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ORIGINAL ARTICLE

CLINICOHEMATOLOGICAL STUDY OF HEMOPHILIA PATIENTS IN BHOPAL

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ABSTRACT: INTRODUCTION: The X-linked inherited coagulation disorders, hemophilia A (Factor VIII deficiency) and hemophilia B (factor IX deficiency), together with Von Willebrand disease comprise 95 to 97 percent of all the Inherited deficiencies of coagulation factors.(1,2) Replacement of the deficient factor is the mainstay of treatment; it may be "on demand" or "prophylactic" to prevent hemarthrosis in severe deficiency**.** The prevalence of hemophilia A is 1 in 5000 and that of hemophilia B is 1 in 30,000(3,4) male live births and Von Willebrand disease with over all prevalence in the general population being 1:100.(4) Clinically both the deficiencies present as a lifelong bleeding disorder with considerable morbidity due to crippling arthropathy. Most common cause of death in these patients is Intra Cerebral Hemorrhage. Hemophilia A and B can only be distinguished on the basis of specific coagulation Factor VIII or IX assays. **AIM:** The present study was conducted with the aim to study the clinico-hematological profile of Persons With Hemophilia(PWH), their clinical presentations, incidence of inhibitors, estimating the burden of transfusion related complications at our hemophilia care center and to compare the findings with other studies of similar nature **MATERIAL & METHOD:** This retrospective study was conducted in the Department of Pathology in collaboration with Hemophilia Care Centre at Gandhi Medical College, Bhopal during the period of August 2003 to July 2013. Diagnosis was made on the basis of history, physical examination and laboratory investigations such as bleeding time (BT), Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT),correction studies(factor VIII and factor IX estimation whenever possible). **CONCLUSION:** Bleeding after injury is obvious in healthy people but difficult to decide, when it is due to bleeding disorder. Serious congenital conditions e. g. severe hemophilia becomes obvious in early childhood but may be misdiagnosed as non-accidental injury, whereas mild cases may go undetected till later years especially those who have not undergone surgery in early adult life. Presence of hemarthrosis, bruises, hematoma either spontaneous or traumatic in an otherwise normal child should warrants for investigating in the line of hemophilia. Repeated episodes early in life show severe hemophilia. Most common cause of death was found Intra Cerebral Hemorrhage (ICH).

KEYWORDS: Hemophilia, clinico-hematological-hemarthrosis, Bhopal.

INTRODUCTION: The X-linked inherited coagulation disorders, hemophilia A (Factor VIII deficiency) and hemophilia B (factor IX deficiency), together with Von Willebrand disease comprise 95 to 97 percent of all the inherited deficiencies of coagulation factors.[1, 2] Both factors take part in the intrinsic pathway of blood coagulation and affected individuals have severe, moderate and mild forms of disease, defined by factor plasma levels of <1%, 2-5%, and 6-40%.respectively. The prevalence of hemophilia A is 1 in 5000 male live births and that of hemophilia B is 1 in 30,000[3,4] and Von Willebrand disease with over all prevalence in the general population being 1:100.[4] Clinically both

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the deficiencies present as a lifelong bleeding disorder with considerable morbidity due to crippling arthropathy. Hemophilia A and B can only be distinguished on the basis of specific coagulation Factor VIII or IX assays.[5]

Hemarthrosis is the most common, the most painful and the most physically, economically and psychologically debilitating manifestation of the hemophilia A.[6, 7] Patient's susceptibility to musculoskeletal hemorrhage can lead to recurrent hemarthrosis and development of target joints. The definition of target joint is controversial but most accepted criterion is minimum of three bleeds into a single joint within a consecutive three month period.[8]

Replacement of the deficient factor is the mainstay of treatment however, if factor concentrates are either not available or not affordable, transfusion options including whole blood, FFP (fresh frozen plasma) & Cryoprecipitate are still being used. Minor bleeds have also been controlled with antifibrinonlytic agents.[9]

The development of inhibitor is the most serious and challenging complication of hemophilia treatment with the enormous economic burden. Inhibitors are usually classified according to their levels in plasma as a "high titre" inhibitors, having activity >5 Bethesda units (BU/ml) or a "low titre" activity <5 BU/ml. In hemophilia an approximately 60-70% are high titre inhibitors and the remainder are low titre. Some patients develop transient inhibitors that never exceed a titre of 5 BU/ml and disappear spontaneously with time.[10]

It is generally accepted that inhibitors screening should occur before invasive procedures and at regular intervals during the initial 50 treatment days as this is the highest risk period for inhibitor development.[11]

AIM: The present study was conducted with the aim to study the clinico-hematological profile of PWH their clinical presentations, incidence of inhibitors, estimating the burden of transfusion related complications at our hemophilia care center. Further which type of clinical presentations must undergo coagulation profile testing to detect hemophilia cases at the earliest to decrease morbidity & mortality. This can be helpful for policy makers to improve services to detect and treat these patients.

MATERIAL AND METHODS: This retrospective study was conducted in the Department of Pathology in collaboration with Hemophilia Care Centre at Gandhi Medical College, Bhopal during the period of August 2003 to July 2013.

A total 256 persons with coagulation disorder visiting for various laboratory tests with different medical and surgical complaints finally diagnosed as hemophilia were included in this study. A thorough history including family history, findings of physical examination & laboratory tests were taken from medical records.

Diagnosis was made on the basis of history, physical examination and laboratory investigations such as bleeding time (BT), Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT),correction studies and wherever possible specific coagulation factor assay. Correction or mixing studies using pooled normal plasma (PNP) was done to identify the prolongation of coagulation time due to factor deficiency or circulating anticoagulant inhibitors.

Other hematological investigations like complete blood counts including peripheral blood smear were also made to see blood cell morphology and platelet count & blood grouping. Transfusion transmitted infections testing by ELISA were done as per the departmental standard operating procedures. Results of the investigations were recorded and analyzed.

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EXCLUSION CRITERION: Patients with platelet disorders were excluded from the study.
Ethical clearance was taken from institutional ethical committee.

RESULTS: In this study 260 cases attending with history of prolonged bleeding along with various medical and surgical complaints, finally diagnosed as hemophilia & Von Willebrand disease in the Department of Pathology GMC & Hamidia hospital Bhopal were included. A total of 254 cases of hemophilia were found, out of which 224 (86.15%) & 30 (11.53%) were hemophila A & hemophilia B respectively, and 6 (2.3%) were Von Willebrand disease. Further analysis of 254 hemophilia patients was done.

Age (in years)	No. of Patients	Percentage
0-5	80	31.50%
6-15	102	40.16%
16-30	56	22.05%
> 30	16	6.30%

TABLE 1: AGE DISTRIBUTION OF THE HAEMOPHILIA PATIENTS (N=254)

The predominant age group affected was between 6-15 years -102 cases (40.16%) (Table 1), although they were ranging from 6 months to 45 years.

	Factor VIII 224 cases		Factor IX 30 cases		Total 254 cases	
Bleeding site	**No.**	**%**	**No.**	**%**	**No.**	**%**
Joints (Haemorthrosis)	148	66.07%	17	56.67%	165	64.96%
Muscle	40	17.85%	10	33.34%	50	19.68%
Gum	18	8.35%	0	0	18	7.08%
Petechiae	8	3.54%	3	10%	11	4.33%
Epistaxis	10	4.46%	0	0	10	3.97%

TABLE 2: 1ST PRESENTATION OF HAEMOPHILIA PATIENTS

In our study most common presentation was joint bleeding-64.96 %, followed by muscle 19.68% &gum bleeding 7.08%, petechiae 3.54%, and epistaxis 4.46% (table 2).

In Von Willebrand disease manifestations are mainly in the form of mucocutaneous bleeding such as petechiae (4/6 cases) and epistaxis (2/6 cases).

Disease	<1 episode / year		1-5 episode / year		6-19 episode / year	
	No.	**%**	**No.**	**%**	**No.**	**%**
Hemophilia A n=224	130	51.18%	60	23.62%	34	13.38%
Hemophilia B n=30	16	6.29%	10	3.93%	4	1.57%

TABLE 3: FREQUENCY OF BLEEDING EPISODE PER YEAR (N=254)

Out of 254patients, 146 (57.48%) cases had at least one bleeding episode during the study. 108 (42.51%) cases experienced two or more bleeding episode per year (Table 3).

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	Hemophilia A N=224		Hemophilia B N=30	
	No.	%	No.	%
Spontaneous bleeding	128	57.14%	16	53.33%
Bleeding following trauma / surgery	96	42.85%	14	46.66%

TABLE 4: TYPES OF BLEEDING AMONG THE HEMOPHILIC PATIENTS (N=254)

In 110/254 (43.30%) patients, the bleeds were trauma induced whereas the majority of patients experienced spontaneous bleeds 144/254 (56.69%) (Table 4).

Severity	Hemophilia A N=224		Hemophilia B N=30	
	No.	%	No.	%
Mild	64	25.19%	18	60%
Moderate	87	38.84%	08	26.67%
Severe	76	33.93%	04	13.33%

TABLE NO. 5 SEVERITY OF HEMOPHILIA (N=254)

Majority were in moderate group in hemophilia A & mild group in hemophilia B. On the basis of clinical features important being number of episodes and type of bleed e.g. ICH always to be considered as severe factor deficiency. Patients of hemophilia A and B were categorized as 61/224(27.23%) and 18 /30(60%) mild hemophilia, 87/224 (38.84%) & 8/30 (26.67%) moderate hemophilia and 76/224(33.92%) & 4/30 (13.33%) severe hemophilia respectively.

Complete blood count was found almost normal in all except 44 (17.32%) patients having frequent bleeding episode who had raised platelet count. Results of coagulation screening tests showed that 100% patients of hemophilia had prolonged APTT, although range was from 43 to 68 seconds in comparison to 30 seconds in control.

In our series HBsAg & HCV seropositivity was found only in 2 & 4 cases where as no patient found HIV positive. Although only 80 patients participated in screening for TTIs (transfusion transmitted infections), although blood/blood products are used in our patients whenever factor concentrates are not available or not affordable, for this low incidence of TTI, credit can be given certainly to good blood bank practices.

We have found inhibitors in 9.09% (4 cases out of 44 cases studied, not all cases were tested for inhibitors due to non-availability of consent)

Most common cause of death in our series was ICH(Intra Cerebral Hemorrhage).>50%(.in 7/13 cases overall) and all 7 were of hemophilia A.

DISCUSSION: The age group in our study ranged from 0-45 years of age compared to less than 15 years by Uddin MM & Karim et al[12,13] & less than 18 years of age by MM Ha et al.[14] All the cases were male as in other studies. Presenting symptoms were most commonly hemarthrosis (64.96%) similar to Uddin MM et al (100%) & Karim et al (82%) while MM Hazewinkel[12-14] reported subcutaneous bleed(45%) as most common symptom.

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Other common symptom in decreasing order of frequency were muscle bleed(19.68%), gum bleed (7.08%), skin bleed (4.33%), epistaxis (3.97%) while Uddin MM[12] reported wound bleeding (52%) & bleeding after tooth extraction (38%), Karim et al[13] reported gum bleeding (38%) & bleed during surgical procedure such as circumcision & tooth extraction (28%) other rare presentations were hematemesis, malena, epistaxis (2%) while mucosal bleeding (15%) was reported by M H Hazewinkel.[14]

Age at first presentation in our study was less than 5 years in 55.1% cases (29.98% were less than 1 year), while Karim MA et al[13] reported 94% cases in less than 5 years age group (64% were less than 1 years). No cases were reported in neonatal period by any study including ours. We found positive family history in 70% of cases same as by Karim et al, while M H Hazewinkel & Uddin MM reported 49% & 30% respectively.[13-15]

We have found mild disease in 25.19 % & 60% of hemophilia A & B, moderate disease in 38.84% & 26.67% in hemophilia A & B, severe disease in 33.93% & 13.33% in hemophilia A & B, while MM Uddin et al[12] reported 45%, 42.5% & 12.5% as mild, moderate & severe respectively. Rahman M [15] found 45.5% each in mild & moderate & 9% in severe group. Rodgers reported 20%, 30% &50% as mild moderate & severe. Karim[13] reported 52.5%, & 40% as mild disease in Hemophilia A & B, moderate-47.5 % & 50% in Hemophilia A & B and 10 % in severe hemophilia B ,no case has been found in Hemophilia A. M H Hazewinkel[14] found 22%, 29% & 43% in mild, moderate & severe respectively. These variations may be due to difference in population studied, health care facilities available & social paradigms. Most important laboratory diagnostic tool was increase in APTT which was found raised in 100% of our hemophilic patients, while same had been found in majority of cases by others workers. Spontaneous bleed was reported in 57.14% & 53.33% cases of hemophilia A & hemophilia B by us, compared to 100% in severe groups & 17.5% in moderate groups by Uddin MM et al.[12]

Confusion may arise when hemarthrosis is not the presenting problem as in our study 35 % of cases first presented with muscle & gum bleed, petechiae & epistaxis, also marked bruising, ecchymosis and epistaxis was the first presenting feature rather than hemarthosis was reported by HL Minhas et al 2014, Morgan LM et al 1993, & Ljung R et al 1990. Primary cause of delayed diagnosis is failure among physicians to recognize the disease when presented with the clinical features more so when not with hemarthrosis.

CONCLUSION: It is the frequency & persistence of blood loss together with minimal trauma, specially presence of hemarthrosis, bruises, hematoma either spontaneous or traumatic in an otherwise normal child should alert the physician to investigate for hemophilia even in the absence of family history. Early recognition is important to establish correct treatment and to avoid unnecessary investigations. Prolonged APTT with normal PT & other coagulation tests favors hemophilia, type of which can be confirmed by mixing studies / specific factor assay. Repeated episodes early in life show severe hemophilia. Most common presenting symptom found was hemarthrosis (64.96%) and cause of death was ICH (>50%).

Most of the centers in developing countries including India do not have facility for factor concentration estimation, hence clinically we can assess severity of hemophilia with type of bleed, like ICH is always to be considered as severe for treatment purposes to save the life. Factor replacement is the only treatment for hemophilia, ideally recombinant one that too preferably prophylactic. The specialty of transfusion medicine can be a core part of hemophilia care by providing

the laboratory services in the form of hemostasis & serology testing, testing for inhibitors, factor concentrates & blood component support. Thus, we can achieve PWH (Persons with Hemophilia) without pain & disability.

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FFP	Fresh Frozen Plasma
VWD	Von Willebrand disease
PWH	Persons with Hemophilia
BT	Bleeding time
PT	Prothrombin time
APTT	Activated Partial Thromboplastin Time
PNP	Pooled normal plasma
ELISA	Enzyme linked immunosorbent assay
TTD	Transfusion transmitted disease
TTI	Transfusion transmitted infection
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus antibody
HIV	Human immunodeficiency virus antibody
ICH	Intra-cranial hemorrhage

ABBREVIATIONS

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