

# Pediatric Severe Hemophilia: Initial Presentation, Characteristics, And Complications

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## Citation

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## Abstract

**Purpose:** To review the natural history of severe Hemophilia A & B (Factor VIII & IX, < 1%), including initial presentation at diagnosis, radiograph characteristics, and complications.

**Methods:** Questionnaires were filled out by families. All inpatient and outpatient records were reviewed, and radiographs were analyzed by one radiologist.

**Results:** 64.3 % of the patients were diagnosed at birth (within 7 days of birth) (0.38, 0.90, 95% CI). The initial event was divided between iatrogenic bleeding event (Total n=9[60%]), with 8(53.3%) cases diagnosed after uncontrolled bleeding with circumcision, and spontaneous bleeding event (Total n=6[40%]), with bruising/hematoma [4(26.7%)] being the commonest cause. 5 (33%) out of 15 developed inhibitors, 8 (53%) had history of severe bleeding episodes (> 25 per year) and 7(46%) had severe joint arthropathy. Hepatitis C was the commonest infectious complication seen in our population, 5(33.3%) cases in total.

**Conclusions:** Severe Hemophilia presents at an early age; therefore, attention to family history and early bleeding episodes is critical. Prophylactic factor therapy should be started at an early age to prevent major bleeding complications.

## INTRODUCTION

Hemophilia is the second most common congenital bleeding disorder, occurring in 20 of every 100,000 males in the United States. Deficiency of Factor VIII (Hemophilia A) accounts for 85% of the cases and 15% are due to Factor IX (Hemophilia B) deficiency. They are both inherited as X-linked recessive disorder. Clinically, it is useful to classify them according to the measured Factor VIII and IX activity in the plasma as: severe < 1 unit/dl, moderate 1-5 unit/dl, and mild > 5 units/dl.

Generally, persons with severe Hemophilia have frequent, spontaneous bleeding episodes that usually involve major joints, muscles, or soft tissue and may lead to residual morbidity. Current estimates of incidence indicate that 1 in 10,000 males are affected by severe Hemophilia A and 1 in 50,000 males by severe Hemophilia B. [1]

## PATIENTS AND METHODS

A total of 15 patients were diagnosed with severe Hemophilia A and B during the period 1974 to 2001 at

Columbus Children's Hospital Hemophilia Clinic. For each of these patients, all available inpatient and medical records were obtained, including records from outside hospitals whenever necessary. In addition, patient or parent interviews and questionnaires were used to supplement information whenever possible

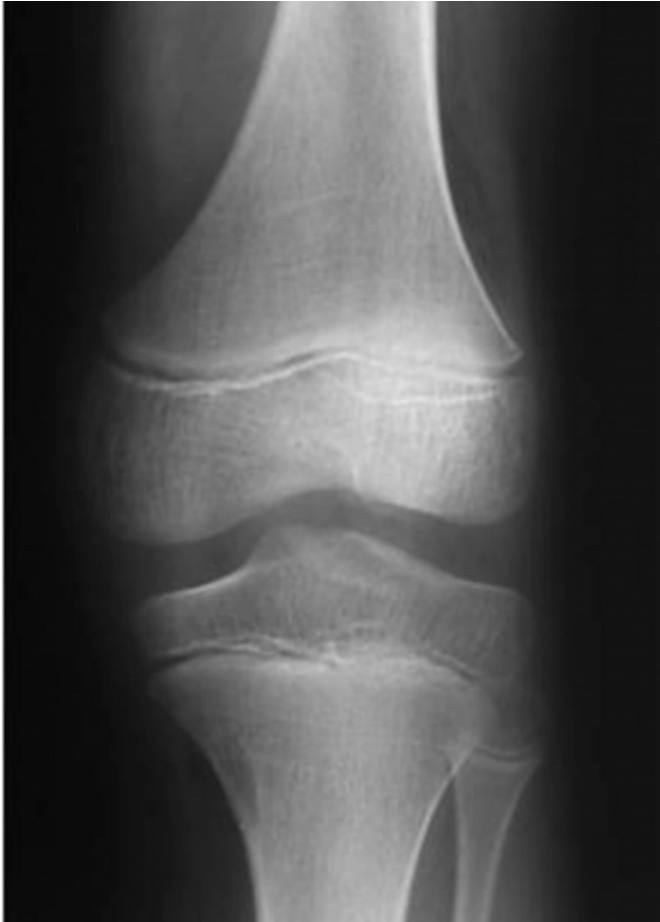
Demographic data such as age, race, type of factor deficiency, and family history of bleeding were collected. We analyzed only the bleeding episodes for which medical assistance was sought. For evaluating joint arthropathy radiographs were reviewed by our staff musculoskeletal radiologist. These films included at least two studies and as many as 16 studies for each patient. Each study included at least two views of the joint involved. Follow-up images were done between 1 year and 7 years from the initial exam. The images were reviewed and retrospectively staged using the five stage scale devised by Arnold and Hilgartner [2].

Arnold's classification system is based on roentgenographic findings and was devised to determine timing for surgical care. The features considered in the classification system are

related to the destruction of articular cartilage and subsequent underlying bone erosion. Figures A, B and C illustrate the various stages of arthropathy seen in our study.

**Figure 1**

Figure A is an example of stage II, notice that there is slight osteopenia and some early overgrowth of the condyles but the joint space is well maintained.



**Figure 2**

Figure B demonstrates Stage III with early narrowing of the joint space from loss of cartilage and spur formation on the margins of the condyles. The patella demonstrates early squaring from hyperemia and overgrowth.



**Figure 3**

Figure C demonstrates more advanced cartilage destruction with more loss of the joint space, cyst formation within the condyles and the articular surface of the patella. The destruction is no longer reversible.



**RESULTS**

**DEMOGRAPHICS:**

Of the 15 patients in our study 13 (86.5%) were Caucasians, while 1 (6.5%) each was African American and Asian. 12 (80%) had Factor VIII and 3 (20%) Factor IX deficiency.

**INITIAL PRESENTATION:**

Table 1 presents the primary presenting signs/ symptoms at diagnosis. The majority (64.3%) of the patients presented at birth (within 7 days of birth) (0.38, 0.90, 95% confidence interval.) The initial reason for attention of a possible bleeding disorder was divided between iatrogenic bleeding events (n=9[60%]), and spontaneous bleeding events (n=6 [40%]). Of the iatrogenic bleeding events, circumcision, (n= 8 [53.3%]) was the commonest while bruising/hematoma (n=4 [26.7%]) was the commonest cause of spontaneous bleeding. No statistically significant difference was noted between iatrogenic and spontaneous bleeding events. It is also important to note that family history was positive in 2 cases.

**Figure 4**

Table 1: The initial sign/symptom leading to diagnosis of hemophilia

CAUSES	NUMBER (PERCENTAGE)
I. Iatrogenic	9 (60%)
1. Circumcision	8 (53.3%)
2. Other surgical procedures	1 (6.7%)
II. Spontaneous	6 (40%)
1. Cephalohematoma	1 (6.7%)
2. Intracranial Hemorrhage	1 (6.7%)
3. Bruising/hematoma	4 (26.7%)
<b>TOTAL</b>	<b>15 (100%)</b>

**INHIBITORS:**

5(33%) out of 15 patients developed inhibitors. Four had Hemophilia A and one Hemophilia B. The average Bethesda titer was approximately 32 units (range 5-45 units). It took on an average of 35 months before the inhibitors completely resolved. Most of the inhibitors developed during the first year of life. Treatment strategies used at our hospital included immune tolerance, prothrombin complex anti-inhibitor coagulant complex (FEIBA), porcine Factor VIII and activated Factor VII. FEIBA, however, was used in all our patients with hemophilia A at some point. Our one patient with Hemophilia B with inhibitors developed anaphylactic reaction to Factor IX products (on two separate occasions). He was then treated with activated Factor VII, and his titers became normal within 6 months of therapy. Similarly, we noted a resolution of inhibitor titers in our only patient with HIV (Human Immunodeficiency virus) once he contracted the virus.

**BLEEDING EPISODES**

Being severe Hemophiliacs, all patients had history of bleeding episodes. 8(53.5%) of the 15 patients had greater than 25 bleeding episodes per year. The bleeding occurred in multiple sites including muscle, soft tissue, and joints. Fortunately only 2(13.3%) had intracranial hemorrhage. Interestingly, there was no reported case of bone fracture. 9(60%) patients received prophylactic factor therapy, one had Hemophilia B & the other 8 had Hemophilia A. Central venous catheter was used in only 7 cases. There was no clotting associated with these catheters.

**JOINT ARTHROPATHY:**

Joint arthropathy was present in 7(46.7%) of cases. 4(26.7%) of those patients went on to have synovectomies, which involved from one (target) to three joints (Table 2). Arthropathy was Staged I-IV, using classification devised by Arnold and Hilgartner (1). 3(42.9% ) cases were stage IV,

2(28.6%) stage II, and one (14.3% ) case each of stage I and III.

**Figure 5**

Table 2: Characteristics of the seven causes with joint arthropathy

CASE	STAGE	NUMBER OF JOINTS INVOLVED	SYNOVECTOMY
1	I	1	No
2	IV	2	Yes, one joint
3	III	2	No
4	II	2	No
5	IV	5	Yes, three joints
6	IV	6	Yes, three joints
7	II	3	Yes, one joint

**INFECTIOUS COMPLICATION**

Hepatitis C was the commonest infectious complication seen in our population. There were a total of 5(33.3%) cases. In addition to Hepatitis C there were 2(13.3%) cases of hepatitis B and one (6.7%) case of HIV. Our only patient with HIV had a coinfection with hepatitis C. Coinfection of HIV with hepatitis C has been reported by others. [2,3]. While none of our patients have developed cirrhosis, they are certainly at risk. Our only HIV positive case has an absolute CD4 count of 445 cells/ cu mm, with a low viral load of 408 RNA copies/ml.

**DISCUSSION**

The Hemophilias are the commonest inherited bleeding disorders to present neonatally [5]. Older studies suggest that bleeding in the neonatal period is a relatively infrequent event. Baehner et al [6], reported <10% of the severe Hemophiliacs had a clinical event within the first month of life. More recent studies, however, suggest that those figures may be an underestimate of the true situation. In a cohort of Swedish Hemophiliac 28/140 (20%) had a clinical event within the first week of life [6,8]. In a similar study for the US, 68.4% were diagnosed in the first month of life [9]. Our study similarly showed that more than half [64%] of severe Hemophiliacs present within the first 7 days of life. The pattern of bleeding episodes in those cases that present at birth differ from that typically seen in older children with Hemophilia, where joint and muscle bleeds predominate [7,9]. Bleeding following circumcision was the commonest mode of presentation. Other causes included spontaneous bleeding events like bruising/hematoma, cephalhematoma and intracranial hemorrhage. Estimates of the frequency of a positive family history in Hemophilia vary. Both older and more recent studies report up to 50% of severely affected cases as having a positive family history [6,9,10]. We found a positive family history in 2 (13.3%) of cases.

Bleeding into the joint accounts for about 75 percent of bleeding episodes in older children with severe Hemophilia [11]. The joints most frequently involved, in decreasing order of frequency, are knees, elbows, ankles, shoulders, wrists, and hips. Hinge joints are much more likely to be involved then ball and socket joints. One of the major complications of repeated hemarthroses is joint deformity. Arnold WD et al [2] has described five stages of progressive distraction of joint cartilage and adjacent bone. The soft tissue swelling of stage I gives way to stage II, in which there is early osteoporosis and overgrowth of the epiphyses. In stage III, disorganization of the joint is evident, with subchondral cyst formation, squaring of the patella etc. This is the final stage at which Hemophiliac arthropathy can be reversed by medical therapy. In stage IV, the cartilage is destroyed and the joint space is narrowed. Stage V, the end stage, is characterized by fibrosis joint contracture and complete loss of cartilage and joint space. We found that approximately half of our patients developed severe arthropathy, with most patients requiring synovectomies.

Before the implementation of donor screening and the development of effective virus inactivation procedures, patients with Hemophilia were at very high risk of transfusion associated diseases such as Hepatitis B viruses (HBV), Hepatitis CV (HCV), and HIV. HCV was the commonest infection seen in our population. HCV is the major cause of chronic liver disease in Hemophilias, and coinfection with HIV accelerates this progression [12]. Fortunately, none of our patients have progressed to this stage, but they certainly are at high risk. The new Factor products are considered to be safe and effective. There is very little risk of transmitting currently known viral disease with these products. With the control of infectious complication the focus has now shifted to the development of antibody inhibitors. Most often inhibitors are of the IgG class and frequently restricted to the IgG4 subclass [13]. Inhibitors usually develop during an early childhood [14] but can occur at any age. Severe Hemophilias are more likely to develop inhibitors. Although inhibitors have been reported to be more frequent in Hemophilia A than B, [15, 16] we found in our population that the percentage was the same (33%). The presence of an inhibitor is confirmed by the Bethesda inhibitor assay. An inhibitor does not cause patients to bleed more often, but it can make it more difficult to treat and control bleeds. The treatment of patients with inhibitors is difficult because each patient reacts differently to the available treatments and products. We used prothrombin complex (FEIBA), porcine Factor VIII, immune tolerance

and activated Factor VII. FEIBA was used in all our patients with Hemophilia A at some point in their treatment. Our only patient with Hemophilia B, who developed an inhibitor, had an anaphylactic reaction to Factor IX. There have been reports of up to 50% incidence of anaphylactic reactions in Hemophilia B patients with inhibitors who receive Factor IX products [15]. We placed this patient on activated Factor VII, his Bethesda titers returned to normal in 6 months time. Similarly, as has been observed by others [17] our only patient with HIV had resolution of his inhibitor titers when he contracted HIV.

## CONCLUSION

The clinical manifestation of Hemophilia A and B are due to deficiency of Factor VIII and IX, respectively. They are the only blood clotting disorders inherited in a sex-linked recessive pattern. The severe form of both Hemophilia A and B usually present at birth. They are characterized by frequent hemarthrosis, leading to chronic crippling hemarthropathy when not treated very early or prophylactically. Highly purified concentrates, manufactured by recombinant technology, are available for treatment and are considered to be both safe and effective. Prophylactic treatment is recommended, when feasible, for all severe Hemophiliacs. The main complication of treatment, since the use of purified factor products, is the development antibody inhibitors.

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