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MANAGING ACQUIRED SEVERE FACTOR XI DEFICIENCY IN CHILDREN: A CASE STUDY WITH LITERATURE REVIEW

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Abstract
Factor XI (FXI) is a blood coagulation protease involved in the coagulation cascade, activating the Factor IX and contributing to hemostasis. Its deficiency is associated with mild to moderate bleeding manifestations that typically occur after injury, mainly in tissues containing activators of the fibrinolysis (urinary tract, oropharynx). FXI deficiency is an inherited bleeding disease which differs from X linked FVIII deficiency (hemophilia A, HA) and FIX deficiency (hemophilia B, HB) by its autosomal inheritance pattern and variable bleeding tendency.
We describe a case of a 6-year-old male who developed an autoantibody directed against FXI in the contest of an autoimmune kidney-related disorder. The patient was initially diagnosed as affected with severe congenital Factor XI deficiency. We report the diagnostic workup of this very rare acquired condition, and the management of kidney biopsy.
Anti FXI, autoantibody was suspected after ineffective incubated aPTT mixing procedure and detected by Bethesda Njimegen assay. Recombinant activated factor VII was successfully used to prevent bleeding complication of kidney biopsy. The coagulopathy preceded the onset and recurrence of the nephrotic syndrome and could be considered a marker of the entire autoimmune disorder.
We describe a case of a child who developed an autoantibody directed against FXI in the contest of an autoimmune kidney-related disorder. His acquired coagulopathy, which never led to bleeding issues, preceded the onset and recurrence of the nephrotic syndrome. We describe the diagnostic workup of this very rare acquired condition, and the management of Kidney Biopsy (KB).
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Keywords: Acquired Factor XI deficiency; Factor XI inhibitor; Renal Biopsy; Autoimmune kidney disease.

Introduction

Factor XI (FXI) is a blood coagulation protease involved in the coagulation cascade, activating the Factor IX and contributing to hemostasis. Its deficiency is associated with mild to moderate bleeding manifestations that typically occur after injury, mainly in tissues containing activators of the fibrinolysis (urinary tract, oropharynx). Commonly this deficit is inherited; meanwhile the acquired form is less common and typically associated to other systemic disorders like Systemic Lupus Erythematosus (SLE), infections, postpartum period and malignancies [1, 2].

Case Presentation

A 6 years old male with a previous diagnosis of autoimmune thyroiditis came to our attention for a story of FXI deficiency. At the age of 7 months, he had an urticarial reaction following the administration

of the hexavalent vaccine; blood tests revealed an autoimmune thyroiditis in euthyroidism; for this reason endocrinological follow up was started. At the age of 21 months an isolated prolonged activated Partial Thromboplastin Time (aPTT) was found with ratio= 3,92; immediate mixing tests corrected the aPTT, consistent with a factor deficiency. During subsequent hematologic follow up the aPTT resulted persistently prolonged; intrinsic pathway factor assays (Factor VIII, IX, XI, XII) depicted a severe deficiency of FXI (<1%); lupus anticoagulant test (LAC) searched with dRVVT resulted also positive.
Family history as well as personal history were unremarkable and did not detect any bleeding issue. In the suspicion of a congenital disorder, FXI gene mutations were searched in the child and not identified. His parents presented normal aPTT as well as normal FXI level.
At the age of 53 months, the boy presented generalized edema, proteinuria (3,7 g/24h) and micro hematuria; in the suspicion of nephrotic syndrome, he was started on oral prednisone 45 mg/day (60 mg/m^2/die). After four weeks the response to the treatment was considered transient due to reduced but persistent proteinuria; consequently, the boy received intravenous (IV) Metil-Prednisolone (MPN) bolus 210 mg/die (10 mg/kg/ die) for three consecutive days. Prednisone was then tapered and, given the clinical history, the patient was referred to our Hospital for further evaluation including a KB.
During the first admission, two weeks from the MPN boluses, the aPTT was shortened but still abnormal (1,33 ratio), associated with a mild deficiency of FXI (33.24%). Four weeks later, while he was still on low dose prednisone, his FXI dropped again (6.21%). aPTT performed on 2 hours incubation mixture with normal plasma, showed no correction (see Table 1).
Considered the fluctuations of FXI activity, the result of incubated mixing test and the autoimmune history of the patient we suspected an acquired FXI deficiency; anti FXI Inhibitor (Bethesda Nijmegen method) was therefore searched and detected at 1.4 Bethesda Njimegen Units (BU).

Age (months)	**aPTT ratio (n.v. 0.82-1.2)**	**aPTT mix ratio (n.v. 0.86-1.2)**	**FXI (%)**	**Inhibitors (BU)**
21	3,92	1,09	<1	
38	3,8		1	
44	3,35	2,68	<1	
49	3,65	2,90	<1	
53	3,73	2,02	0	
54	1,33	2,02	33 , 24	
55	3,08	1,39	6,21	1 , 4

55	3,15	1,18	6	negative
56	4,26	1,18	5 , 51	
58	2,27	1,22	8,35	negative
61	1,49	1,12	16	Not searched
66	4,19	2.94	7	3
72	4,18	1,48	6.20	0 , 8

Thromboelastometric tests (ROTEM), performed before the KB to better assess the global hemostatic process and the bleeding risk, showed prolongation of the clotting time in the INTEM reagent, in line with aPTT prolongation and FXI deficiency.

Table 1: Coagulation parameters during follow up.

Due to the unpredictable bleeding risk of the patient, related to the acquired FXI deficiency. The KB was safely performed after "off label" administration of recombinant activated factor VII (rFVIIa), given IV at 50 mcg/Kg before and 3 hours after the KB. The histological pattern showed a Membranous Glomerulopathy; the nephrologists scheduled treatment with anti-CD 20 MoAb (Rituximab) but, due to the onset of salmonella gastroenteritis, it was postponed until the absence of Salmonella spp. on the stool samples cultures; therapy with oral tacrolimus 0,12 mg/kg/die was pursued in order to wean the boy from steroids which were tapered and suspended.

Two months after tacrolimus therapy he received two doses of IV anti-CD20 MoAb Rituximab (1 g/m^2), given two weeks apart that led to clinical remission of the nephrotic condition. He was therefore discharged and started on regular outpatient follow up.

Subsequent coagulation assays showed persistent prolongation of the aPTT as well as persistent FXI deficiency (see Table 1). FXI antigen levels resulted reduced in accordance with FXI activity.

The boy came back twice to our Centre during the follow up period. His nephrotic condition resulted in remission for six month since rituximab therapy and re-presented in the one-year follow up visit. His FXI levels resulted reduced in both occasions. Anti-FXI inhibitor was detected at the last follow up (3 BU).

During his last admission, he received another Rituximab infusion. At that time, his aPTT was markedly prolonged as well as mixing tests and FXI level was reduced at 6%; Inhibitor test was 0.8 BU.

The boy has never suffered from any bleeding symptoms to

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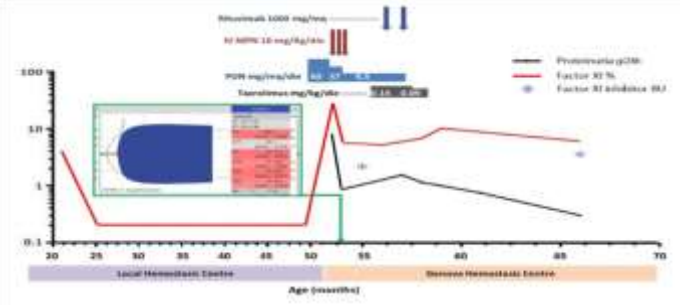

Figure 1

Discussion

FXI deficiency is an inherited bleeding disease which differs from X linked FVIII deficiency (hemophilia A, HA) and FIX deficiency (hemophilia B, HB) by its autosomal inheritance pattern and variable bleeding tendency. FXI deficiency is common in Ashkenazy Jews with a heterozygote frequency of 8% to 10% [3].

The bleeding phenotype in FXI deficiency is generally mild, even in severe deficiency with symptoms often appearing later in life compared to Hemophilia A and B. Clinical symptoms include mucocutaneous bleeding provoked by a surgical hemostatic challenge, post-injury, epistaxis, and heavy menstrual bleeding. Surgery involving areas with high fibrinolytic activity, such as the urogenital tract or the oropharyngeal cavity (tonsillectomy/dental extraction), seems to correlate with the highest bleeding risk (49%–67%) [4].

Unprovoked bleeding episodes that are frequently seen in severe HA or HB, such as hemarthroses, muscle bleeds, or soft tissue bleeds, are not frequently observed in severe FXI deficiency [3]. Importantly, the bleeding phenotype does not correlate with the FXI activity level, with evidence of bleeding reported in heterozygotes with mild deficiency (FXI levels 20%–60%). This lack of correlation between the bleeding risk and FXI activity levels poses a significant therapeutic challenge [3]. Patients with FXI deficiency present with a prolonged aPTT along with a normal Prothrombin Time and Thrombin Time [2]; however, due to the variable sensitivity of available aPTT reagents to coagulation factor deficiencies, whereas a normal aPTT excludes severe FXI deficiency, it may not reveal a partial deficiency (FXI activity 20%–60%), which may be still associated with clinical bleeding complications [3]. In general, the aPTT is prolonged when the FXI activity level is less than 30 % [5]. Severe FXI deficiency is defined as activity level less than 15-20%, which is most commonly found in homozygotes or compound heterozygotes. Heterozygotes typically have FXI activity levels of 20% to 60% [6,7].

The management of bleeding in FXI deficiency includes Fresh Frozen Plasma (FFP), FXI concentrates (currently available in certain European countries), and “off label” use of low-dose activated recombinant Factor VII (rFVIIa) [8]. Antifibrinolytic agents, such as ε-aminocaproic acid or tranexamic acid, may be used for the control of minor bleeding episodes or pre-operatively for certain surgeries. They can be used alone or, as adjunctive therapy, in association to other hemostatic agents [3].

Factors influencing the management include the site and nature of surgery and the presence of any risk factors for thrombosis. The optimal hemostatic level of FXI is debated, but a level of 30 to 45 % is considered probably sufficient [7].

Inhibitors occurring in patients with inherited deficiencies of coagulation factors typically are "alloantibodies," while those developing spontaneously in individuals with previously normal coagulation factor function are designated as "autoantibodies" [9]. The latter category includes inhibitors against coagulation factors I, II, V, VII, VIII (acquired hemophilia A), IX (acquired hemophilia B), X, XI, and XIII. Acquired coagulation inhibitors are autoantibodies that bind to coagulation factors and neutralize their activity or accelerate their clearance [2,10] .

The development of inhibitors to FXI is a rare but significant complication in about one third of individuals with homozygous congenital deficiency. Alloantibodies that inhibit FXI activity develop relatively frequently after replacement therapy with plasma or FXI concentrate in patients with the severest form of deficiency (<1% normal FXI level). These subjects rarely exhibit spontaneous bleeding, and may not respond to therapy with
FXI [9].

Although most patients who develop inhibitors have been previously exposed to plasma or FXI concentrate, they rarely exhibit spontaneous bleeding, and may not respond to therapy with FXI.

Antibody mediated acquired FXI deficiency is rare, being reported with autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, Crohn disease)[1,11], or malignancies (chronic myelomonocytic or lymphocytic leukemias, and gastrointestinal adenocarcinoma) [11].

The most common laboratory finding in patients with FXI inhibitors is an isolated prolonged aPTT that does not correct when repeated on a 1:1 mixture with normal plasma; two hours incubate aPTT mixing procedure should also be performed to better detect autoantibodies against factors due to their particular kinetic secondary to their different thermal sensitivity (Type II inhibitors) [12].

When an inhibitor is suspected by prolonged aPTT, which does not correct after mixing studies, its presence should be confirmed with the "Bethesda" assay [2].

In 2012, McManus described a case of acquired FXI in a child with membranoproliferative Glomerulonephritis. A 7 years old male presented with nephrotic syndrome and subsequently developed FXI deficiency. He developed bleeding after surgical challenge requiring FFP infusion. A low titer inhibitor was detected against factor XI [13]. Here we report the second case of acquired FXI deficiency in a child with membranous glomerulonephritis.

In our case, the presence of inhibitor together with detectable FXI activity suggests Type II kinetic of the inhibitor.

This hypothesis is also supported by the unprolonged immediate aPTT mixing test.

Inhibitors should be suspected when coagulation factor(s) deficiency is found in subjects with autoimmune diseases. To date this is the second report of acquired FXI inhibitor in children in the contest of an autoimmune disorder but, the coagulopathy preceded the onset and recurrence of the nephrotic syndrome and could be considered a marker of the entire autoimmune disorder.

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