the missing correlation of residual factor XI activity and bleeding risk, it remains a challenge to make adequate recommendations for bleeding prophylaxis in affected patients that undergo surgery, dentistry, and interventions. In a recently published study, personal history of bleeding was the best indicator of perioperative or obstetric bleeding. Higher factor XI levels, in particular levels above 40%, were associated with a lower bleeding risk, but this association was not strong enough to allow adequate clinical management. Family history of bleeding, ethnicity, and underlying genetic defect were not associated with the bleeding risk [9].

In this setting, Thrombin Generation Assays (TGA) or Thrombin Generation Tests (TGT) could be a useful tool for risk stratification. Developed in the 1950s as manual procedures, these assays are now available as semi-automated or fully-automated commercially available procedures. They determine the potential of plasma to generate thrombin after recalcification and activation by addition of phospholipids and tissue factor by continuous measurement of cleavage of a fluorogenic substrate by thrombin [10]. The results are influenced by the presence of coagulation factors, activators and inhibitors of hemostasis in plasma. Since platelet-poor plasma (PPP) is used in the standard assays, the assay is not influenced by platelet abnormalities, and platelet dysfunction and thrombocytopenia do not influence the results. Since fibrin generation and stabilization by factor XIII occur after thrombin generation in the coagulation process, fibrinogen and factor XIII disorders do not affect the results.

The results are depicted as a thrombin generation curve showing the thrombin generation over time. From the curves, a number of parameters can be derived and quantified, such as the lag time (time from activation to onset of thrombin generation), peak thrombin (maximum of the thrombin generation curve), and total thrombin (area under the curve [AUC] of thrombin generation) [11,12]. We prefer the use of peak thrombin and total thrombin since these assays are better standardized compared to other parameters derived from the thrombin generation curve. In general, a reduction of thrombin generation should indicate an increased bleeding risk in patients suffering from a plasmatic defect predisposing to bleeding, whereas a normal or even increased thrombin generation should argue for a reduced or even absent risk of bleeding.

Thrombin generation assays have been used for risk stratification and monitoring of hemotherapy in a variety of inherited plasmatic bleeding disorders such as hemophilia [13]. Also, the potential use of TGA to predict bleeding in patients suffering from factor XI deficiency has previously been examined. Kasonga et al. (2021) published a series of 67 patients with confirmed factor XI deficiency, defined as a factor XI activity $< 50\%$ [14]. As a result, they found significantly lower thrombin generation, determined as endogenous thrombin potential (ETP), in patients with factor XI deficiency compared to healthy controls. Factor XI deficient patients with a bleeding phenotype had a lower ETP compared to those with a non-bleeding phenotype and healthy controls; however, this association was not statistically significant. Rugeri et al. (2010) found that patients with factor XI deficiency and severe bleeding had a strongly reduced thrombin generation which was not correlated to their residual factor XI activity. E.g., they reported a patient with only 1% residual factor XI activity without any bleeding symptoms with normal thrombin generation, whereas a patient with severe bleeding tendency and 40% residual factor XI activity showed strongly reduced thrombin generation. These results suggest that determination of thrombin generation is useful to predict the bleeding risk in factor XI deficient patients [15]. Désage et al. (2022) found that 44% of factor XI deficient patients with impaired thrombin generation developed abnormal bleeding during surgery, whereas normal thrombin generation was associated with low bleeding risk. The authors stated that TGA are valuable to determine the bleeding risk in respective patients prior to surgery and to guide the hemostatic management [16]. We recently reported a case of concomitant factor XI deficiency and hypofibrinogenemia, in which the decision not to substitute factor XI but fibrinogen for major dentistry was driven by a normal thrombin generation assay [17].

Both of the patients presented here, had normal results in the TGA despite very low residual factor XI activity. These results were compatible with the non-bleeding phenotype. Since bleeding manifestations in daily life were absent, we did not recommend any treatment for the factor XI deficiency. Even in case of surgery and interventions, no specific prophylaxis would be recommended since abnormal bleeding is not expected. The cases demonstrate, how thrombin generation assays can influence the clinical management of patients and avoid unnecessary and potentially harmful treatment.

In our opinion, risk stratification should be based not only on residual factor XI activity, but also on personal bleeding history, and TGA which are likely to differentiate bleeding and non-bleeding phenotypes of factor XI deficiency (Table 2).

**Table 2**. Risk stratification in patients with factor XI deficiency.

| | Criteria for not increased/normal bleeding risk | Criteria for increased bleeding risk |
|---|---|---|
| Factor XI activity | $> 40\%$ | $< 40\%$ |
| Personal history | absence of abnormal spontaneous and perioperative bleeding | spontaneous bleeding and/or prior perioperative bleeding |
| Thrombin generation | not impaired | impaired/ reduced |

## CONCLUSION

Clinical management of patients suffering from rare inherited factor XI deficiency is challenging for a variety of reasons: missing correlation of factor XI activity with the presence or risk of abnormal bleeding, unavailability of factor XI concentrates in many countries and association of these agents with thrombotic complications, and high volumes of therapeutic plasma needed for sufficient raise of factor XI levels. Most important, thus, is the identification of affected individuals with an increased bleeding risk, especially in order to forecast critical emergency situations, for example in severe trauma. In our opinion, risk stratification should be based not only on residual factor XI activity, but also on personal bleeding history, and TGA which are likely to differentiate bleeding and non-bleeding phenotypes of factor XI deficiency. Accurate selection of patients really needing perioperative treatment should help to minimize bleeding but also to prevent thrombotic complications associated with the use of factor XI concentrates.

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