Original Article

Frequency and clinical spectrum of rare inherited coagulopathies - A tricenter study

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Abstract

Objective: To determine the frequency of rare inherited coagulopathies at three centers of haematology in Karachi and to study the clinical spectrum and laboratory data of these coagulopathies.

Methods: This was a descriptive study conducted from September 2003 to December 2004 on subjects from Aga Khan University Hospital, Husaini Blood Bank and Fatimid Blood Transfusion Centre. All the subjects with bleeding tendency without any acquired causes of bleeding were selected for further investigation, and were asked relevant questions as present in the questionnaire. Screening tests including platelet count, PT, APTT and bleeding time were performed on all patients and subsequently, specific tests including factor assay, clot solubility test, platelet aggregation and vWFAg were performed.

Results: In total, 1100 patients were evaluated for bleeding tendency at the three centers and 65 patients were diagnosed to have inherited coagulopathy other than haemophilia A and B. Out of these 65 patients, 33 (50.7%) were males and 32 (49.2%) were females. Rare inherited coagulopathies that were found in our population included deficiency of factor VII {n =21 (32.3%)}, factor X {n =17 (26.1%)}, factor XIII {n=14 (21.5%)}, factor V {n =9 (13.8%)}, fibrinogen {n =2 (3%)}, prothrombin {n=1 (1.5%)} and factor XII {n=1 (1.5%)}.

Conclusion: Inherited coagulopathies other than haemophilia A and B were noted in the study population (JPMA 58:441;2008).

Introduction

Bleeding tendencies caused by inherited deficiencies of one of the coagulation factors is a rare phenomenon distributed worldwide. The study of these disorders has significantly advanced the understanding of the pathophysiology of blood coagulation mechanisms.[1] The most common and best documented of these inherited disorders are haemophilia A and B, due to mutation in the factor VIIIc gene and the factor IX gene respectively.[2] Mutations have also been identified in deficiency of factors I, II, V, VII, X, XI, XII and XIII. These rare disorders are inherited as autosomal recessive traits with prevalence in the general population varying between 1: 500,000 and 1: 2000,000.[3]

These disorders are generally less severe than the haemophilias caused by factor VIII or IX deficiency. The only exceptions are factor X and XIII deficiencies, characterized by early onset of life threatening symptoms such as umbilical cord and central nervous system bleeding. Bleeding after circumcision is often the revealing symptom in coagulation factor deficiencies.

Results of studies using various immunologic techniques demonstrate that the absence of coagulant activity in the plasma of patients with these disorders may result from either deficient biosynthesis of a requisite protein or defective biosynthesis, leading to the production of normal amounts of functionally inactive or functionally abnormal analogues.[2]

Most of these factor deficiencies are characterized by prolonged prothrombin time and/ or activated partial thromboplastin time except for factor XIII which is characterized by normal initial screening tests. Factor assay is required for the confirmation of diagnosis.

The study was conducted to define the occurrence of these disorders in our population so that these patients are not missed and are managed properly.

Patients and Methods

A descriptive study was conducted from September 2003 to December 2004 at three haematology centers in Karachi- The Aga Khan University Hospital, Husaini Blood Bank and Transfusion Center; and Fatimid Blood Transfusion Center. All the subjects with bleeding tendency of all ages and both gender were selected for further investigation. Prior to asking questions and drawing blood for various tests, patients were informed about the project in detail and an informed consent was taken.

During the study period, a total of 1100 patients were evaluated for bleeding disorder at the three centers. Patients included in the study were asked relevant questions as present in the questionnaire.

Detailed history of bleeding tendency was taken and any history of bleeding at the time of birth including

bleeding from the umbilical cord and circumcision bleed was asked, History of consanguineous marriage of parents, and significant history of bleeding tendency in parents, siblings, cousins or other family members was inquired and menstrual and obstetrical history was also noted.

Patients with a positive history were subsequently investigated. Tests that were performed on blood samples included, platelet count (Coulter STKS), prothrombin time (Dade Behring Inc Newark, DE, USA), activated partial thromboplastin time (Dade Behring Inc, Newark, DE, USA) and mixing studies[4] using normal plasma, adsorbed plasma and aged serum were performed.

(Aged normal human serum- contains factors II, VII, IX, X, XI, XII)

(Adsorbed normal human plasma- contains factors I, V, VIII, XI, XII)

If the prolongation is due to deficiency of a clotting factor, the PT or APTT should return to normal within a few seconds.

The other tests done were, Bleeding time (Ivy's method), Factor assay (II, V, VII, X, XI, XII) Dade Behring Inc, Newark, DE, USA, Fibrinogen assay (Dade Behring Inc, Newark, DE, USA), Clot solubility test for factor XIII, Platelet aggregation studies and Enzyme linked immunosorbent assay for von Willebrand factor antigen.

Screening tests including platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT) and bleeding time were performed on all patients and subsequently, specific tests including factor assay, clot solubility test, platelet aggregation and vWFAg were performed as required.

Patients suffering from inherited coagulopathies other than Haemophilia A and B i.e. fibrinogen deficiency, prothrombin deficiency, deficiency of factors V, VII, X, XI, XII and XIII were included. Patients with acquired coagulopathies including vitamin K deficiency, presence of inhibitors and liver disease were excluded. Patients with platelet function disorders were also excluded.

Results

Of the 1100 subjects, 65 were diagnosed to have some rare inherited coagulopathy other than Haemophilia A and B. Among these, 33 (50.7%) were males and 32 (49.2%) were females. Mean age was 6.3 ± 8.73 years (range 1-54 years). The most common presenting complaints were gum bleeding, epistaxis and bruising after minor trauma. Soft tissue bleeding was the presenting complaint in 2 (3%) patients whereas haemarthrosis was found in 1 (1.5%) patient only. Bleeding from the umbilical cord was found in 52 (80%) patients and significant circumcision bleed in 4 (6.1%). History of consanguineous marriage of parents was observed in 22 (33.8%) patients.

Rare inherited coagulopathies that were found in our population included deficiency of fibrinogen, prothrombin; factors V, VII, X, XII and XIII.

The most common rare inherited coagulopathy that was identified in our population was factor VII deficiency. Twenty-one patients (32.3%) were diagnosed to be factor VII deficient of whom eight were males (38%) and thirteen females (61%). This group of patients had a mean age of 10.3 ± 12.93 years (range 1-54 years). Majority of the patients {n =18 (85%)} had history of epistaxis and gum bleeding off and on since birth. One patient presented at the age of 54 years when she had significant haemorrhage while undergoing hysterectomy. Eleven patients (52%) had history of bleeding from the umbilical cord. Family history of consanguinity was seen in ten patients (47%). There was isolated prolonged PT in all patients and mixing studies revealed correction of PT with normal plasma and aged serum.

Factor X deficiency was seen in seventeen patients (26.1%) and out of these; eleven were males (68%) and six females (32%). Mean age was 3.94 ± 3.74 years (range 1-14 years). Majority of the patients (94.1%) presented with history of bruising and gum bleeding since birth, except for one 14 years old female who presented with complaints of menorrhagia. Significant birth history including bleeding from the umbilical cord was seen in nearly all patients. Only one patient had a family history of consanguinity. Laboratory investigations revealed prolongation of both PT and APTT; correction done with normal plasma and aged serum.

There were fourteen patients (21.5%) with factor XIII deficiency- eight were males (57%) and six were females (42%). Mean age was calculated to be 8.28 ± 6.08 years (range 1-18 years). All patients (100%) had history of prolonged bleeding from the umbilical cord at birth. However, the commonest presenting complaint was bruising after minor trauma (90%). Family history was significant in six patients (42%). Upon investigation, all patients had normal PT and APTT. Subsequently, clot solubility test was done in all patients (100%) and all of them were found to be factor XIII deficient. Quantitative factor XIII assay was not done since it is not available at these three centers.

Factor V deficiency was found in nine patients (13.8%). Two were females (22%) and seven were males (77%). Mean age at presentation was 8.44 ± 6.63 years (range 2-22 years). Patients presented with complaints of

Table. Number of patients and relative frequency of inherited coagulation disorders in iran, italy and united kingdom (excluding vwd)6 and also comparison with present study.

Defect	Iran	Italy	United Kingdom	Present Study
Fibrinogen	70 (1.5%)	10 (0.2%)	11 (0.2%)	2 (3%)
Prothrombin	15 (0.3%)	7 (0.2%)	1 (0.02%)	1 (1.5%)
Factor V	70 (1.5%)	21 (0.5%)	28 (0.6%)	9 (13.8%)
Factor VII	300(6.6%)	58 (1.3%)	62 (1.3%)	21 (32.3%)
FactorV+VIII	80 (1.7%)	29 (0.7%)	18 (0.3%)	-
FactorVIII (Haemophilia A)	3000 (65.4%)	3428 (80%)	3554 (76.8%)	-
FactorIX (Haemophilia B)	900 (19.6%)	626 (15%)	762 (16.1%)	-
Factor X	60 (1.3%)	16 (0.4%)	25 (0.5%)	17 (26.1%)
Factor XI	20 (0.4%)	60 (1.3%)	150 (3.3%)	-
Factor XIII	80 (1.7%)	31 (0.7%)	26 (0.5%)	14 (21.5%)

epistaxis and gum bleeding (100%). Haemarthrosis was seen in one patient. All patients (100%) gave history of prolonged bleeding from the umbilical cord and four male patients (44%) had a significant history of circumcision bleed. There was history of consanguineous marriage of parents in six patients (66%). Siblings of two patients had factor V deficiency. When investigated, all of these patients had prolonged PT and APTT. On mixing studies, correction was observed with normal and adsorbed plasma. Factor assay was performed and all patients had low factor V levels.

Fibrinogen deficiency was seen in two patients (3%). Both of them presented at an early age with a mean age of 2 ± 1.4 years (range 1-3 years). Both had history of hematomas off and on after minor falls. One patient had prolonged bleeding from the umbilical cord at birth. Initial screening tests including PT and APTT were both prolonged. Mixing studies were performed and correction was achieved with normal and adsorbed plasma. Plasma fibrinogen levels were performed and were detected to be low.

There was only one (1.5%) male patient with factor XII deficiency who was diagnosed incidentally when pre-surgical assessment was done before tonsillectomy. Age of this patient was 8 years. Both PT and APTT were prolonged and were corrected with normal and adsorbed plasma and aged serum. Factor XII levels were then performed and were found to be reduced.

Prothrombin deficiency was found in one patient (1.5%) who was a 4 years old male. However, clinical details were not available.

Factor XI deficiency was not discovered in any patient in this study.

Discussion

The inherited disorders of coagulation are a fascinating group of diseases that have provided important insights into the structure and function of their respective deficient protein(s). These disorders have many and varied effects on patients and families at all stages of life.

This study was conducted to determine the frequency and clinical spectrum of rare inherited coagulopathies other than Haemophilia A and B. Inherited coagulopathies that were found in our population, in descending order of frequency, were deficiency of factors VII, X, XIII, fibrinogen, prothrombin and factor XII. Deficiency of fibrinogen, prothrombin and factor XII were extremely rare.

These disorders are also reported in other populations as well. Karimi M et al[5] did a comprehensive survey concerning demographics in the Southern Iranian population with haemophilia and allied disorders. The total number of patients with coagulation disorders was 367. Haemophilia A was found in 271, 39 had Haemophilia B and 24 had vWD. The rare coagulation disorders (n=33) included eleven patients with factor X deficiency; ten with factor VII; six with factor XIII; two with afibrinogenemia; two with factor XI; one with combined factor V and VIII; and one with combined factor VII, VIII and IX deficiency.

Data obtained from the most recent adjournments (1996) of the registries of inherited bleeding disorders kept in Iran, Italy and United Kingdom is summarized in Table[6] and it is also compared with the present study.

A North American registry for rare bleeding disorders[7] (factor II, VII, X, V, XIII and fibrinogen deficiencies) was established to gather information about disease prevalence, genotyping frequency, diagnostic events, clinical manifestations and prophylaxis strategies. Questionnaires were sent to 225 haemophilia centers in USA and Canada. Among 26% of responding centers, 294 individuals were diagnosed with one of the rare bleeding

disorders included in the survey. The most common coagulopathy was factor VII deficiency. Factor X and factor XII caused the most severe bleeding manifestations. There is very limited published local data on rare inherited coagulopathies. In a combined study conducted at Aga Khan University Hospital and Fatimid Foundation[8] from 1985 to 1992, nine patients were diagnosed to have factor XIII deficiency on the basis of clot solubility test. A high incidence of consanguinity was observed in this study.

Comparing the results of our study with similar studies conducted worldwide, the frequency of these inherited disorders is variable. In populations where consanguineous marriages are frequent, as those from Muslim countries including our population, recessive coagulation disorders are more frequent representing a significant clinical and social problem.

The total number of patients with rare inherited coagulation disorders studied by us is limited, although there are a large number of patients who remain undiagnosed since the general practitioners do not refer all patients with suspected bleeding disorders. There is a need of large scale studies in all parts of our country to determine the actual burden of these disorders.

Conclusion

Inherited coagulopathies other than Haemophilia A and B were found in our study population. However, a high index of clinical suspicion is required to diagnose these patients. Majority of the patients remain undiagnosed due to the lack of appropriate diagnostic facilities in all parts of our country. More prospective studies are required to define the occurrence of these disorders.

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