Case Report

"Familial Multiple Coagulation Factor Deficiencies of FXI and FXII in an Asymptomatic Saudi Woman"

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Abstract

Factor XI deficiency (FXI) is the third most common coagulation factor deficiency after hemophilia A and B, ie, in the hierarchy after factors VIII and IX, taking into account von Willebrand's factor deficiency, as bleeding disorders are higher than in hemophilia C. Factor XII deficiency (FXII) is a congenital condition, inherited in the vast majority of cases in an autosomal recessive manner, more often associated with thromboembolic complications. A combination of both factor deficiencies has been found very rarely, and it can be familial multiple coagulation factor deficiency (FMCFD). This study reports the case of a 39-year-old woman from Saudi Arabia who had the combination of FXI and FXII deficiencies, known to be on treatment for hypothyroidism and was referred to a hematology clinic with an incidental finding of prolonged activated partial thromboplastin time (aPTT). Although there was no history of bleeding tendency, her siblings had a family history of an unknown type of bleeding disorder. On physical examination, the patient did not show any bruising, petechiae, or ecchymosis. The aPTT was 69 seconds (27-38) with normal use of other hemostatic agents and was corrected after a 50:50 mixing study. Intrinsic coagulation factors were evaluated, and they revealed severe FXI and moderate FXII deficiencies. Due to a strong family history, the patient was diagnosed with FMCFD. In conclusion, familial combined multiple clotting factor deficiency (FCMFD) is a rare condition that requires attention and reporting. The management strategy in such cases has not been well studied, especially in the long-term symptomatic patient with severe but asymptomatic combined FXI and FXII deficiencies, which is an area for review and further study.

Keywords

bleeding, coagulation, factor deficiency, factor XI, factor XII

Introduction

There are two types of combined deficiency of blood coagulation factors: heridatort (familial), inheredited by an autosomal recessive type, or acquired (non-familial) type.[1,2] Familial multiple coagulation factor deficiency (FMCFD) is a group of rare hereditary disorders of hemostasis characterized by a simultaneous decrease in plasma activity of more than 1 clotting factor caused by genetic defects in 1 or more major genes. Hereditary deficiencies of certain coagulation factors other than hemophilia A (factor VIII deficiency) and B (factor IX deficiency) and von Willebrand's disease are rare diseases transmitted in an autosomal recessive manner.[1-3] Thus, factor XI deficiency (FXI) and factor XII deficiency (FXII) are rare genetic blood disorders, occurring separately in 1 in 1 000 000 people.[4,5] Factor XI or hemophilia C, also known as Rosenthal's disease, is a rare bleeding disorder caused by a mutation in the F11 gene responsible for blood clotting. Factor XI deficiency is the third most common coagulation factor deficiency after hemophilia A and B, ie, in the hierarchy after factors VIII and IX, taking into account von Willebrand's factor deficiency, as bleeding disorders are higher than in hemophilia C. Additional evidence suggests that prevalence is 2 to 20 times higher likely due to the wide range of bleeding risk associated with FXI deficiency, which is, however, less explored.[6] Factor XII or Hageman factor is

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Table 1. The Complete Blood Count, Hemostatic Profiles and the Results of Coagulation Factors Studies Showing Combined FXI and FXII Deficiencies.

Test name[a]	Result	Confirmatory result (%)	Reference range
Hemoglobin	13 g/dL	—	12-16 g/dL
MCV	83 fl	—	80-94 fl
MCH	26.6 pg	—	27-32 pg
White blood cell counts (WBCs)	$6.5 \times 10^3/\mu L$	—	$4\text{-}11 \times 10^3/\mu L$
Platelet count (plt)	$322 \times 10^3/\mu L$	—	$140\text{-}450 \times 10^3/\mu L$
Activated partial thromboplastin time (aPTT)	69 seconds	—	27-38 seconds
Prothrombin time (PT)	10.4 seconds	—	10.1-13.6 seconds
Bleeding time	4 minutes	—	1-8 minutes
Thrombin time	19.6 seconds	—	16.7-22.1
von Willebrand's factor	115%	—	46-165
FVIII	97.6%	93.1	66-130
FIX	101%	76.5	73-131
FX	103%	99	71-133
FXI	1.1%	1.0	60-130
FXII	44%	34.4	73-121

Abbreviations: MCV: mean corpuscle volume; MCH: mean corpuscle hemoglobin.
[a]F = Factor VIII: 8; IX: 9; X: 10; XI: 11; XII: 12.

a congenital condition, inherited in the vast majority of cases in an autosomal recessive manner, more often associated with thromboembolic complications, which are sometimes life-threatening.[7] The half-life of FXI and FXII is 50 and 60 hours, respectively.[3,5]

Further evidence suggests rare occurrences of combined factor deficiencies where coagulation factors were combined with other (eg, factor VIII and X) or bleeding factors. However, a combined deficiency of FXI and FXII has not been previously reported in Saudi Arabia or the Arab countries.[8,9] This study reports the case of a 39-year-old woman from Saudi Arabia who was referred to a hematology clinic because accidentally found prolonged activated partial thromboplastin time (aPTT); the investigation showed a combination of FXI and FXII deficiencies.

Case Report

A 39-year-old Saudi woman who had a case of hypothyroidism while taking L-thyroxine 50 mcg once a day was referred to the hematology clinic due to the incidental discovery of prolonged aPTT. The patient underwent an appendectomy, a tonsillectomy, a cholecystectomy, and 3 vaginal deliveries without complications and did not require a transfusion of blood or blood products or factor replacement. The patient did not report any bleeding anywhere, bruising, or ecchymosis. The sibling discussion revealed that she has 4 siblings; her brother had a positive history of hemophilia (of unknown type) and her sister had hemostasis problems that were not followed up for a specific diagnosis. The other 2 siblings are free from bleeding symptoms, but they did not do hemostatic or coagulation laboratory test, so an advice was sent through the patient to encourage her remaining siblings to visit the hematologist for evaluation. Otherwise, both mother and father were free from blood clotting disorders and were in consanguineous marriage.

On physical examination, the patient appeared healthy, with no ecchymosis, petechiae, or bruising; no other hypo/hyper skin lesions. Vital signs were within normal limits. The rest of the examinations were unremarkable, with no signs of organomegaly.

Investigation

Complete blood count (CBC) showed normal hemoglobin 13 g/dL, mean corpuscle volume (MCV) 83 fl, mean corpuscle hemoglobin (MCH) 26.6 pg, white blood cell counts (WBCs) were normal of $6.5 \times 103/\mu L$, and normal platelet count (plt) of $322 \times 103/\mu L$, with prolonged aPTT of 69 seconds, prothrombin time (PT) 10.4 seconds, bleeding time 4 minutes, and thrombin time 19.6 seconds. von Willebrand's factor was normal at 115% with normal activity (Table 1). Both renal function and liver enzymes were at normal levels. Peripheral blood smear was unremarkable.

Plasma mixing analysis immediately corrected the aPTT to a normal level, indicating the presence of a factor deficiency. A differential diagnosis of types of hemophilia was proposed, and blood plasma was analyzed for common intrinsic factors (VIII, IX, X, XI, XII) (Table 1). On subsequent hematological follow-up, the result was confirmed as a combined deficiency of FXI and FXII (Table 1). Further genetic testing was considered to confirm the hereditary or familial type of the disease. However, due to limited resources and lack of testing at the health facility, additional testing was infeasible.

Discussion

Activated partial thromboplastin time is one of the clot-based screening tests and a coagulation monitoring parameter in some medications. It may be isolated due to deficiency of intrinsic coagulation factors (eg, factors VII, IX, XI, XII), von Willebrand's type 2, or drug-induced, as in anticoagulant therapy (eg, unfractionated heparin and/or low molecular weight heparin), or secondary to some acquired and autoimmune conditions, as in antiphospholipid syndrome.[10] However, if the patient is not taking anticoagulants, an aPTT mixing study is indicated in which the same amount of normal plasma is incubated with the patient's plasma (1:1), followed by a new aPTT analysis. This step helps differentiate coagulation factor deficiency as the cause of a prolonged aPTT if the aPTT normalized in the mixing study and/or an autoimmune disease if the delay or aPTT did not normalize after the mixing study.[10,11] In this case, the aPTT was isolated with a direct correction of the aPTT after the mixing study, reflecting the presence of a factor deficiency. The next step was to measure the level of each factor affected by the aPTT, starting with the more common ones like FVIII and FIX, which were normal, followed by the less common factors like FXI and FXII, which were low.

Factor XII deficiency plays a significant role in the internal coagulation cascade and the formation of prothrombin and fibrinogen.[12] Although the prevalence of FXII defiance is low, there may still be more obscure and unreported cases than expected. Thus, a cohort of 115 cases in Saudi Arabia showed that most of the patients were asymptomatic and were found incidentally before surgery.[13] Further summary of the latest available literature reported a number of cases of incidental prolonged aPTT due to FXII deficiency.[5,7] This suggests the possibility of a thrombotic mechanism rather than FXII deficiency bleeding, as previously highlighted in some studies.[7,13,14]

Similar to FXII, FXI contributes to the intrinsic pathway and promotes the formation of both thrombin and the kallikrein-kinin system, composed of the zymogens prekallikrein, high molecular weight kininogen cofactor, and FXII.[4,15] Clinical manifestations in patients with FXI deficiency range from no bleeding tendency (most common) to minimal nosebleeds or heavy menstruation and bleeding due to surgery or trauma. Severe FXI deficiency is defined as a factor level of less than 20%, with no correlation between bleeding capacity and factor level.[4] Bleeding secondary to FXI deficiency can be treated with fresh frozen plasma (FFP), recombinant factor VIIa, FXI concentrates, and antifibrinolytics (tranexamic acid).[4,16]

This case showed that the patient had a severe FXI deficiency at a rate of 1.1% (less than 20%) along with mild-to-moderate FXII impairment at 30% to 40%. Due to a strongly positive family history of bleeding disorders, FMCFD was suspected. Familial multiple coagulation factor deficiency is an inherited hemostatic condition in which the levels of 2 or more clotting factors are simultaneously reduced. Familial multiple coagulation factor deficiencies are into 3 subgroups based on presentation, underlying conditions, and factors involved.[1,17,18] In their review of 50 reported cases of FMCFD, Preisler et al[1] found that almost all factors were associated with various combinations, but not with FXII deficiency, as in this case with a patient from Saudi Arabia. Molecular and cytogenetic testing is needed to confirm the diagnosis in this condition. However, in this case, this was not feasible due to limited resources in the medical facility.

In 1985, Hellstern et al[19] reported a case of combined dysform of homozygous FXI and heterozygous FXII, with heredity of the coagulation defects confirmed by family studies. In this case, although there was no history of bleeding tendency, the siblings of the Saudi women had a family history of an unknown type of bleeding disorder, which could be potential genetic consequences of homozygous XI deficiency and heterozygous XII deficiency. However, it is a hypothesis stemming from previous evidence and the findings of this case that needs further study.

In 2008, a similar combination was reported as this case, but both factors were at the level of 40%,[20] making the case with Saudi patient more recent with an FXI level of up to 1% and no bleeding at either level or during previous surgical interventions. In 1996, the combination of FXI and FXII with von Willebrand's disease occurred in 2 brothers.[21] Thus far, no more cases of this combination have been reported since 2008, making this case the newest of the rarest reported combined FXI and FXII deficiencies.

Conclusions

Familial combined multiple clotting factor deficiency (FCMFD) is a rare condition that requires attention and reporting. The management strategy in such cases has not been well studied, especially in the long-term symptomatic patient with severe but asymptomatic combined FXI and FXII deficiencies, which is an area for review and further study.

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Author Contributions

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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