Haemophilia A (Factor VIII:C deficiency) A clinicohaematological Study of 20 Cases

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Hereditary disorders of blood coagulation are 2nd common congenital disorders. Haemophilia A is the most frequently encountered serious disorder of coagulation, if not properly diagnosed and managed, can lead to severe disability in the male child of the family and at times can be life threatening also. Present clinicohaematological study was carried out on 20 cases of haemophilia A at the Pathology Deptt. of King Edward Medical College, Lahore. Coagulation study and factor VIII assays were carried out and severity of the disease determined. In our study 5 (25%) of the cases had severe deficiency, 5(25%) moderate deficiency and 10 (50%) of cases were of mild factor VIII deficiency. The clinical presentations correlated with level of factor VIII in the plasma.

Key Words: Haemophilia A, blood coagulation, factor VII,

Haemophilia A is the most common hereditary disorder of blood coagulation.[1] The inheritance is sex-linked resulting in deficiency of plasma factor VIII coagulant activity. The Factor VIII is defined as the protein that circulates in the plasma and functions in the intrinsic pathway of fibrin formation.[2] The properties of factor VIII are VIII:C and VIII:Ag.[3] The gene controlling the production of factor VIII is located at the terminal end of long arm of X-chromosome.[4] Cells in which factor VIII is synthesized are unknown, although hepatocyte is strongly suggested.[5] Genetic defects in factor VIII include point mutation, gross deletions and regulatory defect.[6] Clinical severity of the disease correlates well with the extent of coagulation factor deficiency. The level of factor VIII is similar in all affected males in a given family.[7] Infants may suffer from post-circumcisional haemorrhage. Recurrent painful haemartheroses and muscle haematomas dominate the clinical course of severely affected patients with progressive deformity and crippling.[8] Prolonged bleeding after tooth extraction, operative and post traumatic haemorrhage are life threatening both in severely and mildly affected patients.[9] Most severely affected patients possess less than 1% activity of factor VIII:C, moderately affected patients have 2% to 5% activity, and mildly affected patients generally have more than 5% factor VIII:C activity.

Patients and Methods

This study was carried out at Pathology Department of King Edward Medical College, Lahore. The patients with bleeding disorders were referred from various hospitals of Lahore and outside cities. A total number of 100 coagulation disorders were investigated and clinicohaematological study was carried out on 20 cases of Haemophilia A (Factor VIII:C deficiency).

Clinical Data:

A detailed personal and family history was obtained and physical examination carried out in each case. Pedigree was drawn and relatives were investigated. History of spontaneous bleeding or following trivial injury, bleeding into deep, or subcutaneous tissues, joints or abdominal viscera was asked.

Sample Collection:

The blood samples were collected:

1. In 3.13 g/dl trisodium citrate in 1:9 ratio for coagulation study.
2. In sodium oxalate salt for routine blood examination.
3. Three 1-ml samples were delivered into small uncoated glass tubes (at 37°C) to measure coagulation time.

With each batch of test, a normal control was put up every time. All the coagulation tests were carried out without delay. Complete blood examination, smear, reticulocyte count, platelet count, bleeding time (Ivy's method) coagulation time (Lee and White Method), Prothrombin time, Activated Partial thromboplastin time and thrombin time was carried out in each case (manual tilt tube technique).

Mixing experiment and correction study was performed with normal plasma, Aged serum and Adsorbed plasma. (Dacie and Lewis). To confirm the diagnosis, specific coagulation factor assay was carried out by using Factor VIII deficient plasma. (Dade).

Results

Clinical Features:

Out of 100 cases of coagulation disorders, there were 20 patients of Haemophilia A. All were males (100%) with age ranging from 2 months to 35 years. 10 patients (50%) were below the age of 10 years, whereas there were 10 adults (50%) (Fig.1). 5 patients (25%) presented with haemartheroses. 4 out of them had ankylosis of previously affected joints and positive family history of bleeding. Spontaneous hematoma formation was seen in 3 cases (15%). Commonest complaint was easy bruising (100%) followed by prolonged bleeding from cuts and wounds, haemarthroses, epistaxis, bleeding gums, and haematoma formation (Table-1). Two children at the ages of 2 months

and 10 months had profuse bleeding from circumcision wound.

Fig.1. Pie Diagram showing frequency of haemophilia A. Total Coagulation dierders = 100

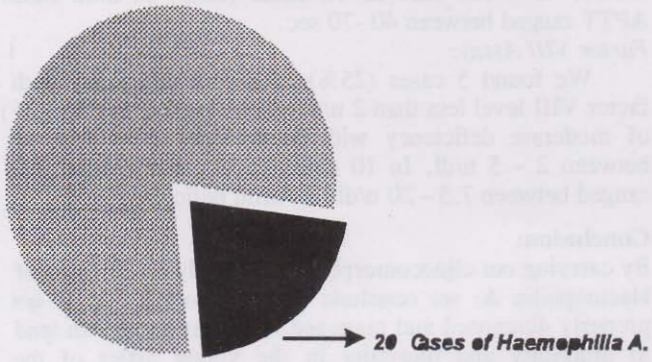

Fig. 2. Bar graph showing the age wise distribution of patients with factor VII deficiency

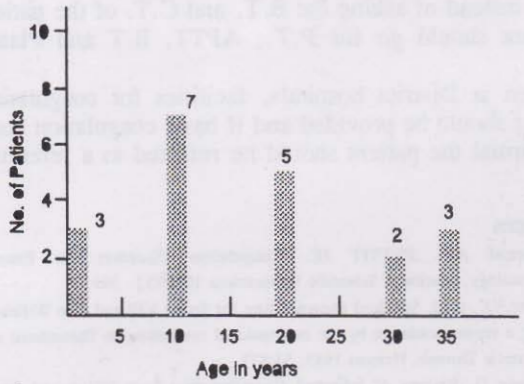

Fig. 1

Table - 1 Frequency Of Presenting Symptoms (n=20)

Symptoms	n= (%age)
Prolonged bleeding from cuts.	05 (25%)
Haemarthrosis	05 (25%)
Ankylosis	04 (20%)
Haematoma	03 (15%)
Menorrhagia	---
Epistaxis	05 (25%)
Bleeding gums	05 (25%)
Easy Bruising	20 (100 %)
Bleeding after tooth extraction	---
Haematuria	02 (10%)
Post-circumcision. Bleeding	02 (10%)
C.N.S. bleeding	
Bleeding from cord	---
Haemoptysis	---
Haematemesis	01 (5%)

Laboratory Investigations:

Routine blood examination, Platelet count, bleeding time, Prothrombin time, thrombin time was normal in all cases.

Clotting Time(C.T)

In 20 cases, C.T. ranged from 9 - 30 mins. In 5 cases of severe deficiency clotting time ranged between 25 - 30 minutes (Table-2)

Table - 2 Whole Blood Coagulation Time (Lee & White Method) (N=20)

C.T. IN MINUTES	n=	%age
9	13	65%
9.1 -- 14	02	10%
14.1 -- 19	---	----
19.1 -- 24	---	----
24.1 -- 29	05	25%

Normal range:4 - 9 minutes at 37°C (Dacie and Lewis, 1993).

Activated Partial Thromboplastin Time:

In 5 patients (25%) APTT ranged between 85 - 120 sec. These were the patients who presented clinically with haemartheroses, ankylosis and contractures. Clotting time in these cases ranged between 25 - 30 mins. I.e., severe deficiency (Table-3).

Table - 3 Activated Partial Thromboplastin Time In Factor Viii Deficiency (20 Cases)

APTT IN SECONDS	n=	%age
40	---	----
41 -- 60	09	45%
61 -- 80	04	20%
81 -- 100	03	15%
101 -- 120	04	20%
121 -- 140	---	----

Normal range of 20 controls: 25 - 35 seconds.

Average: 27.5 sec.

Correction Study:

All the 20 cases (100%) showed correction of prolonged APTT with Adsorbed plasma. By mixing 50 : 50 mixture of test and control Plasma, test was performed and APTT corrected. (Dacie and Lewis)

Factor VIII Assay:

In 5 cases (25%) factor VIII level was below 2U/dl. (Severe deficiency). In 5 cases (25%) factor VIII level ranged between 2 - 5 u/dl. 10 cases (50%) were grouped into mild deficiency as factor VIII level ranged between 7.5 - 20 u/dl. (Table-4).

Table - 4: Coagulation Factor Levels In Factor Viii Deficiency (20 Cases)

FACTOR LEVEL IN u/d l	n=	%age
2	05	25%
2.1 – 5	05	25%
5.1 – 10	02	10%
10.1 – 15	05	25%
15.1 – 20	03	15%
20.1 – 25	---	----
25.1 – 30	---	----

Prothrombin time and thrombin time was normal in all 20(100%) cases.

Discussion

Discussion

Hemophilia A is the most common hereditary disorder of blood coagulation.[1] However we received only 20 (20%) cases of haemophilia A in this study. The most probable reason being lack of health education and lack of lab. facilities even at district hospitals for coagulation screening and onward referral of the patients to reference centres since most of our population is living in villages. Age range in our patients was from 2 months to 35 years, 10(50%) were children below the age of 12 years, whereas there were 10 adults (50%). In all of them History of bleeding dated back to early childhood. This finding of ours is consistent with studies carried out by Owenetal[11], and Rizza[12] who are of the opinion that patient's history of bleeding dates back to early childhood and haemophilia is present at birth.

Clinical Features:

Haemarthrosis was the mode of presentation in 5 cases (25%). In 4 patients, spontaneous haemarthrosis was also accompanied by ankylosis of the previously affected joint. They were children below the age of 12 years. Bithell[6], Owen[11], Rizza[12] all state that haemarthrosis are characteristic feature of coagulation factor deficiencies, particularly classical Haemophilia. This finding was in agreement with a study carried out by Hougie[13] (1977), who concluded that 75% of severely affected children were found to have haemarthrosis of at least one joint by age of 4 years. At the age of 10 years, 90% had some impairment of function in the joint involved. Spontaneous haematoma formation was seen in 3 (15%) cases. Haematuria was the presenting symptom in 2 (10%) cases. Hougie[13] (1976) found haematuria to be the presenting symptom in approximately 20% of the moderate and severe cases and in 5% of mild cases.

Epistaxis and bleeding gums and bleeding after tooth extraction was observed in 5 (25%) cases. However epistaxis was the main symptom in these patients. This finding was in agreement with Hougie 1977 who states that epistaxis is common in haemophilia and sometimes the main symptom. Bleeding after circumcision was the presenting feature only in 2(10%) children, which was profuse. Bithell[6] state that it was prolonged bleeding after circumcision which brought haemophilia to the attention of ancient Herbews. 2 (10%) cases presented with prolonged bleeding from cuts, although there was a History of prolonged bleeding from cuts and wounds in 100% of cases.

This finding is in agreement with Bithell[6], who states that most dramatic manifestation of haemophilia is haemorrhage from a minor traumatic injury.

Laboratory Investigations:

All the routine tests carried out in the laboratory were normal. Hougie[13] and Eyster[14] are also of the opinion that all the routine tests are normal and bleeding time is also usually normal but with severe impairment of clotting it may be prolonged. We could not find a prolonged bleeding time even in severely deficient cases.

Activated Partial Thromboplastin time:

We found a significant prolongation of APTT in 5 cases (25%) of severe deficiency. APTT ranged between 85 - 120 sec. We had a moderate prolongation of APTT in 5 (25%), 48 - 104 sec. In 10 cases (50%) of mild cases APTT ranged between 40 -70 sec.

Factor VIII Assay:

We found 5 cases (25%) of severe deficiency with factor VIII level less than 2 u/dl. There were 5 cases (25%) of moderate deficiency with factor VIII level ranging between 2 - 5 u/dl. In 10 cases (50%) factor VIII level ranged between 7.5 - 20 u/dl i.e, mild deficiency.

Conclusion:

By carrying out clinocomorphological study on 20 cases of Haemophilia A, we conclude that haemophilia A. if not properly diagnosed and managed in expert hands can lead to morbidity and mortality in the young males of the family. This leads to potential source of tension and financial burden on the parents of haemophiliac child. If proper investigations are not done before any surgical procedure is carried out, even mild deficiency of VIII can be a hazard for the surgeon.

So instead of asking for B.T. and C.T. of the patient. Consultant should go for P.T., APTT, B.T and Platelet count.

Even at District hospitals, facilities for coagulation screening should be provided and if basic coagulation tests are abnormal the patient should be referred to a reference centre.

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