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Original Article

Haemophilia; Pattern of Clinical Presentation and Disease Severity

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Abstract

Objective: To observe pattern of clinical presentation in patients of Hemophilia A and B.

Materials and Methods: Fifty one patients of Haemophilia A and B were evaluated on the basis of Patient`s demographic data, history (family, medication, past) and parameters like age, clinical features (pallor, number of joint involved, ankylosis and pain). Blood complete picture, Coagulation screening tests, bleeding time, PT, APTT, mixing studies and factor assays were documented.

Results: In total of fifty one patients, twenty two (43.13%) had severe degree of disease (<1% factor concentrate), while 19(37.2%) patients were diagnosed to have moderate degree of disease (factor concentrate 1-5%) and 10 (19.6%) had mild disease (factor concentrate 5-50%). Patients having severe disease were diagnosed earlier than those having moderate and mild disease, and had frequent episodes of bleeding in soft tissues, joints, muscles etc.

Conclusion: Pattern of clinical presentation helps to categories the haemophilia patients as having mild, moderate or severe degree of disease

Key words: Haemarthrosis, haemophilia A, haemophilia B, spontaneous bleeding, ankylosis.

Introduction

Haemophilias are rare X linked hereditary bleeding disorders classified into Haemophilia A (Deficiency of Factor VIII) and Haemophilia B (Deficiency of Factor IX) characterized by the body's inability to control blood coagulation resulting in bleeding either spontaneously or after a trauma.[1] Haemophilias usually affects males and females are carriers transmitting the disease to their sons [2] while thirty percent of the patients have no family history and are a result of de novo mutations.[3] The incidence of Haemophilia A (Classical) is 1 per 5000 male births [4] and Haemophilia B (Christmas Disease) is 1 in 30,000 [5] and estimated number of Haemophiliacs worldwide is 400,000.[6] Both the disorders (A & B) are indistinguishable clinically from each other as the signs and symptoms are same and diagnosis is established by performing mixing studies and specific factor assay.[7]

Clinically patients present with recurrent, spontaneous, and usually post-traumatic hemorrhages which may involve deep muscles, resulting in hematoma formation, hemarthrosis, and easy bruising.[8] Infants may develop excessive bleeding after circumcision. The clinical severity of the disease mainly correlates with the level of the factor in the blood and it is said to be severe when the level is below 1% of the normal,[9] while it is said

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to be moderate when the level is between 1-5% of normal and the disease is taken as mild when factor level is >5% but <40% of normal.[10] Severity of the disease is assessed by measuring the clotting factor level % activity (IU/ml)) in patients plasma.[11] According to the guidelines for management of Haemophilia by WFH 2007[12] the incidence of different sites of bleeding include haemarthrosis: 70%-80%, muscle/soft tissue:10%-20%, other major bleeds 5%-10% and central nervous system (CNS) bleeds: < 5%. Bleeding into calf, forearm or perineal muscles can lead to ischemic necrosis and contractures.[13] In severe cases , the relative incidence of spontaneous bleeding is 50% which is predominantly in joints and muscles while "Spontaneous bleeding" refers to those episodes of bleeding in which there is no obvious cause or history of trauma. Minor tissue damage which results from everyday activities initiates bleeding in patients of severe haemophilia. The relative incidence of occasional spontaneous bleeds and bleeding after trauma or surgery is 30% in moderate cases while in milder cases severe bleeding only occurs with major trauma or surgery and the relative incidence is 20% .[11]

Hemarthrosis (intra articular bleeding) is the most common clinical manifestation in severe cases of both Haemophilia A and B with an incidence of 80%.[14, 15] Haemarthrosis in hemophiliacs is also due to synthesis of tissue factor pathway inhibitor (TFPI) in synovial tissue[13] or due to low level of tissue factor (TF) expression in synovial tissue.[11] In patients with severe haemophilia the spontaneous bleeding into joints initiates a vicious cycle of bleeding followed by partial healing with synovial thickening and cartilage damage. This leads to a sequence of events of acute and chronic haemarthrosis and acute and chronic synovitis which results in disabling arthropathy.[16] Typically, hinge joints (weight bearing) like knees, elbows, and ankles are most frequently affected. Recurrent joint and muscle bleeds ultimately lead to crippling joint deformities and muscle wasting resulting in severe handicaps. Arthropathy leads to morbidity in a majority of patients of haemophilia. [17] Joint damage can occur after only a few haemarthrosis.[18] It is therefore of critical importance to prevent initial joint bleeds, and the resulting synovial hypertrophy and joint destruction.[19] In developing countries these patients are managed by replacement of the deficient factor by blood and blood products (cryoprecipitate, fresh frozen plasma) which has raised the issue of transmission of Hepatitis B, C and HIV in these patients.[20]

Although 80% of the haemophilics live in developing world but there is significant lack of data on the incidence of haemophilia in developing world. Out of 191 member states of World Health organization, 143 are developing countries which are within Asia, Africa and South America.[21] The data collection is improper and it does not accurately represent the epidemiology of haemophilia in these countries.[22] Pakistan stands at 122nd position among the countries with the poor health system as reported in a publication in year 2000.[23]

Today five centers are working under the supervision of Pakistan Hemophilia Patients Welfare Society (PHPWS) which was formed in 1998. Lack of awareness among general public, illiteracy, poverty, Poor acceptability of disability and social taboos are additional influences which create "Gap" of access to diagnosis and treatment of Hemophilia. Similarly deficiency in training of medical and paramedical staff and unavailability of factor concentrates are the main causes of under diagnosis and mismanagement of haemophilia patients in Pakistan. Six chapters are working diligently to provide education, medical relief, and physiotherapy to hemophilia patients under the supervision of Pakistan Hemophilia Patients Welfare Society (PHPWS) which was established

in 1998. The number of patients registered with the (PHPWS) is more than 1200 patients with Karachi chapter, Seven hundred and eighteen with Rawalpindi/ Islamabad, more than six hundred with Lahore and others with Peshawar, Quetta and Muzaffarabad Azad Kashmir making a total of4500 approximately. This study was designed to see the association of clinical sign and symptoms with the severity of disease in Haemophilia A and B patients at a single centre in Islamabad.

Materials and Methods

A total of 51 patients of haemophilia A and B including those who were already registered and those who attended the haemophilia centre for the first time were included. A detailed history including patient`s demographic data, clinical information about chief complaints at the time of presentation, disease history like first bleeding episode, symptoms, past history of use of crutches or wheel chair, presence or absence of bleeding episodes in last 12 months and circumcision was taken. Medication history included exposure of patient to either FFPs/blood or factor VIII and IX concentrates (recombinant/ viral inactivated) and age of first exposure to anyone/more than one of the above was noted. It also included average number of days of treatment, bleeding episodes per year, total number of treatment and type of both factor/product.

Clinical presentation of the patient which included pallor, pain, the type and site of bleeding, joint involvement, number of joints involved and complications like ankylosis were recorded. Baseline laboratory tests included blood complete picture, coagulation screening tests including bleeding time, prothrombin time and activated partial thromboplastin time. For coagulation assays, venous blood samples were collected in Biotubes (vacuum) containing 0.109 mol/L (3.2%) tri sodium citrate in a ratio of 9 parts blood to 1 part anticoagulant and then centrifuged without delay at 1500g for 15 minutes. Prothrombin time (PT), activated partial thromboplastin time (APTT) were carried out on this platelet poor plasma by manual method.

All the patients had normal Prothrombin time (PT), Platelet count and Bleeding time (BT) but the Activated Partial Thromboplastin Time (APTT) was prolonged. The remaining plasma was stored in 2 aliquots at _70C° for factor assay. Mixing studies were performed using aged and adsorbed plasma, APTT was measured after making 1:1 ratio of patient's plasma with aged and adsorbed plasma. In mixing studies Hemophilia A patients showed correction of APTT by adsorbed plasma but no correction with aged plasma while correction with aged serum was documented in Hemophilia B patients.

Factor assays were performed on automated blood coagulation analyzer CA-500series by Sysmex (550), using appropriate quality control materials and standard reagents (Dade Behring, Germany). Factor VIII levels were decreased in Hemophilia A and patients of Hemophilia B had lower level of Factor IX. All the results were entered on SPSS 16.0 for further analysis.

Results

Out of 51 patients of Hemophilia, factor VIII deficiency was documented in 41 (80.3%) patients (Hemophilia A), while 10 (19.6%) patients were deficient in Factor IX (Hemophilia B).Twenty two (43.13%) had severe degree of disease (<1% factor concentrate), while 19(37.2%) patients were diagnosed to have moderate degree of disease (factor concentrate 1-5%) and 10 (19.6%) had mild disease (factor concentrate 5-50%). (Table 1)

First bleeding episode which led to diagnosis of hemophilia occur after circumcision in twenty four (47%) patients while fifteen patients (29.4%) were found to be Hemophilic after exposure to injury (trauma). Table 2 shows the age at diagnosis in mild, moderate and severe hemophiliacs.

Table 1: Severity of disease (factor levels in %) and Arthropathy (n=51)				
Severity	No of patients	Hemarthrosis	No. of Joints involved	Ankylosis
Severe	(<1%) 22	20	2-6 (13)	3
Moderate	(1-5%) 19	15	2-6 (12)	2
Mild	(>5%) 10	9	2-6 (4)	1

Table 2: Association of factor (FVIII & FIX) levels with age at diagnosis in Patients of Hemophilia A & B (n=51)			
Age at Diagnosis (in years)	**Severe (<1%)**	**Moderate (1-5%)**	**Mild (>5%)**
0-5	22	4	1
6-10	00	6	3
11-15	00	6	2
16-20	00	3	1
21-25	00	00	3
Total Patients	22	19	10

Clinical features included prolonged bleeding after injury in 50 (98%) patients, 46 (90%) patients had hematomas at different body sites. Hemarthrosis (bleeding in the joints) was noted in 44 (86%) of the patients. Rest of the patients had prolonged bleeding after tooth extraction, epistaxis, bleeding from gums, deep bleeding, malena and hematuria. (Table 3)

Table3: Association of clinical presentation with severity of disease in haemophilia patients (n=51)				
Clinical presentation	**Mild cases**	**Moderate cases**	**Severe cases**	**Total cases**
Post traumatic bleeding	10	19	21	50
Hematomas.	8	16	22	46
Haemarthrosis	9	15	20	44
Bleeding after tooth extraction	4	10	13	27
Epistaxis	4	7	10	21
Bleeding Gums	5	7	6	18
Deep bleeding (abdomen,muscles)	-	3	4	7
Melena	-	2	2	4
Haematuria	-	1	3	4

Haemarthrosis was directly proportional to severity of disease. Children under the age of 5years did not show significant arthropathy. In our study, Hemarthrosis was seen in 86% of the patients, 15.7% patients had single joint involvement. Three to six joints were involved in 43.1% of patients while 11 (21.6%) patients had no joint involvement. Knee joint was the most commonly involved joint (47.83% episodes). Right Knee was the most commonly involved joint, in 27 (53%) patient, followed by left knee. Ankylosis was documented in 12% of the patients. Eight percent patients were using crutches.

Discussion

Hemophilia A and B are lifelong bleeding disorder so they impart not only a social but also financial burden on the families and ultimately the society.[24] In the present study twenty two (43.13%) patients hadsevere degree of disease, 19(37.2%) patients were diagnosed to have moderate degree of disease and only 10 (19.6%) had mild disease. Zafar et al in a study reported clinical stratification as severe, moderate and mild hemophilia seen in 55.55%, 18.8% and 25.64% cases, respectively.[25] Borhany et al documented that majority of hemophiliacs had moderate severity (52.0%) both in HA and HB.[10] A study from Egypt showed that severe manifestations were reported in majority in 76.7% followed by moderate severity in 17.2%.[26]

Out of 51 patients, four (7%) patients were diagnosed at birth while 23 (44.6%) patients were diagnosed below the age of five months. All the severe cases (22 cases) were diagnosed before the

age of 5 years, whereas majority of moderate cases were diagnosed between 5-10 years and 90% of mild cases were diagnosed above 5 years of age. Zafar et al reported the age at diagnosis as up to 1 year in 62 (53%), 1 to 5 years in 23 (20%) and > 5 years in 32 (27%) of the patients. Borhany et al reported mean age of presentation as 2.1 years for HA and 2.3 years for HB. Similar data from India revealed that 21% (109/510) of severe hemophilia A patients had reported their first symptoms before they were 1 year old.[27] In Egypt, majority of hemophilia patients presented before they were 1 year old.[26]

First bleeding episode leading to diagnosis was prolonged bleeding after circumcision in twenty four (47%) out of a total of 51 patients of Hemophilia. Fifteen patients (29.4%) were found to be Hemophilic after exposure to injury (trauma). At birth six (11.8%) patients were suspected and found to have Hemophilia due to either prolonged bleeding from umbilical cord or due to positive family history. Mohsin et al reported in their study that first bleeding episode occurred after circumcision in 142 (62%), prolonged bleeding after injury in 42(18.4%), bleeding from umbilical stump in 12(5.2%), and after tooth extraction in 02(0.9%). In an Egyptian study the main presenting symptoms was bleeding following circumcision 51% followed by post traumatic bleeding in 36.%.

Hemarthrosis was directly proportional to severity of disease and children under the age of 5years did not show significant arthropathy. In our study, Hemarthrosis was seen in 86% of the patients, 15.7% patients had single joint involvement. Ankylosis was documented in 12% of the patients. Eight % patients were using crutches. Zafar et al also document that arthropathy was found in 75.21% of the patients and permanent disability was seen in31.62% of cases. Knee joint was the most commonly involved joint, results comparable to our study. Borhany et al reported Hemarthrosis in 102 patients of Hemophilia A and 23 patients of Hemophilia B. Similarly Mohsin et al reported that Arthropathy was the most frequently (76.4%) occurring complication. Knee joint was involved alone in 59(25.8%) and in combination with elbow, shoulder and ankle joints in 22(9.6%), 10(4.4%) and 4(1.7%) patients respectively. Knee joint was found to be involved in 42% patients either alone (26 %) or in combination with other joints (16%).Studies from Egypt showed that joint involvement was present in 8.3% of the patients only, while 44.4% of patients had no complication. This was due to prophylaxis given to most of the hemophilia patients. Aznar JA et al, in Spain observed that 30 % of patients had established hemophiliac arthropathy in at least one joint.[28] The reason for this difference in the frequency of arthropathy is the early diagnosis and prophylactic treatment in developed countries.[29]

Conclusion

Lack of awareness among general public, illiteracy, poverty, poor acceptability of disability and social taboos are the factors which create "Gap" of access to diagnosis and treatment of Hemophilia. Similarly deficiency in training of medical and paramedical staff and unavailability of factor concentrates are the main causes of under diagnosis and mismanagement of hemophilia patients. As noted about 60% of our patients had joint involvement and among these 12% had ankylosis with use of crutches by 8% patients. It is thus suggested that establishment of hemophilia centers with collective support from physiotherapy, dental, psychiatry and orthopedic departments and productive adjustment of hemophiliacs in the society are the keys to fulfill this gap. Moreover continuous education and awareness of patients and their families about the disease manifestation, treatment options available and

awareness about the risk of complication will prevent these patients from the catastrophic complications of the disease.

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