# Clinical Profile of Haemophilia in a Tertiary Care Hospital in Pune, Maharashtra, India

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**ABSTRACT**

**BACKGROUND**

Haemophilia's are X-linked hereditary blood clotting disorders due to deficiency of factor VIII (haemophilia A) or factor IX (haemophilia B) & also has identical clinical manifestations, screening tests abnormalities and sex-linked genetic transmission. Haemophilia's result from defects in the factor VIII / IX gene that lead to decreased amount of factor VIII / IX protein, the presence of a functionally abnormal protein, or combination of both. Haemophilia A is a classic example of an X-linked recessive trait. The severity of their bleeding depends on their factor VIII activity level; and, rarely, a woman can have very low factor VIII activity, and present with symptoms of moderate or even severe haemophilia. We wanted to study the clinical profile of patients of haemophilia admitted in a tertiary care hospital.

**METHODS**

This is a cross-sectional study enrolling 60 known cases of haemophilia A & B admitted in wards & ICU / attending OPD of a tertiary care hospital. History was obtained in detail & thorough clinical examination was carried out. Precipitating factors for bleeding (spontaneous / minor trauma / major trauma / surgical operation / dental procedure / others), family h / o bleeding were studied in detail.

**RESULTS**

Of the total 60 cases of haemophilia, majority (49) of cases were of haemophilia A and 11 cases were of haemophilia B. In the study, majority (28.33 %) of cases belonged to 12 - 20 years age group and the most common presentation was haemarthrosis (61.67 %). 6 patients had factor VIII inhibitor antibodies and all of them were of haemophilia A.

**CONCLUSIONS**

Haemarthrosis is the most common clinical presentation of haemophilia and most common cause for haemarthrosis is spontaneous bleeding. Most common joint involved in bleeding was knee joint (target joint). Presence of factor VIII inhibitor antibodies specially in haemophilia A patients is not uncommon.

**KEYWORDS**

Haemophilia, Factor VIII, Factor IX

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## BACKGROUND

Haemophilia's are X-linked hereditary blood clotting disorders due to deficiency of factor VIII (haemophilia A) or factor IX (haemophilia B) & also had identical clinical manifestations, screening tests abnormalities and sex-linked genetic transmission. It is the second most common inherited clotting factor abnormality (after Von Willebrand disease). Haemophilia's result from defects in the factor VIII / IX gene that leads to decreased amount of factor VIII / IX protein, the presence of a functionally abnormal protein, or combination of both.

Haemophilia A is a classic example of an X-linked recessive trait. In such a disorder, the defective gene is located on the X chromosome 12. In males who lack a normal allele, the defect is manifested by clinical haemophilia. The affected male does not transmit the disorder to his son because his Y chromosome is normal. However, all of his daughters are obligate carriers of the trait because they inherit his X chromosome. Most of these women are unaffected clinically because of the presence of a normal allele from the mother. The female carrier transmits the disorder to half of her sons and the carrier state to half of her daughters. Due to lyonization of the X chromosome, if the normal factor VIII allele is inactivated more often by chance, then some of the carrier females may have clinical bleeding. The severity of their bleeding depends on their factor VIII activity level; and, rarely, a woman can have very low factor VIII activity and present with symptoms of moderate or even severe haemophilia. Clinical features include excessive bleeding into various parts of the body; haemarthrosis, haematomas, haematuria, haemorrhage into the central nervous system, mucous membrane haemorrhage pseudo tumours (blood cysts), dental and surgical bleeding. Haemorrhage into the central nervous system is the most dangerous event in haemophilic patients. Intracranial bleeding may be spontaneous or follows trauma, which may be trivial. Haemophilic patients with unusual headaches should always be suspected of having intracranial haemorrhage. Haemorrhage into the spinal canal can result in paraplegia. Peripheral nerve compression is a frequent complication of muscle hematomas, particularly in the extremities. Delayed bleeding is common. Thus, although haemostasis after an injury or a minor surgical procedure may appear to be adequate, haemorrhage, often of sudden onset and serious proportions, may develop several hours or even days later. This phenomenon apparently occurs because the processes of primary haemostasis are only temporarily effective. Delayed bleeding may occur in patients with mild haemophilia and is a significant hazard after minor surgical procedures, particularly those performed on an outpatient basis, such as tooth extraction and tonsillectomy.

Venipuncture, if skilfully performed, is without danger for the person with severe haemophilia, primarily because of the elasticity of the venous walls. If venipuncture is traumatic, digital pressure on the puncture site or a pressure dressing may prevent further complications. Subcutaneous, intracutaneous, and small intramuscular injections seldom produce hematomas if firm finger pressure is maintained for at least 5 minutes. Large intramuscular injections should be avoided. Vaccination using intramuscular injections is acceptable with minimal increase in bleeding risks.

Severity wise haemophilia can be classified as mild, moderate & severe haemophilia depending on levels of factor VIII or IX in circulation. Clinical features also depend on severity of haemophilia.[1,2,3] Complications due to recurrent bleeding includes flexion contractures, joint arthritis, chronic pain, muscle atrophy, compartment syndrome, neurologic impairment, pseudotumors.[1,2] The frequency and severity of joint bleeds are related to the functional activity level of factor VIII in plasma.[4,5] In many patients permanent joint damage, detectable by magnetic resonance imaging (MRI), appears to occur after one or two minor bleeds into a single joint.[6]

Laboratory findings include - Prolonged activated partial thromboplastin time (aPTT) - the aPTT is corrected when haemophilic plasma is mixed with an equal volume of normal plasma, normal prothrombin time, thrombin-clotting time, bleeding time. A definitive diagnosis of haemophilia A / B should be based on specific assay for factor VIII / IX coagulant activity.

Therapy in haemophiliacs include avoidance of aspirin, non-steroid anti-inflammatory drugs, and other agents interfering with platelet aggregation (exception - the pain of haemophilic arthropathy), cautious use of addictive narcotic agents, avoidance of intramuscular injections, factor VIII / IX replacement therapy, factor VIII prophylactic therapy to prevent chronic complications like joint deformity, fibrinolytic inhibitors [Epsilon-Aminocaproic Acid (EACA), tranexamic acid] as adjunctive therapy for bleeding from mucous membranes, particularly for dental procedure.

We wanted to study the clinical profile of patients of haemophilia admitted in tertiary care hospital.

## METHODS

The study was conducted in a tertiary care hospital from August 2014 to December 2015. Study protocol was presented to the institutional ethics committee and clearance was taken. Study was conducted after taking informed consent from the patients. This was a cross-sectional study where 60 known case of haemophilia A & B admitted in wards & ICU / attending OPD of a tertiary care hospital, were included after ruling out exclusion criteria.

### Inclusion Criteria

1. Patients more than 12 years of age admitted in medicine wards & in medical intensive care unit.
2. Patients with the presence of an appropriate clinical picture supported by aPTT / factor VIII or IX assays.

### Exclusion Criteria

1. Patients less than 12 years of age.
2. Patients whose written consent can't be obtained & relatives were unwilling to give consent.

3. Patients with other coagulation (primary or secondary) disorders.

History was obtained in detail & thorough clinical examination was carried out. Precipitating factors for bleeding (spontaneous / minor trauma / major trauma / surgical operation / dental procedure / others), family h / o bleeding was studied in detail. Clinical suspicion for presence of inhibitors were studied. Patients were investigated with following lab studies –haemoglobin (Hb), prothrombin time (PT), PT- international normalised ratio (INR), PTT / aPTT, factor VIII assay, factor IX assay, and inhibitor assay.

### Statistical Analysis

Descriptive analysis of qualitative variables were expressed in frequency and percentages.

## RESULTS

Of the total 60 cases of haemophilia, majority (49) of cases were haemophilia A and only 11 cases were haemophilia B. In the study, majority (28.33 %) of cases belonged to 12 - 20 years age group, followed by (23.3 %) cases in 21 - 25 years age group. In this study, family history of haemophilia was positive in 32 patients (53.33 %). In this study, most common presentation was haemarthrosis (61.67 %).

| Type | Numbers |
|---|---|
| Haemophilia A | 49 |
| Haemophilia B | 11 |
| **Total** | **60** |

***Table 1. Type of Haemophilia***

| Age (Years) | Haemophilia A | Haemophilia B | Total |
|---|---|---|---|
| 12 – 20 | 14 | 03 | 17 |
| 21 - 25 | 09 | 05 | 14 |
| 26 - 30 | 11 | 02 | 13 |
| 31 - 35 | 03 | 01 | 04 |
| 35 - 40 | 09 | 0 | 09 |
| > 40 | 03 | 0 | 03 |
| **Total** | **49** | **11** | **60** |

***Table 2. Age Distribution of Patients***

| Family History | Haemophilia A | Haemophilia B | Total (%) |
|---|---|---|---|
| Positive | 26 (53.06 %) | 06 (54.54 %) | 32 (53.33 %) |
| Negative | 23 (46.93 %) | 05 (45.45 %) | 28 (46.67 %) |
| **Total** | **49 (100 %)** | **11 (100 %)** | **60 (100 %)** |

***Table 3. Family History of Haemophilia***

| Clinical Presentation | Haemophilia A | | Haemophilia B | | Total | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Haemarthrosis | 31 | 63.30 | 6 | 54.53 | 37 | 61.67 |
| Intramuscular bleed | 6 | 12.24 | 2 | 18.18 | 08 | 13.33 |
| Post traumatic bleed | 6 | 12.24 | 2 | 18.18 | 08 | 13.33 |
| Gum bleeding | 1 | 2.01 | 0 | 0 | 01 | 1.67 |
| Epistaxis | 3 | 6.11 | 1 | 9.1 | 04 | 6.67 |
| Hematuria | 2 | 4.10 | 0 | 0 | 02 | 3.33 |
| **Total** | **49** | **100** | **11** | **100** | **60** | **100** |

***Table 4. Clinical Presentation of Haemophilia***

| Precipitating Factor | Haemophilia A | Haemophilia B | Total (%) |
|---|---|---|---|
| Spontaneous | 26 | 04 | 27 (45) |
| Minor trauma | 14 | 04 | 21 (35) |
| Major trauma | 09 | 03 | 12 (20) |
| **Total** | **49** | **11** | **60** |

***Table 5. Precipitating Factors for Bleeding***

Most of the haemophilia patients (45 %) presented with spontaneous bleeding. The above table shows that knee (69.23 %) is the most common site of repetitive bleeding i.e., target joint. Out of 60 patients of haemophilia, 6 patients had factor VIII inhibitor antibodies and all of them were haemophilia A type.

| Site | Haemophilia A | Haemophilia B | Total No. | % |
|---|---|---|---|---|
| Knee joint | 31 | 05 | 36 | 69.23 |
| Elbow joint | 09 | 02 | 11 | 21.15 |
| Ankle joint | 04 | 01 | 05 | 9.62 |
| Hip joint | 00 | 00 | 00 | 00 |
| **Total** | **44** | **08** | **52** | **100** |

***Table 6. Target Joint***

| Inhibitors | Haemophilia A (%) | Haemophilia B (%) | Total (%) |
|---|---|---|---|
| Present | 6 | 0 | 6 (10) |
| Absent | 43 | 11 | 54 (90) |
| **Total** | **49** | **11** | **60 (100)** |

***Table 7. Presence of Inhibitors in Haemophilia Patients***

## DISCUSSION

### Type of Haemophilia (Table 1)

In the above study, of the total 60 cases of haemophilia, majority of cases were haemophilia A (81.67 %) and only 11 cases were haemophilia B. The ratio of haemophilia A / haemophilia B has been reported between 78 / 22 and 87 / 13 throughout the world. Agarwal et al.[7] had found the percentage of haemophilia A being 78.6 % (236 / 300 cases), which was similar to the present study. In a study, out of the 50 cases diagnosed with haemophilia based on the laboratory tests, majority of cases, 82 % were haemophilia A and only 18 % were haemophilia B.[8] The pattern of haemophilia patients of this study was similar to the study by Dube et al.[9]

### Age Distribution of Patients (Table 2)

In the study, majority (28.33 %) of cases belonged to 12 - 20 years age group, followed by (23.3 %) cases in 21 - 25 years age group.

### Family History (Table 3)

In this study, family history of haemophilia was positive in 32 patients (53.33 %). i.e. the family history was present in more than half of the patients in this study. Similar percentage was reported by Parthiban et al.[8] in which 52.2 % of the patients had family history of haemophilia.

### Clinical Presentation of Haemophilia (Table 4)

In this study, most common presentation was haemarthrosis (61.67 %). This feature correlated with Dube et al.[9] Agarwal et al.[7] Agarwal and Mehta.[10] Karim et al.[11] and Nigam et al.[12] they described haemarthrosis as the most common symptom.

**Precipitating Factors for Bleeding (Table 5)**
Most of the haemophilia patients (45 %) presented with bleeding because of spontaneous bleed. Spontaneous bleeding in the form of subcutaneous haematomas or bruises was the most common symptom in all patients with haemophilia irrespective of the type, which is in accordance with Agarwal et al.[7] Conway and Hilgartner[13] and Uddin[14] respectively.

**Target Joint (Table 6)**
The above table shows that knee (69.23 %) is the most common site of repetitive bleeding i.e. target joint. followed by elbow joint (21.15 %). These findings were similar to Alok Srivastava et al.[15]

**Presence of Inhibitors and Factors Relating in Haemophilia Patients (Table 7)**
Out of 60 patients of haemophilia 6 patients had factor VIII inhibitor antibodies and all of them were haemophilia A type (severe). Various studies showed that 10 - 20 % of people with FVIII deficiency and 2 - 3 % of people with FIX deficiency develop persistent inhibitors. All patients with inhibitor factors were having severe type of haemophilia. ABO blood group relation with inhibitor positivity: Among 6 patients 3 were AB positive, 2 were B positive and 1 was A positive. In various studies, it was shown that there is no correlation between ABO blood group and F VIII inhibitor formation.[16] All patients with inhibitors were having family history of haemophilia.

## CONCLUSIONS

Haemarthrosis is the most common clinical presentation of haemophilia and the most common cause for haemarthrosis is spontaneous bleeding. The most common joint involved in bleeding was knee joint (target joint). Presence of factor VIII inhibitor antibodies specially in haemophilia A patients is not uncommon.

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