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Factor XIII deficiency in Pakistan

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FACTOR XIII DEFICIENCY IN PAKISTAN

Pages with reference to book, From 67 To 69

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ABSTRACT

Patients with undiagnosed haemostatic defects seen at The Aga Khan Hospital and Fatimid Blood Transfusion Centre during the period of 7 years (1 985-1 992) were screened with routine tests including bleeding time (BT), whole blood clotting time (CT), platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT) and 5 molar urea test. Nine patients had a positive 5 molar urea test indicating factor XIII deficiency. Rest of the screening tests were normal in these patients. High incidence of consanguinity was observed in affected families. Clinical features included excessive bleeding from umbilical stump, bruising, post-traumatic bleeding, epistaxis, melaena and intracerebral bleeding. All the patients were treated with fresh frozen plasma and cryoprecipitate (JPMA 43: 67, 1993).

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Patients with undiagnosed haemostatic defects seen at The Aga Khan Hospital and Fatimid Blood Transfusion Centre during the period of 7 years (1 985-1 992) were screened with routine tests including bleeding time (BT), whole blood clotting time (CT), platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT) and 5 molar urea test. Nine patients had a positive 5 molar urea test indicating factor XIII deficiency. Rest of the screening tests were normal in these patients. High incidence of consanguinity was observed in affected families. Clinical features included excessive bleeding from umbilical stump, bruising, post-traumatic bleeding, epistaxis, melaena and intracerebral bleeding. All the patients were treated with fresh frozen plasma and cryoprecipitate (JPMA 43: 67, 1993).

INTRODUCTION

Factor XIII deficiency is a rare disorder. Over 100 cases have been reported in the world literature[1,2]. Factor XIII, a fibrin stabilizing factor (FSF) also called fibrinologase, is a zymogen with a molecular weight of 320,000. It is composed of four dissociable subunits a2b2. Factor XIII has been purified from both human and bovine plasma by procedures involving differential precipitation and column chromatography. The ‘a’ subunit is synthesized by platelets and megakaryocytes whereas the ‘b’ subunit may be produced by the liver. Factor XIII is present in platelets and placenta but only in the form of active ‘a’ subunits[3,4]. Factor XIII after activation to XIIIa by thrombin requires calcium as co-factor to form a transamidase. This catalyses the formation of t-glutamyl-E-lysine bonds between adjacent strands of fibrin monomer. The formation of t-glutamyl-E-lysine bond introduces the important properties to fibrin namely, increased stability to mechanical disruption and increased resistance to lysis by proteolytic enzyme. These properties are advantageous in wound healing[5]. Deficiency of factor XIII renders clot unstable. They lack elasticity and are more susceptible than normal to digestion by plasmin. In the laboratory, these are soluble in 5 molar urea in 1% monochloroacetic acid[3]. Failure of fibrin cross linking as a result of factor XIII deficiency leads to the formation of an unstable clot which is susceptible to fibrinolysis and does not support the proper growth of fibroblasts. In an apparently homozygous individual, levels of factor XIII are virtually absent

when measured biochemically or when assayed by immunological methods[6,7]. Routine haemostatic screening tests used in Pakistan do not include factor XIII screening test except in a few centres and hence patients with factor XIII deficiency may be missed. First cousin and inter-family marriages are common in Pakistan and autosomal recessive coagulopathies like factor XIII deficiency will have a higher incidence in Pakistan than in the West. This study reports 9 cases of factor XIII deficiency diagnosed at The Aga Khan University Medical Centre and Fatimid Hemophilia Centre during the period 1985- 1992.

PATIENTS AND METHODS

All patients with undiagnosed haemostatic defects were screened with routine screening tests including platelet count, bleeding time (B.T.), whole blood clotting time (C.T.), activated partial thromboplastin time (A.P.T.T.), prothrombin time (P.T.) and 5 molar urea test for factor XIII deficiency. The techniques utilized standard methodology[8].

RESULTS

Nine patients (7 males and 2 females) had a positive 5 molar urea test indicating factor XIII deficiency. Their ages ranged from 1 year to 26 years. Six (66.6%) were in 1-10 years age group, two (22.2%) in 11-20 years and 1 (11.11%) in 21-30 years age group. Consanguinity was observed in 4 (45%) of the affected families and pattern of inheritance favoured an autosomal recessive trait. Excessive bleeding from umbilical stump was reported during the first few days of life in seven (78%) cases. Other features included haematoma formation, easy bruising, post-traumatic bleeding, delayed wound healing, gastrointestinal bleeding and epistaxis. One child presented with intracerebral bleed. Secondary or acquired causes of factor XIII deficiency were ruled out by history, clinical examination and relevant investigations. The presenting symptoms and haematological parameters are shown in Table.

TABLE. Clinical picture - factor XIII deficiency.

Patient No.	Sex/age	Signs and symptoms	Investigations	Family history	Treatment
Patient No.1	Male 11 years	Injuries, hematoma, bleeding per rectum, bleeding from umbilical stump	BT 6 min. 20 sec, CT 4 min. 40 sec, PT 13 sec, plt. 250,000, 5 MU test positive	No family history of bleeding disorder	FFP every 2 weeks
Patient No.2	Male 3 years	Injuries, hematoma skull, gum bleeding, bleeding from umbilical stump. Bleeds on 2nd or 3rd day from wound after injury	BT 3 min, CT 4 min, 5 sec, PT 15 sec, APTT 35 sec, plt. 259,000, 5 MU test positive	2 sisters and 1 brother died of bleeding, intracerebral hemorrhage	FFP every 3-4 weeks
Patient No.3	Female 7 years	Bruising, bleeding from umbilical stump on 9th day	BT 5 min, CT 3 min, 50 sec, PT 15 sec. APTT 31 sec, plt. 300,000, 5 MU test positive	One younger sister has same problem. Parents first cousins	FFP every 3-4 weeks
Patient No.4	Male 20 years	Hematomas, bleeding from umbilical stump, bruising, epistaxis	Initial workup at Lahore. 5 MU test positive	Parents distantly related. One sister suffering from same disease	FFP every 3-4 weeks
Patient No.5	Female 26 years	Melaena, post-traumatic hematoma and bleeding	Initial workup at Maryland Centre, Lahore. 5 MU test positive	Parents cousins. One sister suffering from same disease	FFP every 3-4 weeks
Patient No.6	Male 10 years	After circumcision, bleeding from umbilical stump on 5th day, bruising, hematoma, gum bleeding	BT 2 min. 58 sec, CT 5 min, 45 sec, PT 13 sec, APTT 43 sec, plt. 260,000, 5 MU test positive	No history of bleeding disorder	FFP every 2-3 weeks
Patient No.7	Male 1 year	Circumcisional bleeding	BT 2 min. 50 sec, CT 4 min. 25 sec, PT 13 sec, APTT 38 sec, plt. 275,000, 5 MU test positive	No history of bleeding disorder	FFP/cryo-precipitate every 3 weeks
Patient No.8	Male 2 years	Circumcisional bleeding, umbilical stump bleeding, gum bleeding	BT 4 min. 30 sec, CT 4 min, PT 14 min, APTT 34 min, plt. 304,000, 5 MU test positive	Sister had the same problem	FFP/cryo-precipitate every 3 weeks
Patient No.9	Male 4 years	Circumcisional bleeding umbilical stump bleeding, intracerebral bleed	BT 5 min. 15 sec, CT 6 min, PT 16 sec, APTT 34 sec, plt. 310,000, 5 MU test positive	Parents first cousins	FFP/cryo-precipitate every 2-3 weeks

B.T. = Bleeding Time, C.T. = Clotting Time, P.T. = Prothrombin Time, APTT = Activated Partial Thromboplastin Time, plt = Platelet count, 5 MU = 5 molar urea.

DISCUSSION

Introduction of factor XIII screening test in routine coagulation tests enabled us to detect 9 cases of factor XIII deficiency hitherto unrecognized. in this country. This is to be expected in the arena of inter family marriages. Ratnoff and Steinberg in 1978 suggested a sex linked component to the inheritance pattern, but the development of electrophoretic methods for studying subunit 'a' and 'b' have clarified the position regarding their inheritance[1,9]. The studies by Losowsky2 have confirmed that structural loci for the 'a' and 'b' sub-units lie on autosomal chromosomes. The consanguinous marriages are fairly common in Pakistan and a high incidence of genetic coagulopathies like factor XIII deficiency are to be expected. The inheritance pattern in our patients appears to be an autosomal recessive trait.

Acquired cases of factor XIII deficiency may be seen in liver diseases, disseminated intravascular coagulation, renal insufficiency and in association with anti-tuberculosis therapy[10,11]. Atleast nine inhibitors to factor XIII have been described. One developed in a patient with congenital factor XIII deficiency. Four arose in patients on long term treatment with isoniazid. One in a patient with drug induced lupus syndrome. These inhibitors persisted for upto 5 years and eventually disappeared. Study of these inhibitors showed IgG immunoglobulins directed against factor XIII itself, activated factor XIII or both[5,9]. Existence of patients with non-functional forms of factor XIII was reported by Duckertin 1972[11]. There is a reported high incidence of intracerebral bleed in factor XIII deficiency than in other inherited bleeding disorder. Spontaneous abortions have also been reported in adult female patients, though none of our patients were in this group[12,13]. Factor XIII is relatively stable in plasma and has a very long post transfusion life in circulation. Half life of transfused factor XIII is 6-10 days and the plasma concentration required for haemostasis is about 5%. Accordingly, haemostasis can easily be achieved by giving transfusion of fresh frozen plasma, cryoprecipitate or concentrated factor XIII[5]. Prophylactic treatment is done by administering fresh plasma, cryoprecipitate or freezed dried concentrate in the dosage of 10- 15 units per kilogram body weight every 3-6 weeks[5,12,13]. The only freezed dried concentrate at present available is prepared from human placenta. Question remains as to whether placental tissue will produce any long term immunological effect or if the Rivanol which is used in the manufacturing process will prove to be toxic in any way.

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