FACTOR X DEFICIENCY IN NORTH PAKISTAN

Masood Anwar, Syed Naeem Raza Hamdani, Muhammad Ayyub, Waqar Ali

Armed Forces Institute of Pathology, Rawalpindi, Pakistan

Background: Factor X deficiency is one of the most rare hereditary coagulation disorders. In populations where rate of consanguineous marriages is high, rare hereditary disorders also flourish. Pakistan is one of those countries. The study was conducted to estimate the incidence of factor X deficiency in patients with bleeding disorders in North Pakistan. **Methods:** The records of the patients referred to Armed Forces Institute of Pathology for investigations of a suspected bleeding disorder were reviewed from 1st January 1997 to 30th June 2002. All patients referred for the investigations of a suspected bleeding disorder were included in the study. All patients underwent clinical interview and examination at the department. Factor X deficiency was diagnosed on the basis of prolonged prothrombin time and prolonged partial thromboplastin time with kaolin, which were corrected by addition of aged serum but not with adsorbed plasma. Factor X assays were carried out where possible. **Results:** Only 24 patients of factor X deficiency were detected in 571 patients presenting with coagulation disorder. In 4 cases deficiency was thought to be secondary history, clinical findings and lab results. Inherited deficiency of factor X was thus detected in only 20/571 (3.5%) of the patients. Family history was positive in 8/20 (40%) patients. Consanguinity was noted in 12/20 (60%) patients. Median age of patients was 3 years. Male and females were in equal numbers. Most common clinical presentations were prolonged bleeding after trauma and mucosal bleeding seen in 80% and 70% of patients respectively. In patients in whom factor X assay was performed only one had <1% levels. **Conclusion:** Factor X deficiency although rare in American and European populations is not that rare in this part of the world. Its existence should be kept in mind in patients presenting with mucosal bleeding and prolonged PT and PTTK but normal platelet count and TT. The mutations in factor X, in this part of the world are most probably not the one, which would cause a severe bleeding diathesis.

Keywords: Haemophilia, Factor X deficiency, Consanguinity, Inherited coagulopathy

INTRODUCTION

Coagulation factor X is also known as the Stuart-Prower factor named after the first male and female patients.[1] It is a vitamin K dependent serine protease that circulates in plasma. It comprises two chains joined together by disulfide linkages. A light chain of molecular weight 17000 contains Gla domains. A heavy chain of molecular weight 40,000 is actually responsible for catalytic activity. Plasma levels are 8-10 μg/ml. Half-life in plasma is 34-40 hours. It plays a crucial role in the coagulation cascade. Factor X is activated either by factor VIIa/TF (tissue factor) complex via extrinsic pathway or by IXa/VIIIa complex via

intrinsic pathway. It is also activated by Russell Viper venom (RVV). Factor Xa subsequently forms a macromolecular complex with its cofactors Va, a phospholipid surface and calcium ions to convert prothrombin into thrombin.[2-4]

Specific functional properties of factor X including gamma-carboxylase recognition, calcium binding, phospholipid surface interaction as well as co factor and substrate binding are governed by specific structural domains. Each of such domain is encoded by a specific exon in the factor X gene. The gene for factor X maps to the long arm of chromosome 13q34. It consists of 8 exons and 7 introns. Both the gene structure and aminoacid sequences show homology to other vitamin K-dependent factors.[2,3]

A variety of mutations result in defects involving either reduction in antigen or defect in one or more activation pathways.[4] Two types are described. Type-I, in which reduction in factor X activity parallels reduction in factor X antigen, and type-II in which activity is less than antigen.[5] Deficiency is also classified in CRM^+, CRM^- and CRM^{red}. CRM^+ variants affect the activation. These are of two types. One, which affect activation preferentially through intrinsic pathway and second which affect activation through both pathways. CRM^- variants affect synthesis and secretion of factor X, hence also result in deficiency of factor X antigen. CRM^{red} variants result in reduced activity. In some variants RVV activation is relatively preserved.[4]

Factor X deficiency is one of the most rare inherited clotting disorders. Homozygous factor deficiency has an incidence of 1:1,000,000 in the general population.[2] In addition to inherited deficiency an acquired deficiency of factor X activity is also described that is even more uncommon.[6] It has occasionally developed in patients with liver diseases, vitamin K deficiency, amyloidosis, multiple myeloma, mycoplasma pneumoniae infection, leprosy and methyl bromide exposure.[1,7,8]

In spite of very low gene frequency, factor X deficiency is expected to be more common in populations where the rate of consanguineous marriages is very high. In Pakistan, consanguinity in certain areas, particularly in Northern Pakistan is reported to be as high as 50%[9]. A higher incidence of factor X deficiency is therefore expected in these areas. This study was aimed at estimating the incidence of factor X deficiency in patients presenting with bleeding disorders and its clinical presentations.

MATERIAL AND METHODS

Patients included in the study were those referred to Armed Forces Institute of Pathology, Rawalpindi for investigations of a suspected bleeding disorder.

These patients were referred from civil and military hospitals of Rawalpindi, Islamabad, adjoining areas of Punjab, NWFP and Azad Kasmir. During the period of study, January 1997 to June 2002, a total of 2049 patients were referred.

Brief history and important physical findings were noted. Blood samples were collected in EDTA and trisodium citrate for Complete Blood Counts (CBC) and clotting tests. CBC was carried out on automated haematology analyzer, Sysmex KX-21. All patients of thrombocytopenia were excluded from further tests.

Bleeding time was performed (only in patients with normal platelet count) by Ivy method. Prothrombin time (PT), partial thromboplastin time with kaolin (PTTK) and thrombin time (TT) were performed using standard commercially available kits by the procedures recommended by manufacturers.

Based on history, clinical findings initial studies, patients were divided into two categories. One, who were suspected of having quantitative or qualitative platelet disorder and second suspected of coagulation disorder. Correction studies were performed using pooled normal plasma, aged serum and adsorbed plasma prepared in the laboratory by standard methods in the second group.

Diagnosis of factor X deficiency was based upon prolongation of both PT and PTTK with normal TT, which were corrected by addition of aged serum. Adsorbed plasma is deficient in factors II, VII, IX and X hence is not expected to correct factor X deficiency. Aged serum is deficient in factors II, V and VIII but contains factor X and is therefore expected to correct factor X deficiency[10]. To assess the severity of deficiency, factor X assays were suggested in all these cases but only 05 patients reported for the test.

Statistical analyses were performed using SPSS 10.0 for Windows

RESULTS

A total of 2049 patients were referred for investigations of a suspected bleeding disorder. Of these a bleeding disorder was confirmed on primary coagulation screen in only 571 patients. Factor X deficiency was detected in 24 of these. In four patients a secondary cause was suspected because of a short history and associated disease and absence of family history. Hereditary deficiency of factor X was thus diagnosed in 20 (3.5%) of the patients with coagulation disorder (n=571).

Age of these patients ranged from 6 months to 27 years with a median age of 3 years. Both males and females were equally distributed, that is 10 each. Family history could be elicited in 8 (40%) patients whereas consanguinity was present in 12 (60%) patients.

There was considerable overlap in presenting signs and symptoms. Prolonged bleeding after trauma was the commonest presenting complaint and was seen in 16 (80%) of the patients. This was followed by complaints of mucosal bleeding like epistaxis, gum bleed, haemetemesis, menorrhagia etc. seen in 14 (70%) of cases. Other presentations are listed in table-1.

Mean haemoglobin level of these patients was 10.0 g/dl (95% CL 8.9-11). Mean bleeding time was 4 min 12 sec (95% CL 3 min 53 sec – 5 min 9 sec). Mean PT was 64 sec (95% CL 47-81 sec), whereas mean PTTK was 84 sec (95% CL 66-101 sec) against control of 14 and 32 sec respectively.

TT was 16 sec against control of 16 sec in all patients. Factor X assays were carried out in 5 patients. These were <1% in one, 1% in one, 2% in two and 4% in one.

Table-1: Clinical presentation of patients with factor X deficiency (n=20)

S.NO.	SYMPTOM/SIGN	NO OF PATIENTS	FREQUENCY

1.	Excessive bleeding after trauma	16	80%
2.	Spontaneous bruising	09	45%
3.	Epistaxis	07	35%
4.	Bleeding from gums	07	35%
5.	Echymoses	05	25%
6.	Prolonged bleeding from umbilical stump	03	15%
7.	Prolonged bleeding after circumcision (n=10)	03	30%
8.	Menorrhagia (n=10)	01	10%
9.	Haemetemesis	01	05%
10.	Bleeding per rectum	01	05%
11.	Haematuria	01	05%
12.	Joint bleed	01	05%

DISCUSSION

Hereditary deficiency of factor X is a rare coagulation disorder first reported in 1956.[11] Its incidence is one in million in Caucasian population.[2] Incidence in other populations is not reported. However incidence in patients with coagulation disorders has been determined in other populations and is very low. In a study of haemophiliac patients from Iran factor X deficiency was responsible for 2.3% of cases.[12] In a study of rare inherited disorders of coagulation factors from India, factor X deficiency was the most common (8/24).[13] In another Indian study of inherited disorders of coagulation in women presenting with menorrhagia factor X deficiency constituted for 1.2% of patients.[14] In this study we report it at 3.5%, a figure close to that reported from India. This relatively high incidence is possibly because of higher rate of consanguineous marriages. In this study 60% patients were product of consanguineous marriages.

Being an autosomal recessive disorder it is expected to affect both sexes equally as is evident from results of this study. Heterozygotes have factor X levels 50% of normal and are asymptomatic. In symptomatic patients clinical phenotype is that of a variable bleeding tendency depending upon the activity of factor X. Severe bleeding is only seen when factor X levels are <1%.[2] There was only one such patient in this cohort. In other four patients factor X levels were I-4%. As expected, by far the commonest clinical presentations were of excessive bleeding after trauma and spontaneous mucosal bleeding. Joint bleed was seen only in one patient and the same patient had bleeding per rectum, haematuria and menorrhagia. Factor X level in this patient was <1%.

Mutation analyses could not be done because of lack of facilities. Mainly three types of mutations have been described. These are point mutations, splice site mutations and missense mutations. Later cause type-II deficiency, whereas the first two cause type-I disease.[15] Most of the cases in whom mutations have been characterised originate from Middle East, particularly Iran. In no Pakistani patient mutation analyses have been performed[15-17]. Mutation analyses in affected families makes prenatal diagnosis which has been made possible by using combination of more than one techniques.[18]

We therefore conclude that factor X deficiency although rare in American and European populations is not that rare in this part of the world. Therefore its existence should be kept in mind in patients presenting with mucosal bleeding and prolonged PT and PTTK but normal platelet count and TT. It appears that the deficiency in Pakistani patients is usually not severe. The mutations in factor X, in this part of the world are not the one, which would cause a severe bleeding diathesis. It will be interesting to study mutations in Pakistani patients.

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Address For Correspondence:

Prof. Masood Anwar, Head Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan, Phone: (051) 561 30077, Fax: (051) 9271247

Email: afippak@yahoo.com**,** afipcomdt@hotmail.com