Thrombosis & Hemostasis

research paper

haematologica 2002; 87:512-514

http://www.haematologica.ws/2002_05/512.htm

Factor XI deficiency in Iranians: its clinical manifestations in comparison with those of classic hemophilia

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Background and Objectives. In patients with factor XI (FXI) deficiency the bleeding tendency is poorly correlated with plasma factor levels. The purpose of this study was to evaluate whether or not this discrepancy is also present in a large series of patients from Iran, a previously unexplored ethnic group.

Design and Methods. In 28 FXI - deficient patients bleeding symptoms and their relation to FXI levels were compared with those of 100 patients with factor VIII (FVIII) deficiency (classic hemophilia), matched for severity of factor deficiency.

Results. Spontaneous bleeding was definitely less frequent in FXI deficiency than in hemophilia, whereas post-operative and post-traumatic bleeding occurred with comparable frequencies. Among FXI-deficient patients the severity of symptoms was poorly correlated with FXI levels, mildly deficient patients bleeding almost as frequently as those severely deficient. In contrast, in patients with classic hemophilia there was a close relation between the severity of bleeding and degree of FVIII deficiency.

Interpretation and Conclusions. As in other ethnic groups, in Iranians factor XI deficiency is less severe than classic hemophilia and the bleeding tendency is poorly correlated to plasma factor levels.

Key words: factor XI deficiency, hepatitis C, hepatitis B.

The inherited deficiency of coagulation factor XI is a rare bleeding disorder with an estimated prevalence in the general population of one case in one million people.[1] Transmitted as an autosomal trait, it is much more frequent among Ashkenazi Jews than in other ethnic groups, with an estimated prevalence of heterozygosity as high as 8%.[1] A peculiarity of factor XI deficiency that distinguishes it from the hemophilias (factor VIII and factor IX deficiencies) is the poor association between the degree of plasma factor XI deficiency in these patients and their clinical tendency to bleed.[2-4] This discrepancy has not been evaluated extensively in Asian patients, and particularly in such a homogenous ethnic group as Iranians. In this report we describe the type and frequency of bleeding symptoms and their relation to factor XI levels in a relatively large series of 38 patients from Iran, compared with 100 patients with factor VIII deficiency (classic hemophilia) matched for age and degree of factor deficiency. The prevalence of blood-borne viral infections was also compared in these two groups of multitransfused patients.

Design and Methods

Patients

We investigated 38 factor XI deficient patients (25 males, 13 females, age 2 to 63 years) included in the Iranian National Registry of Inherited Bleeding Disorders. These patients had been diagnosed over a period of 6 years and belonged to 30 unrelated families with a high frequency of consanguinity. Since the Islamic Republic of Iran has a population of 60 million people, assuming a prevalence of the defect of one case in 1 million people, our series of factor XI deficient patients is likely to be a representative one. Each patient was seen by the same physician (ML) who evaluated the following bleeding symptoms if they occurred at least once in the lifetime of the patients: hemarthrosis, soft-tissue hematoma, umbilical cord bleeding, epistaxis, hematuria, menorrhagia, gastrointestinal (GI) bleeding, central nervous system (CNS) bleeding, oral cavity bleeding (including bleeding after dental extractions) and post-operative bleeding (including post-circumcision bleeding). A few criteria were established before the study to evaluate whether or not symptoms as reported by the patients could be accepted as valid. Epistaxis qualified only when it occurred spontaneously more than five times lifelong, from both nostrils, lasted more than 10 min or required hospital admission. Menorrhagia, evaluated in 13 women of reproductive age, was defined by menstrual periods requiring the therapeutic use of combined estrogen-progestogen preparations or causing iron deficiency. Bleeding in the gastrointestinal and urinary

tracts and in the central nervous system had to be documented by hospital records. Muscle hematomas and hemarthroses qualified if they occurred spontaneously or following minor trauma and caused at least transient signs of functional joint or muscle impairment. Excessive bleeding after dental extractions or other surgical operations was considered only when it occurred in patients who had not received prophylactic replacement therapy, usually before the coagulation defect had been diagnosed. Oral bleeding had to last more than 10 min or to require the intervention of an oral surgeon, whether caused by dental extractions or by bites to lips, cheeks and tongue. Surgical bleeding and post-partum bleeding qualified only if they caused a delay in discharge from hospital or required blood transfusion. Easy bruising was not considered because the evaluation of this symptom by patients was considered too subjective.

As a comparison group, 100 Iranian patients with classic hemophilia (factor VIII deficiency), matched with the factor XI-deficient patients for age and level of deficient clotting factor, were also evaluated. Since no factor XI-deficient patients had inhibitors (see Results), factor VIII-deficient patients were chosen among those with no history of inhibitors.

Laboratory methods

Factor XI coagulant activity was measured in plasma using a one-stage method based upon the activated partial thromboplastin time and on the use, as substrate, of factor XI-deficient plasma obtained from a patient with unmeasurable factor XI activity and antigen (in-house enzyme immunoassay). The presence of factor XI inhibitors was evaluated with a method adapted from the Bethesda assay used routinely in our laboratories for factor VIII inhibitors. Serum markers for hepatitis B and hepatitis C viruses (HBV and HCV) and human immunodeficiency virus (HIV) were analyzed using standard enzyme immunoassays.

Results

Among factor XI-deficient patients, 18 had severe or moderate factor deficiency (arbitrarily defined as plasma levels ranging from less than 1% to 5%), 20 had mild deficiency (6 to 30%). None of them had an inhibitor to factor XI coagulant activity. In the comparison group of 100 patients with factor VIII deficiency and no inhibitor, 50 had severe or moderate deficiency and 50 had mild deficiency defined with the same criteria used above. Table 1 indicates that patients with severe/moderate or mild factor XI deficiency had almost the same frequencies of spontaneous bleeding symptoms such as hemarthrosis and hematomas. Bleeding in the oral cavity and after surgical procedures (of which the most frequent was circumcision) was more frequent in patients with severe/moderate disease, but often occurred also in those with mild deficiency. Other bleeding symptoms were rare in both groups with the exception of epistaxis. In hemophilia A patients, hemarthrosis and hematomas were much more frequent than in factor XI deficiency and in patients with severe/moderate deficiency than in those with mild deficiency. Other bleeding symptoms, spontaneous or post-traumatic, were also definitely more frequent in hemophiliacs with more severe deficiency (Table 1). No factor XI-deficient patient was infected by HIV or HBV, but the prevalence of HCV infection was high (50% vs 90% in hemophilia A patients) (Table 2).

Table 1. Percentages of Iranian patients with severe/moderate (n=18) and mild factor XI deficiency (n=20) who had a given bleeding symptom at least once in comparison with the same percentages in patients with severe/moderate (n=50) and mild (n=50) factor VIII deficiency.

Bleeding symptom	*Factor XI deficiency*		*Factor VIII deficiency*	
	Severe/moderate	*Mild*	*Severe/moderate*	*Mild*
Hemarthrosis	27% (5/18)	30% (6/20)	86% (43/50)	6% (3/50)
Hematoma	22% (4/18)	40% (8/20)	82% (41/50)	8% (4/50)
Hematuria	0	5% (1/20)	12% (6/50)	0
GI bleeding	0	0	10% (5/50)	0
CNS bleeding	0	0	4% (2/50)	0
Menorrhagia	0/3	10% (1/10)	–	–
Epistaxis	27% (5/18)	40% (8/20)	20% (10/50)	12% (6/50)
Post-operative bleeding	66% (12/18)	60% (12/20)	76% (38/50)	30% (15/50)
Oral cavity bleeding	78% (14/18)	35% (7/20)	64% (32/50)	30% (15/50)

Table 2. Prevalence of serological markers for hepatitis B and C and human immunodeficiency virus in 38 Iranian patients with factor XI deficiency and in 100 patients with hemophilia A.

	In patients with factor XI deficiency	*In patients with hemophilia A*
HBsAg	0%	2.6%
Anti-HBs	40%	65%
Anti-HCV	50%	90%
Anti-HIV	0%	5%

Discussion

In an ethnically homogeneous group of factor XI-deficient patients from Iran bleeding occurred less frequently than in patients with classic hemophilia of comparable severity, as previously reported in other ethnic groups.[1-4] The pattern of symptoms was also different between the two inherited bleeding disorders, with a much lower prevalence of hemarthrosis and hematomas and with a relatively high prevalence of post-operative bleeding in factor XI deficiency. In general, the clinical manifestations of Iranian patients with factor XI deficiency reflected those reported in the literature, with the exception of a lower percentage of women with menorrhagia.[4] As previously observed in other ethnic groups,[1-4] in Iranians the bleeding tendency of factor XI deficiency was poorly correlated to plasma factor levels, with mildly deficient patients bleeding almost as frequently as more severely deficient patients. There is no clear explanation for this paradox that is quite unique among inherited coagulation deficiencies. Perhaps the one-stage factor XI activity assay used in this and other studies does not reflect some effects of factor XI that are crucial for hemostasis, such as those on the function of platelets and of the fibrinolytic system.[5-7]

An additional goal of this study was the comparison, in two groups of multitransfused patients, of the prevalence of serum markers of blood-borne viral infections. In Iran, patients with factor XI deficiency are usually treated with locally-produced, single-donor fresh frozen plasma, whereas hemophilia A is treated with a wider spectrum of products, ranging from locally-produced, single-donor cryoprecipitate to large-pool commercially- and locally-produced factor VIII concentrates, that only in the last decade have been virally inactivated. The use of single donor fresh-frozen plasma and the lesser clinical severity of factor XI deficiency leading to less transfusions is likely to explain the lower prevalence of markers of active viral infection in factor XI-deficient patients than in hemophiliacs.

Contribution and Acknowledgments

FP did the analysis of the data collected and supplied by ML. They both conceived the study and wrote the manuscript which was substantially revised by PM. We thank Dr. Sharifian for helpful criticism and advice.

Funding

This study was supported in part by the Fondazione Italo Monzino, Italy.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Paul Giangrande, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Giangrande and the Editors. Manuscript received January 30, 2002; accepted March 13, 2002.

What is already known on this topic

Factor XI levels correlate poorly with the bleeding tendency and spontaneous bleeding in factor XI deficiency is less frequent than in hemophilia.

What this study adds

This study focuses on a large cohort of patients from Iran, an ethnic group which has hitherto not been studied in detail. The study also reports on seroprevalence of viral markers in this group.

Potential implications for clinical practice

The possibility of factor XI deficiency should be considered in patients of both sexes with a history of bleeding problems, including menorrhagia, post-traumatic and/or operative bleeding.

Paul Giangrande, Associate Editor