International Journal of Biomedical and Advance Research
ISSN: 2229-3809 (Online); 2455-0558 (Print)
Journal DOI: https://doi.org/10.7439/ijbar
CODEN: IJBABN

Original Research Article

A study of clinical characteristics and factor assays of 100 cases of Hemophilia in Bihar, India

Anil Kumar Thakur[1], Dilip Kumar Pandey[1], Om Prakash Dwivedy[*2], Subhash Chandra Jha[3], Navin Chandra Prasad[3] and Manoj Kumar Sinha[3]

[1]*Assistant Professor, Department of Pathology, Anugrah Narayan Medical College and Hospital, Gaya*
[2]*Associate, Professor, Nalanda Medical College and Hospital, Patna*
[3]*Hematologist, New Gardiner Road Superspeciality Hospital, Patna*

QR Code

***Correspondence Info:**
Dr. Om Prakash Dwivedy
Associate Professor
Department of Pathology,
Nalanda Medical College and Hospital, Patna 800026, India

***Article History:**
Received: 28/10/2018
Revised: 14/11/2018
Accepted: 17/11/2018
DOI: https://doi.org/10.7439/ijbar.v9i11.4943

Abstract

Background: The common bleeding disorder, hemophilia, is an X-linked genetic disorder characterized by a deficiency or absence of factor VIII (FVIII) (hemophilia A or classic hemophilia) or factor IX (FIX) (hemophilia B or Christmas disease**.** They are typically inherited from mother through an X chromosome with a defective gene.
Materials and method: This study was conducted in the departments of pathology of Medical Colleges and Hemophilia Superspeciality Hospital of Bihar, India, during the period of August 2017 to August 2018. Clinical parameters and factor assay result along with APTT values were systematically recorded**.**
Result: 81% patients had hemopilia A and 19 % patients had hemophilia B, ratio was 4.2:1. As per severity of hemophilia A, 20%, 62% and 18% were respectively mild, moderate and severe type. Severity of hemophilia was inversely proportional to level of factor. Hemophilia A was clinically more severe than hemophilia B for same level of factor.
Discussion and Conclusion: 54% patients presented with symptoms in the age group of 0-10 years and 1% in 55-65 years age group in this study. Mildly severe hemophilia presents in older age group.
Recurrent joint swelling was the predominant clinical finding followed by wound bleeding in this study. Hemophilia is major health problem in Bihar, India that has got huge financial and social significance Provision of proper treatment and physiotherapy is needed at hemophilia treatment centres to prevent disability and disfigurement.
Keywords: Bleeding disorder, Hemophilia, Hemophilia A, Hemophilia B, Factor, Inhibitor, Hemarthrosis.

1. Introduction

Inherited disorders of coagulation usually are result of a defective or abnormal single plasma protein [1].

The common bleeding disorder, hemophilia, is an X-linked genetic disorder characterized by a deficiency or absence of factor VIII (FVIII) (hemophilia A or classic hemophilia) or factor IX (FIX) (hemophilia B or Christmas disease**.** They are typically inherited from mother through an X chromosome with a defective gene[1,2]. Rarely a new mutation may occur during early development or hemophilia may develop later in life due to antibodies forming against a clotting factor that is called acquired hemophilia. Almost one third hemophilia is due to new mutation [3]. Persons with hemophilia suffer from complications of both disease and inhibitor. Treatment is by replacing the missing plasma clotting factors that is called replacement therapy [4]. This may be done on a regular basis (prophylactic) or during bleeding episodes (on demand) [5]. Replacement may take place at home or in hospital. In India, on demand therapy in hospital is usual mode of treatment. The clotting factors are either plasma derived) or recombinant type. Plasma derived is cheaper but efficacy wise both are similar. However chance of viral disease transmission is more in plasma derived [5,6]. In hemophilia A, 20% to 33% of people develop antibodies to the clotting factors during early phase of therapy which makes treatment more difficult. In hemophilia B, chance of inhibitor development is only 1% to 6%. The chance of

development of antibodies is almost similar with both types of factor replacement. Hemophilia A affects about 1 in 5,000 while hemophilia B affects about 1 in 30,000, males at birth [7]. Characteristic symptoms vary with severity. In general symptoms are internal or external bleeding episodes, which are called bleeds [8,9].

People with more severe hemophilia suffer more severe and more frequent bleeds, usually spontaneous swelling and bleed, while people with mild hemophilia usually suffer minor symptoms except after surgery or serious trauma. In cases of moderate hemophilia symptoms are variable which manifest along a spectrum between severe and mild forms.

In both hemophilia A and B, there is spontaneous bleeding but a normal bleeding time (BT), normal prothrombin time (PT), normal thrombin time (TT), but prolonged activated partial thromboplastin time (APTT). Internal bleeding is common in people with severe hemophilia and some individuals with moderate hemophilia. The most characteristic type of internal bleed is a joint bleed (hemarthrosis) where blood enters into the joint, most commonly presents as knee swelling [10]. This is most common in severe hemophiliacs and can occur without evident trauma.

Severe complications are much more common in severe and moderate hemophilia.

Deep internal bleeding i.e. deep-muscle bleeding, leading to swelling, numbness or pain of a limb. Joint damage from hemarthrosis, potentially with severe pain, disfigurement, and even destruction of the joint and development of debilitating pain. Adverse reactions to clotting factor treatment, including the development of an immune inhibitor (antibody) which renders factor replacement less effective or ineffective. Intracranial hemorrhage is a serious medical emergency caused by the build-up of intracranial pressure. It can cause disorientation, nausea, loss of consciousness, brain damage and even death.

Mild hemophilia may only be discovered later, usually after an injury or a dental or surgical procedure Genetic testing can determine the risk of passing the condition onto a child [10,12]. This may involve testing a sample of tissue or blood to look for of the genetic mutation in mother that causes hemophilia.

There are three types of hemophilia, two genetical types: *hemophilia A, hemophilia B* and one acquired hemophilia.

On the basis of clinical severity and factor levels, hemophilia is classified into mild, moderate and severe type.

Table 1: Severity of hemophilia as per individual factor concentration:

Grading	Factor level% Normal level:50-150	IU/ml Normal:0.50-1.50	Clinical presentation
Mild	6-40%	0.06-0.40	Bleeding during major surgery/injury
Moderate	1-5%	0.01-0.05	Bleeding after minor surgery/injury. Less frequent bleed (once/month)
severe	<1%	<0.01	Spontaneous bleed in into joints and muscles, bleed once or twice/week

The aim of this study was to find present demographic characteristics and clinical features of hemophiliacs in Bihar, India and status of present treatment and other facilities available to them by government and hemophilia society.

2. Materials and method

This study was conducted in the departments of pathology of Medical Colleges and Hemophilia Superspeciality Hospital of Bihar, India, during the period of August 2017 to August 2018. Patients came for registration in State Hemophilia Society was also included in this study. Those came for disability certificate were also included in this study. Hundred patients attended with history of pronged bleeding from cut site, hematuria, melena and spontaneous swelling in joint or muscle with deficiency of factor 8 or factor 9 were included in study. They came to hospital to get factor assay, hemophilia card, and disability certificate or to have factor replacement. Short clinical history, family history, factor levels and APTT values were recorded. Factor assay was done either in SRL Diagnostics or Dr. Lal Path Lab, India.

3. Results

Age range of patients was 9 months to 55 years. Obviously all were male. 9 month boy presented with prolonged bleeding from cut site and 55 years old male presented with excessive and prolonged bleeding from tooth extraction site. 81(81%) patients had hemopilia A and 19 (19%) patients had hemophilia B, ratio was 4.2:1. As per severity of hemophilia A, 20%, 62% and 18% were respectively mild, moderate and severe type. Two cases were with inhibitor. The most common was moderate type. In hemophilia B, 4%, 7%, and 8 % were mild, moderate and severe. The mild type was most common type in Hemophilia B.

Most common age group was 0-10 years (54%) [Table 2).

Table 2: Age distribution of the patients *(n=100)*

Age range (years)	Number of patients (%)
0-10	54
11-21	22
22-32	15
33-43	07
44-54	01
55-65	01

Table 3: Signs and symptoms of the patients *(n=100)*

Signs/Symptoms	Number of patients (%)
Joint swelling/hemarthrosis	95
Prolonged wound bleeding	70
Bleeding after tooth extraction	25
Bleeding after circumcision	05
Signs of arthritis	60
Psoas muscle hematoma	10
Hematuria	05
Melena	04

Table 4: Type of bleeding among the hemophilic Patients *(n=100)*

Type of bleeding	Number of case	%
Spontaneous bleeding	25	25
Bleeding following trauma/ surgery	75	75

Table 5: Results of the factor assay *(n=100)*

Reduced Factor VIII level (81%)		
Reduced Factor IX level Number (19%)		
Severity of haemophilia A (n:81)		
Level of factor FVIII	No. of patients	**%**
Mild (6-30%)	20	24.6%
Moderate (1-5%)	42	51.8%
Severe (<1%) 05	19	23.6 %
Severity of haemophilia B (n:19)		
Level of factor FIX	No. of patients	
Mild (6-30%)	8	42.10 %
Moderate (1-5%)	7	36.80 %
Severe (<1%)	4	21.10%

Recurrent joint swelling was the predominant presenting symptoms. Thirty (70%) patients had positive family history of bleeding. 75% had positive findings in X-ray which was characteristic of chronic Haemarthosis. Complete Results of coagulation screening tests showed that 95 patients had prolonged APTT. Spontaneous bleeding history was present in all severe hemophilic patients.

4. Discussion

Regarding age distribution of the patients, 54% patients presented with symptoms in the age group of 0-10 years and 1% in 55-65 years age group in this study. It correlates with findings of international and national published reports [17, 18].

Recurrent joint swelling was the predominant clinical finding followed by wound bleeding in this study. Although recurrent joint swelling was present in 95% cases however chronic hemarthosis, characteristic of joint bleeding was present in 80% cases. The increased incidence of joint bleeding in this series may be due to the inclusion of mainly referred cases presenting with recurrent joint swelling and other bleeding for replacement therapy.

The incidence of wound bleeding in this study was 70%. Hoyer found wound bleeding in 48% cases [20]. Other symptoms such as bleeding after tooth extraction and bleeding after circumcision were present in 38% and 5% cases respectively in this study, which is similar to other published studies except difference in circumcision bleeding. India comprises almost 80% Hindu population in which circumcision is not practiced as ritual.

This study showed that out of 100 patients, 70 % had positive family history of bleeding. Amongst the relatives, history of bleeding was found in maternal uncles and brothers. These findings of present study are almost similar to national and international published studies [22,23].

In this study, complete blood count and X-ray of the affected joint of all patients were done. Out of 100 patients, 80 patients showed changes in X-ray, which is characteristic of chronic hemarthosis. Factor assay and APTT were available in 100 patients, all patients showed prolonged APTT with deficiency of FVIII or FIX .Out of 100 patients having prolonged APTT, 81% cases were diagnosed as hemophilia A and eight (19 %) cases as hemophilia B[Table 5]. Shrivastava *et al* showed almost similar incidence of hemophilia A (80%) and hemophilia B (20%) [29]. Mori PG, Pasino *et al* also showed almost similar incidence of hemophilia A and hemophilia B. Mild hemophilia was found in 24.6% cases whereas moderate and severe hemophilia were found in 51.80% and five 23.60%) cases respectively.

These findings are almost similar to those of Shrivastava who found 45.50% cases as mild, 45.50% as moderate and 9% cases as severe hemophilia [29].

Spontaneous bleeding history was present in all severe hemophilic patients and also many moderate grade patient Hemophilia A has been recognized in all areas of the world [30]. In India, a number of studies were carried out on hemorrhagic disorders including hemophilia. In this study an attempt has been made to find out the incidence of hemophilia in Bihar, India. Those presented with the history of recurrent joint swelling and other bleeding episodes and diagnosed as hemophilia were included in this study and the clinical and laboratory findings were compared with other studies of similar nature. However, more extensive studies of similar nature should be done in this country, especially in Bihar to generate a better result for formulation of policy. Presently plasma derived Factor FVIII and FIX are provided by Government Medical Colleges and Hemophilia hospital But supply is erratic and inadequate. Recombinant Factors are distributed by State Hemophilia Society on and off. With increase in longevity of patients, development of

inhibitor is becoming major problem for treatment [24]. The cost and availability is making management very much complicated.

5. Conclusion

Hemophilia is major health problem in Bihar, India that has got huge financial and social impact. Although state is financially supported by National Health Mission of central Government of India and patients are also supported through state Hemophilia Society by World Hemophilia Federation, but better policy formulation is needed to have continuous factor availability as on demand and prophylactic basis. Provision of proper physiotherapy is needed at hemophilia treatment centres to prevent disability and disfigurement. Genetic counseling and establishment of genetic laboratory may decrease the incidence of birth of hemophiliac boys.

References

[1]. Kenneth D, Friedman, Rodgers MG. Inherited coagulation disorders, In Wintrobe's Clinical Haematology, Twelfth edition. Baltimore: Wilkins, 1998. pp-1379-1416.

[2]. Forbes CD, Madhok R. Genetic disorders of blood coagulation. In: Haemostasis and Thrombosis, second edition. Philadelphia: WB Saunders Company, 1991.

[3]. GC 2d White and CB Shoemaker. Factor VIII gene and hemophilia A: *Blood* 1989 73:1-12.

[4]. Ramgren O. A clinical and medicosocial study of haemophilia in Sweden. *J Intern Med* 1982; 171: 759.

[5]. Gaffney PJ, Thomas DP. Haemostasis and Thrombosis. *Am J Clin Path* 1997; 69: 299-359.

[6]. Pierce GF, Lusher JM, Brownstein SP, Goldsmith JC, Kessler CM. The use of purified clotting factor concentrates in hemophilia: influence of viral safety, cost, and supply on therapy. *JAMA* 1989; 261: 3434.

[7]. Gill FM. The natural history of factor VIII inhibitors in patients with hemophilia A. In: Hoyer LW, ed. Factor VIII inhibitors. Vol. 150 of Progress in clinical and biological research. *New York: Alan R. Liss*, 1985:19–29.

[8]. Van den Berg HM. "A Cure for Hemophilia within Reach". *N. Engl. J. Med.* 2017; 377 (26): 2592–2593. Doi: 10.1056/NEJMe1713888.

[9]. Lowe GD. "Haemophilia, blood products and HIV infection". *Scott Med J.* 1987; 32 (4): 109–11. Doi: 10.1177/003693308703200404.

[10]. Antonarakis SE, Youssoufian H, Kazazian HH Jr. Molecular genetics of hemophilia A in man (factor VIII deficiency). *Mol Biol Med* 1987; 4: 81–94.

[11]. Levine PH. Efficacy of self-therapy in hemophilia: A study of 72 patients with hemophilia A and B. *N Engl J Med* 1974; 291:1381–4.

[12]. Aledort LM. Lessons from hemophilia. *N Engl J Med* 1982; 306:607–609.

[13]. Brettler DB, Levine PH. Factor concentrates for treatment of hemophilia: which one to choose? *Blood* 1989; 73: 2067–73.

[14]. Wood WI, Capon DJ, Simonsen CC, *et al*. Expression of active human factor VIII from recombinant DNA clones. *Nature* 1984; 312: 330–7.

[15]. Toole JJ, Knopf JL, Wozney JM, *et al*. Molecular cloning of a cDNA encoding human antihaemophilic factor. *Nature* 1984; 312:342–7.

[16]. White GC II, McMillan CW, Kingdon HS, Shoemaker CB. Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia. *N Engl J Med* 1989; 320:166–70.

[17]. Kar A, Phadnis S, Dharmarajan S, Nakade J. Epidemiology & social costs of haemophilia in India. *Indian J Med Res*. 2014; 140(1):19-31.

[18]. Kasper CK, Aledort LM, Counts RB, et al. A more uniform measurement of factor VIII inhibitors. *Thromb Diath Haemorrh* 1975; 34:869–72.

[19]. Hoyer LW. Hemophilia A. *N Engl J Med*. 1994 Jan 6; 330(1):38-47.

[20]. Messori A, Longo G, Matucci M, Morfini M, Ferrini PL. Clinical pharmacokinetics of factor VIII in patients with classic haemophilia. *Clin Pharmacokinet* 1987; 13:365–80.

[21]. Esmon PC, Kuo HS, Fournel MA. Characterization of recombinant factor VIII and a recombinant factor VIII deletion mutant using rabbit immunogenicity model system. *Blood* 1990; 76:1593–60.

[22]. Berntorp E, Shapiro AD. Modern haemophilia care. *Lancet* 2012; 379: 1447-56.

[23]. World Federation of Hemophilia (WFH). Report on the Annual Global Survey 2010. Canada: WFH, 2011. Available from: http://www.wfh.org/en/page.aspx?pid=492, accessed on May 9, 2013

[24]. Haya S, Moret A *et al*. Inhibitors in haemophilia A: current management and open issues. *Haemophilia* 2007; 13(5):52-60.

[25]. Mannucci PM. Hemophilia: treatment options in twenty-first century: *Journal of Hemostasis and thrombosis* 2003; 1(17):1349-1355.

[26]. Pier Mannuccio Mannucci, Maria Elisa Mancuso and Elena Santagostino. How we choose factor VIII to treat hemophilia: *Blood* 2012; 119:4108-411. doi: https://doi.org/10.1182/blood-2012-01-394411

[27]. Johannes Oldenburg. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens: *Blood* 2015: blood-2015-01-528414; doi: https://doi.org/10.1182/blood-2015-01-528414

[28]. Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, *et al* (2007). "Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia". *N. Engl. J. Med*. 357 (6): 535–544. Doi: 10.1056/NEJMoa067659.

[29]. A. Srivastava, A. K. Brewer *et al*. A. WHF Guidelines for the management of hemophilia. *Haemophilia*, (2013)19, e1-e47; https://doi.org/10.1111/j.1365-2516.2012.02909.

[30]. Carcao MD. The diagnosis and management of congenital hemophilia. *Semin Thromb Hemost*. 2012 Oct; 38(7):727-34. doi: 10.1055/s-0032-1326786.