A Clinico – Haematological Study of Factor IX Deficiency. Haemophilia B.

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A total of 100 cases of hereditary coagulation disorders were investigated in the city of Lahore – Punjab. Out of them 38 were found to have factor IX deficiency, Haemophilia B. All were males. 25 patients were children below the age of 12 years where as 13 were adults. Common presenting symptoms in these patients were easy bruising, prolonged bleeding from cuts, post circumcision bleeding, haemarthrosis, and haemotoma formation. Clotting time and Activated partial thromboplastin time were prolonged in all the cases. Mixing experiments were performed on 38 cases and all (100%) showed partial or complete correction of APTT with serum. A mild to moderate reduction of factor IX level was found in most of the cases. Only 3 patients had factor IX level of less than 2 U/dl i.e. severe deficiency of factor IX. Message to be conveyed is that, although factor IX deficiency is clinically indistinguishable from Haemophilia A, correct diagnosis of deficient factor is very important as further therapy and management of the patient in factor IX and factor VIII deficiency is different
Key Words: Hemophilia B, Factor IX deficiency, coagulation disorders.

Disorders of blood coagulation have always been a clinical and diagnostic problem. A timely and accurate diagnosis becomes absolutely essential in surgical patients as well as in those bleeding profusely.[1]

Coagulation factor disorders can either arise from deficiency of single coagulation factor, usually congenital deficiency or from multiple factor deficiencies, which are often acquired. Out of the single factor deficiencies, Haemophilia A and B are the commonest.[2] Factor IX is a Vit. K dependent serine protease that functions in the intrinsic pathway of fibrin formation.[3] Haemorrhagic disorders due to congenital deficiency of factor IX was detected by Aggeler et al in 1952 and was named after the surname of one index patient.[4] Most commonly, factor IX is quantitatively reduced but in 1/3rd of cases an abnormal functioning molecule is immunologically present.[5] Mode of inheritance is X – Linked recessive. Most of the patients show mild to moderate severity.[6] Severity of bleeding is usually similar within the family[7]; severe deficiency states being rare.[6]

Factor IX deficient patients have fewer symptoms than do the patients with Factor VIII deficiency. Nevertheless factor IX deficiency causes serious bleeding problems,[7] frequency of bleeding episodes is related to the severity of deficiency of plasma factor IX level[2]. Patients with severe disease can develop muscle haemotoma, gastrointestinal haemorrhage and bleeding into large joints with progression to crippling joint deformities.[7] Because many patients are asymptomatic and until their homeostatic mechanism is stressed by surgery or trauma, they may not seek medical advice until haemorrhage is far advanced.[7] Post circumcision bleeding may be the first symptom of congenital factor deficiency.[3,7] Mild cases can produce APTT value within normal limits, yet these patients may exhibit severe bleeding with trauma or surgery. Moderate to severe factor IX deficiency is revealed by a prolonged APTT that is corrected with aged serum but not with adsorbed plasma.[3,4]

However the diagnosis and severity of the disease is confirmed with the level of factor IX in the plasma i.e. factor IX level less than 2u/dl is severe deficiency, between 2-5u/dl moderate deficiency and 5-25 percent is graded as mild deficiency.[3]

Results

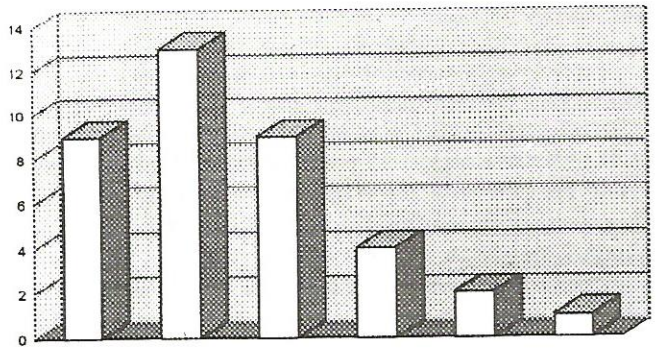
Clinical Features: (Fig. I, Table I)

Out of 100 cases of coagulation disorders, there were 38 patients of Haemophilia B. All were males (100%) with age ranging from 3 months to 52 years, with an average age of 10-48 years, and 13 patients (34.21) were adults. (Fig. – 1)

The commonest symptom was easy bruising (100%) followed by prolonged bleeding from cuts (36.84%). Haemarthrosis and postcircumcision bleeding (13.16%), Haematoma formation, bony ankylosis and haematuria were next common mode of presentation in our study (Table I). The most common combination of symptoms was easy bruising haemotoma formation and increased bleeding from cuts and wounds. Minimum number of patients presented with haematemesis, haemoptysis, C.N.S. bleeding, haematuria and bleeding after tooth extraction (Table – I)

Figure - 1 Age Distribution in Haemophilia B 38 cases

X – axis = age in years Y – axis = No. of Patients



2 years 2-10 years 11-20 years 21-30 years 31-40 years 51-60 years

Table - 1 Frequency of Presenting Symptoms in of Haemophilia B. (Factor IX deficiency) 38 – cases

Symptoms	Haemophilia B
Cases:-	38
1. Prolonged bleeding from cuts.	14(36.84%)
2. Haemarthrosis	5(13.16%)
3. Ankylosis	3(7.89%)
4. Haematoma	4910.53%)
5. Menorrhagia	–
6. Epistaxis	1(2.63%)
7. Bleeding gums	–
8. Easy bruising	38(100%)
9. Bleeding after tooth extraction	2(5.26%)
10. Haematuria	3(7.89%)
11. Post-circumcision, bleeding	5(13.16%)
12. C.N.S. bleeding	1(2.63%)
13. Bleeding from cord	–
14. Haemoptysis	1(2.63%)
15. Haematemesis	2(5.26%)

Laboratory Investigations:

Hemoglobin, TLC, DLC, reticulocyte count, platelet count and bleeding time were normal in all the patients. Prothrombin time and thrombin time was also normal in all patients. Table - 2

Table - 2 Whole Blood Coagulation Time (Lee & White Method) in Haemophilia b (Factor IX deficiency) 38 – cases

C.T. in Min.	Haemophilia B
Cases	38
- 9	29(76.3%)
9.1 - 14	6(15.8%)
14.1 - 19	–
19.1 - 24	1(25%)
24.1 - 29	2(5.26%)

Normal Range=4 – 9 min. at 37°C(Dacie & Lewis 1975b)

The clotting time in 38 patients ranged from 7 min. 50 sec. to more than 25 minutes with average of 13.13 mins. The clotting time in 29 cases ranged from 4 minutes to 7 minutes 50 seconds with an average of 5.64 mins. These cases had a factor IX level ranging between 5-25.5u/dl with an average value of 17.52% i.e. mild deficiency. The clotting time in 6 patients ranged between 4 min. 20 sec. to 10 min. 30 sec. with an average value of 6.90 minutes. Factor IX level in this group ranged between 2-5 u/dl with an average value of 3.5%. They were cases of of moderate deficiency. Clotting time in 3 patients ranged between 25 – 30 min. with an average of 26.6 minutes. Factor IX level in these patients ranged between 0.5 – 1u/dl with an average value of 0.83% and were grouped as severe deficiency. All the three patients had haemarthrosis with contratures. Table - 3

Table - 3 Activated Partial Thromboplastin Time in Haemophilia B (Factor IX Deficiency) 38 – cases

APTT in Sec.	Haemophilia B
Cases	38
- 40	–
41 – 60	13(34.21%)
61 – 80	12(31.6%)
81 – 100	6(15.8%)
101 – 120	6(15.8%)
121 – 140	1(2.63%)

Normal Range of control: 25 – 35 seconds.

In 3 patients (7.89%) APTT ranged between 110-127 second with an average of 120.67 seconds as compared to the normal controls having average value of 30 seconds and APTT ranged between 27-35 seconds. Factor assay showed factor IX levels less than 2u/dl in these patients. Mode of presentation was spontaneous haemarthrosis and they had multiple contractures also. APTT in these severely deficient patients showed an average prolongation of 90.67 seconds as compared to average value of normal controls.

In 6 patients (15.78%) APTT ranged between 70-111 seconds with an average value of 96 seconds as compared to the normal controls in whom APTT ranged between 25-35 seconds with an average value of 30.83 second. Average prolongation was 65.17 seconds. The range of APTT in 29 patients (76.31%) was between 38-105 seconds with an average value of 64.41 seconds. In controls it ranged between 23-35 seconds with an average value of 29.95 seconds. It was prolonged on an average by 34.46 seconds as compared to the average control. ***(Table – 4)***

Table - 4 Coagulation factor level in factor IX deficiency (Haemophilia B) 38 – cases

Factor level in U/dl	Haemophilia B
Cases:-	38
- 2	3.(7.89%)
2.1 – 5	6(15.78%)
5.1 – 10	6(15.78%)
10.1 – 15	7(18.41%)
15.1 – 20	8(21.04%)
20.1 – 25	5(13.16%)
25.1 – 30	3(7.78%)

Expanded APTT was performed on 38 cases and all (100%) showed partial or complete correction of prolonged APTT with aged serum. Factor IX assay was done on all the patients. In 3 (7.9%) patients factor IX level was less than 2u /dl i.e. severe deficiency. They had haemarthroses and contractures. In 6 patients (15.78%) factor IX level ranged between 2-5u /dl with an average value of 3.5u/dl. In 29 patients (76.31%) factor IX level ranged between 6-27.5u/dl with an average value of 17.52u/dl. These patients presented mostly with bleeding after trauma or surgery and never had haemarthroses and most of them had history of bruises and epistaxis.

Parients and Methods

A total of one hundred coagulation disorders were investigated and a clinico haematological study was carried out on 38 cases of Haemophilia – B.

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.

Clinical Data:

A detailed personal and family history was obtained with a stress on age of appearance of symptoms, type and extent of bleeding. History of spontaneous bleeding or following trivial injury, bleeding into deep or subcutaneous tissues, joints or abdominal viscera was asked. Pedigree was drawn and relatives were investigated.

Sample Collection:

The blood samples were collected:

In 3.13 g/dl trisodium citrate in 1:9 ratio for coagulation study.

In sodium oxalate salt for routine blood examination.

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 IX deficient plasma. (Dade).

Discussion

The commonest symptoms in present study were easy bruising (100%), prolonged & delayed bleeding from cuts and wounds. (36.48%), followed by Haemarthrosis (13.16%), Post Circumcision bleeding (13.16%), Haematoma formation (10.53%), Bony ankylosis (7.89%), and Haematuria (7.89%).

The least common mode of presentation was Haematemesis (5.67%), Haemoptysis (2.63%), and C.N.S. bleeding (2.63%) etc.

Similar findings have been reported in their studies by Rizza,[1] Hougie,[8] Bowie et. al.[9] and Wintrobe et. al.[10]

Investigations:

Clotting Time: In the present study, there was no prolongation of clotting time in 29 patients who had mild deficiency of factor IX. It ranged from 4 mins. ___ 7 mins. 50 sec. with an average value of 5.64 mins.

Similar results have been produced by Rizza,[1] Williams and Wintrobe[10] et. al. who are of the opinion that Clotting time is prolonged only in severe cases of factor VIII or IX deficiency i.e., coagulation factor level less then 2u/dl.

Activated Partial Thromboplastin Time:

All the patients in our series (100%) showed significant prolongation of APTT.

Hougie etal[8] and Wintrobe atal[10] also state that APTT is always significantly prolonged in patients with less than 20-25 u/dl of factor VIII or IX level i.e., in all the three grades of severity.

Factor IX Assay:

In a total of 38 cases, we found only 3 patients (7.89%) with severe, 6 patients (15.78%), with moderate and 29 (76.31%) patients with mild factor IX deficiency. In our study the number of patients with mild to moderate deficiency of factor IX were more as compared to severe deficiency. We had a greater number of patients with mild deficiency of factor IX, even when compared with Haemophilia A. This finding is in agreement with Owen el. al.[11] & Wintrobe et. al.[10] who state that although factor IX deficiency is clinically indistinguishable from Haemophilia A, there seems to be a higher proportion of mild cases in the former and severely affected patients (factor IX level less then 2u/dl) are less common in Haemophilia B.

Conclusion

By carrying out clinico haematological study on 38 cases of Haemophilia B, we conclude.

In Haemophilia – B number of patients with mild deficiency are more as compared to moderate & severe deficiency.

These patients give past history of prolonged bleeding from cuts and wounds and easy bruising but history of Spontaneous bleeding was not there. They will only create a problem when subjected to trauma or surgery.

Clinically Haemophilia A and B are indistinguishable from each other. Mode of presentation being similar in both. So every patient with past or family history of bleeding should be carefully investigated. If APTT and /or

C.T. are prolonged, deficient factor should be carefully detected by coagulation factor assay as further management and therapy of factor VIII and IX deficiency are different and patient has to be labeled for the rest of his life.

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