Factor XI deficiency: About 20 cases and literature review

Déficit en facteur XI: A propos de 20 cas et revue de la littérature

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RÉSUMÉ

Introduction : La déficience en facteur XI est un trouble rare de la coagulation entraînant des manifestations hémorragiques variables.

Objectifs : Evaluer la corrélation entre le degré du déficit en facteurXI et l'expression clinique de la maladie.

Méthodes : Etude rétrospective, s'étalant sur 10 ans du 1ier javier 2010 au 31 décembre 2019, concernant les patients suivis au Centre d'hémophilie à l'hôpital Aziza Othmana de Tunis. Les données ont été recueillies à partir du registre des dossiers médicaux. La détermination du TP, TCA, taux du fibrinogène et le dosage des facteurs de la coagulation sont réalisés par technique coagulométrique sur STA® compact / ACL TOP®. Le déficit en FacteurXI a été confirmé sur deux prélèvements différents. L'analyse statistique de la corrélation clinico-biologique a été réalisée à l'aide du testdu chi-deux. Le seuil de signification était de 0,05.

Résultats : vingt patients ont été colligés. L'âge moyen de découverte était de 25 ans avec un sex-ratio (M /F) =0,33. Les circonstances de la découverte étaient fortuites chez 14 patients. Les antécédents familiaux hémorragiques ont été rapportés dans 30% des cas. 8 patients ont subi un acte chirurgical dont 6 avaient des suites opératoires simples. Le TCA était allongé et isolé dans 75% des cas. Le bilan d'hémostase a été revenu normal dans 5 cas. Le taux de FacteurXI moyen était de 24%. La tendance aux saignements ne semblait pas être corrélée aux taux de FacteurXI.

Conclusion : Des études prospectives multicentriques incluant l'étude moléculaire seraient nécessaires afin de mieux élucider ce trouble rare.

Mots clés : Trouble de la coagulation, facteur XI, déficit en facteur XI, déficit rare, syndrome hémorragique.

ABSTRACT

Introduction: Factor XI deficiency is a rare coagulation disorder with variable bleeding manifestations.

Aim : To evaluate the correlation between the degree of factorXI deficiency and the clinical expression of the disease.

Methods: Retrospective study, spanning 10 years from January 1, 2010 to December 31, 2019, concerning patients followed at the Hemophilia Center at Aziza Othmana Hospital in Tunis. The data were collected from the medical records. The determination of PT, APTT, fibrinogen level and coagulation factors are performed by coagulometric technique on STA® compact / ACL TOP®. FactorXI deficiency was confirmed on two different samples. Statistical analysis of the clinical-biological correlation was performed using the chi-square test. The significance level was 0.05.

Results: Twenty patients were collected. The mean age of discovery was 25 years with a sex ratio (M/F) =0.33. The circumstances of discovery were incidental in 14 patients. A family history of bleeding was reported in 30% of cases. Eight patients underwent surgery, six of whom had a simple postoperative course. The APTT was prolonged and isolated in 75% of cases. The hemostasis test was normal in 5 cases. The average FactorXI level was 24%. The tendency to bleed did not seem to be correlated with FactorXI levels.

Conclusion: Prospective multicenter studies including molecular study would be necessary to better elucidate this rare disorder.

Key words: Coagulation disorder, factor XI, factor XI deficiency, rare coagulation deficiency, bleeding syndrome.

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LA TUNISIE MEDICALE - 2022 ; Vol 100 (01) : 60-65

INTRODUCTION

Factor XI deficiency is a rare inherited bleeding disorder first described in1953 by Rosenthal and al [1, 2]. Affected individuals may have bleeding symptoms following a trauma or a surgery and some of them have few of any symptoms. It is often asymptomatic with a variable hemorrhagic tendency, rarely spontaneous, but mostly hemorrhage related to surgery or trauma [3]. Bleeding in this disorder occurs especially in areas of high fibrinolytic activity: oral and nasal mucosa and urogenital tract [3].

In Tunisia, very few studies have focused in exploring the particularities of FXI deficient patients. In view of the lack of correlation between bleeding symptoms and FXI levels, the aims of our study were to report clinical and biological data of constitutional FXI deficiency in patients diagnosed and treated at the Aziza Othmana Hospital in Tunis with a literature review.

METHODS

All patients with FXI deficiency who were followed up at the Hemophilia Center (CH) of Aziza Othmana Hospital in Tunis for a period of 10 years from January 2010 to December 2019 were included in this retrospective study. The data were gathered from the medical records registry. The criteria of inclusion were two separate FXI assays to establish the diagnosis of a deficiency.

The data collected were:

- Clinical (age, sex, family history, circumstance of discovery, characteristics of the bleeding syndrome),
- Biological (PT, APTT, fibrinogen and FXI factor levels)
- Therapeutic.

The FXI deficiency was considered severe for levels < 15%, moderate for levels between 15 and 50% [3].

The SPSS version 20 software was used for data analysis. The analysis of the clinical-biological statistical correlation was performed using the chi-square test. The significance range was 0.05.

Confidentiality and anonymity were respected in the study.

RESULTS

Clinical Data

Twenty cases of FXI deficiency were identified during the period studied, which represent a prevalence of 4 cases/1 000 000 inhabitants in northern Tunisia. The average age at diagnosis was 25 years [1 - 68 years], with a sex ratio (M/F) of 0.33. Family and personal bleeding histories were observed in 6 and 5 cases respectively.

The personal hemorrhagic history was essentially mucocutaneous: epistaxis and ecchymosis. One case of hemarthrosis and one case of hemorrhagic miscarriage were reported.

The diagnosis of FXI deficiency was mainly made incidentally during a preoperative assessment of 11 patients (Table 1). Four patients presented a hemorrhagic syndrome that motivated them to consult.

Table 1. Circumstances of FXI factor deficiency diagnosis

Purpose of consultation Number		Effectifs	Pourcentage (%)
Pre-operative extended APTT		11	55
Bleeding Symptoms	* Post-operative	2	20
	* Post-dental-care	1	
	*Hemarthrosis(knee injury)	1	
Family Survey		2	10
During Pregnancy		3	15
Total		20	100

Eight patients had undergone a surgery, 5 had simple post-operative outcomes (Table 2).

The surgical procedure was a circumstance of diagnosis in a single patient with post-surgical (surgery unspecified) with a strictly normal hemostasis assessment (normal APTT).

Bleeding events after tooth extraction were observed

Table 2. Surgical History and Postoperative Outcomes

Patient #	Age (year)	Gender (M/F)	Surgery	Post-operative outcomes	Diagnosis	Pre-operative treatment	recourse to per-operative treatment
1	44	F	*Caesarean section	Simples	Unknown	No	---
			*Thyroid goiter	Simples	known	5FFP+Tranexamic acid	
2	20	M	Circumcision	Bleeding on Day 1	Unknown	No	No
3	26	F	Caesarean section	Simples	Unknown	Unspecified	--
4	37	F	Unspecified	Post-urgical bleeding	Unknown	Unspecified	No
5	38	F	*Tumor of the thigh	Simples	Unknown	No	--
			*In vitro fecondation	hemorrhagic punction	Unknown	PRBC+FFP	
6	43	F	Caesarean section	Post-partum hemorrhagie	Unknown	No	No
7	13	M	*Facial tumor *Circumcision	Simples	Unknown	No	--
8	68	F	*Uterine fibroids *Ovarian cyst	Simples	Unknown	No	--

• **M**: male; **F**: female; **PRBC**:packed red blood cells; **FFP**:fresh frozen plasma.

in 13% of our patients who didn't need a prophylactic treatment. Tranexamic acid is prescribed for all planed ….

Family survey was conducted in only 2 patients:

The patient n°7 had no post-circumcision bleeding event in her three sons, two of whom, however, had bilateral episodes of epistaxis during the summer. (Figure N°1).

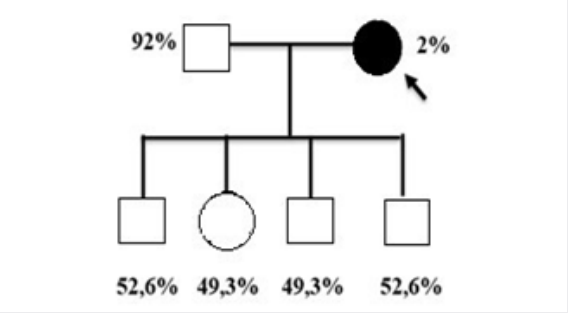

Figure 1. Family tree patient 7.

For the second family: the survey revealed 2nd degree consanguinity of the parents.

The factor XI dosage was carried out in the presence of an extended preoperative APTT (dermoid scalp cyst) in patient n#15 (Figure N°2).

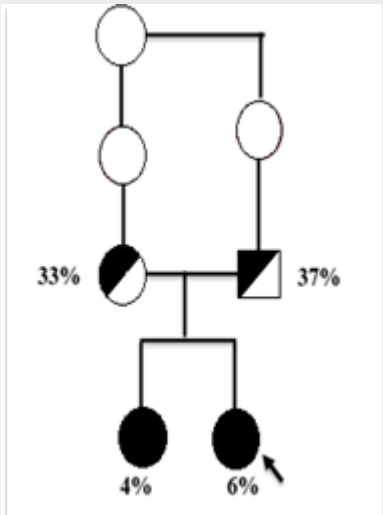

Figure 2. Family tree patient 15.

We realized an FXI assay for three newborns whose mothers were diagnosed with FXI deficiency. The FXI levels were lowered (28%, 13%, and 21%) and not thereafter controlled.

Laboratory

The APTT was prolonged in 75% of the cases and corrected on the mixing test in all cases with a normal TQ. The average fibrinogen level was 3.69 g/l (2.28 to 7.3). The mean FXI level was 23.9% [1-58%]. Severe deficiency was reported in 45% of cases (Tables 3 and 4).

Table 3. Distrubition of patients accorrding to Factor XI levels

FXI deficiency	Effectifs	
	Number	Pourcentage (%)
Severe (<15%)	9	45
Moderate (15-50%)	11	55
Total	20	100

In our study, factor XI levels were not correlated with bleeding disorders (p=0.29).

Table 4. Demographic, clinical and biological caracteristics of patients included in our study

Patient #	Gender (M/F)	Age at diagnosis (years)	Bleeding symptoms	Surgery	APTT	FXI
1	M	54	No	No	Prolonged	1%
2	F	36	Yes	Yes	Normal	54%
3	F	68	No	No	Prolonged	54%
4	M	11	No	Yes	Prolonged	30%
5	F	28	No	No	Prolonged	1%
6	F	20	No	No	Prolonged	32%
7	F	40	No	Yes	Prolonged	2%
8	F	26	No	No	Prolonged	4%
9	F	22	No	No	Prolonged	4%
10	M	16	Yes	Yes	Prolonged	20%
11	F	12	No	No	Prolonged	21%
12	F	31	Yes	No	Normal	58%
13	M	2	No	No	Normal	49%
14	F	5	No	No	Prolonged	5%
15	F	1	No	No	Prolonged	9%
16	F	35	Yes	Yes	Normal	7%
17	F	38	No	No	Prolonged	24%
18	F	28	No	No	Normal	58%
19	F	35	No	No	Prolonged	1%
20	F	44	Yes	Yes	Prolonged	24%

M: male; **F**: female

Treatment of FXI Deficiency

No data were available for analysis. Tranexamic acid used to be prescribing for minor surgery and fresh frozen plasma for major surgery with tranexamic acid.

All the patients were treated with the tranexamic acid (Exacyl®) for minor superficial bleeding.

For programmed surgical procedures as well as for dental extractions, fresh frozen plasma (FFP), sometimes in combination with exacyl®, was used. Both oral and local exacyl was used in all symptomatic patients.

All symptomatic patients were treated with oral and local exacyl and received intravenous treatment the day before tooth extraction and oral treatment on the following days. FFP was recommended for surgery such as caesarian section.

DISCUSSION

Inherited factor XI deficiency is a rare bleeding disorder, often autosomal recessive with a prevalence of 1 case/1, 000,000 people. Indeed, a low frequency has been found in many populations around the world [3]

Nevertheless, FXI deficiency is particularly common among Ashkenazi Jews [4], in whom the frequency of carrying an abnormal FXI allele is about 5% [2]. Other populations seem to have an increased frequency starting with Iraqi Jews, but also French Basques [3] and a group residing in a region of northeast England [5]. In northern Tunisia, where 50% of the population is registered, the prevalence of FXI deficiency is 4 cases/1, 000,000 inhabitants. However, this prevalence may be underestimated, due to non-diagnosed cases of FXI deficiency that are not recorded in the registry of the hemophilia center of the Aziza Othmana Hospital in Tunis, which manages inherited bleeding disorders. This prevalence remains fairly high due to the frequent parental consanguinity in Tunisia. This makes necessary the establishment of a national register.

In our series, the mean age at diagnosis was 25 years (1 to 68 years). Our results were similar to some of the data in the literature. In an Italian study of 34 cases of FXI deficiency, the mean age was 22 years (14 to 83 years) [6], and in a study conducted in the French Basque Country, Bauduer F.al. reported a mean age of 21 years [7]. A female predominance with a sex ratio of 0.33 was found in our series, comparable with the Santoro R. study in 2011 [6]. Regarding family history, 6 patients had FXI deficiency in the family leading to a family survey or screening at birth. Some authors have taken an interest in the study of families with factor XI deficiency [8,9], but according to some authors, screening at birth is not justified because of its relatively limited clinical consequences and due to hepatic immaturity [3].

Based on the literature, there is a wide clinical heterogeneity with diverse circumstances of discovery [3]. Some forms may be asymptomatic while others can be symptomatic with potentially life-threatening hemorrhagic syndrome [3].

In our series, patients were frequently asymptomatic and the circumstance of discovery was mainly fortuitous because of a prolonged APTT. As well in he series of Santoro R et al, 70% of patients were asymptomatic [6].

Bleeding symptoms due to FXI deficiency are variable from one patient to another and within the same person under the same risk situations [10]. In our study, 5 patients had a personal history of bleeding. The most common type of hemorrhagic events was mucocutaneous. Santoro C. al, in a series of 95 patients treated for FXI deficiency, 59% of the patients had non-surgical bleeding episodes [11]. The main bleeding symptoms reported were easy ecchymosis followed by epistaxis. in the series of Santoro R. [6], 29% of patients had experienced hemorrhagic symptoms such as epistaxis and menorrhagia. This was also observed by Castaman al, [12]. Indeed, severe spontaneous bleeding is rarely reported to occurin FXI deficient patients, although menorrhagia and epistaxis are relatively common [13]. In fact, the clinical manifestations do not affect the daily life of the patients, so they are not motivated to seek treatment. On the other side, the localization of bleeding episodes is explained by the existence of a predilection for tissues with high fibrinolytic activity (ORL area, urogenital tract, digestive mucosa. Bleeding, particularly after circumcision or in skin wounds, is even less frequent [14]. Phenotypic heterogeneity may be partly due to variability in the definition of “bleeding”, or due to the presence of other associated hemostasis disorders, particularly Willebrand factor deficiency, a common pathology of homeostasis in all populations [3], or also due to the underlying molecular abnormality. The postoperative was without complications in the majority of cases in our series, except for 3 patients (caesarean section and circumcision//unspecified surgery) who had presented bleeding complications. Santoro C. et al [11] found a prevalence of bleeding after major or minor oropharyngeal (especially tonsillectomy and adenoidectomy) or genito-urinary surgery in 40% and 38% of cases respectively.

During the period of the study, only one patient had a pre-diagnosed hemorrhagic delivery (postpartum hemorrhage) and one patient had a hemorrhagic miscarriage.

The literature review revealed an incidence of bleeding during childbirth,in severe deficits, estimated at 20% [13, 15].

Other authors reported a higher rate than ours. Kadir et al found a 40% prevalence of deliveries complicated by postpartum hemorrhage, while none of the women who received prophylactic treatment had hemorrhagic complications [13]. However, according to Santoro et al., only two bleeding complications were noted in 30 spontaneous deliveries without prophylaxis [6].

The laboratory diagnosis of FXI deficiency is based on simple routine tests. A deficit can be suspected during a systematic haemostasis test by the detection of an isolated prolonged APTT. APTT is more likely to be sensitive to severe FXI deficiency, its sensibility is very dependent on the reagents used [3].

We found normal APTT in 25% of patients. A recent study conducted by Puetz J. in 2018 in the United States over a period of 10 years, involving 7 children with FXI deficiency, revealed that 3 children had a normal APTT [16]. Therefore, in the presence of a normal APTT and evocative clinical features, an FXI assay should be performed considering the variability of APTT reagent sensibility, particularly in a bleeding disorder.

Depending on the reagent used, the sensibility of APTT to factor deficiency is very different. This should be considered during the assay of patient plasma [17]. Several Commercial reagents are available with different performance characteristics [18]. The most recommended reagents to screen bleeding risk are particulate activator reagents (kaolin, micronized silica, colloidal silica) [19].

We have used kaolin and then micronized silica in our laboratory. The norms for the FXI level varied from one

author to another, but generally the normal FXI level is between 60-120%. An FXI deficiency is considered severe for < 15% rates whereas some authors considered it severe if < 20%; corresponding generally to homozygous or heterozygous composite mutations.

Salomon O. has shown that patients with a severe deficit have a more significant bleeding risk than those with a mild deficit, with a relative risk of 13 for severe deficits compared to 2.6 for moderate deficits [20].

As reported by other authors, hemorrhage has been observed in more than 60% of patients with severe deficiency undergoing tooth extraction, tonsillectomy, nasal surgery or urological surgery [2]. We have found that most of our patients had one or more dental extractions without prophylaxis, 13% have had bleeding at least once.

Depending on the studies, the incidence of hemorrhage tooth post-extraction, among patients, varied from 25 to 65% [21,22].

After displaying the different bleeding symptoms in patients with FXI deficiency, our second aim was to assess the correlation between this disorder and the occurrence of hemorrhage.

In the present study, there is a poor association between FXI level and bleeding tendency in patients with FXI deficiency. This finding has been confirmed by larger studies [2, 6, 11]. In fact, the bleeding tendency may also vary in the same individual

It is important to note that many patients with severe FXI deficiency do not bleed, although several authors have reported difficulties to classify severe and moderate FXI deficiency at levels around 20%. It should be noted that studies showing an association between FXI levels and bleeding tendency use data collected from Jewish patients [10,22], while studies reporting a non-association usually involve groups from different ethnic backgrounds [9].

Recently a survey has concluded that the correlation between factor level and symptom severity is lowest for FXI among all congenital coagulation factor disorders [24, 25].

Many factors could be implicated in this variation: presence of other associated hemostasis abnormalities, type of mutation, type of surgical situation, which makes difficult to develop a recommendation for managing this condition [2].

As bleeding syndrome is often poorly correlated with FXI levels, other coagulation tests such as thrombin generation tests or rotational thromboelastometry may be useful to evaluate bleeding risk, but there is currently insufficient data to use these tests in clinical practices [2].

Genetic anomalies responsible of the deficiencies are various (false or non-sense mutations, deletions, insertions or splicing anomalies) also periodically new variants are identified. More than 188 mutations have been described. These mutations may affect the 4 domains of the FXI factor. The majority of mutations were responsible of simultaneous decrease in coagulant and antigenic activities (CRM-) while only 4% ofCR M+ forms were observed [23].

The molecular analysis of our patients with FXI deficiency is currently being conducted in our center.

The management of FXI deficiency should be individualized based on the type of procedure, the FXI level and the history of bleeding. In general, there is no need for prophylactic therapy for daily activities even for patients with severe FXI deficiency. However, in cases of major surgery or trauma, treatment may be required [14].

Anti-fibrinolytics such as tranexamic acid (Exacyl®) are used for low bleeding conditions (dental surgery, menstrual bleeding) and FXI concentrates (not available in Tunisia) or FFP are used for high bleeding risks (surgical prophylaxis, symptomatic bleeding) [9].

Combinations of anti-fibrinolytics and recombinant FVIIa concentrate can also be used in some cases, particularly in the presence of a specific FXI inhibitor [26].

Such treatments are subject to a very strict risk/benefit balance because of the possible important side effects: in particular, FXI concentrates may have a serious prothrombotic effect [27].

In cases of minimal superficial bleeding, tranexamic acid exacyl® is the most frequently used to manage our patients. The combined use of FFP and exacyl was for cold-programmed surgical procedures.

CONCLUSION

This study certainly has some weaknesses due to retrospective character of the data analysis and the unavailability of the molecular analysis of the factor XI gene.

Due to the limited frequency of this deficiency and the lack of clinical manifestations in many cases, it was not possible to have a large number of patients.

However, this is the first and largest Tunisian survey to our knowledge, which allowed us to confirm the heterogeneity of the hemorrhagic phenotype in FXI deficient patients.

Molecular investigation combined with rotational thromboelastometry seems to be needed in order to better elucidate the pathogenesis of this disorder and thus provides an optimal personalized therapeutic approach.

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