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An observational study of haemophilia patients attending a tertiary care centre in West Bengal

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ABSTRACT

Background: Haemophilia is the most common inherited coagulation disorders transmitted by X-linked recessive fashion affecting the males and females are the carriers of the disease. Haemophilia is distributed worldwide and has heterogeneous presentation depending on its severity starting from neonatal period. Knowledge of spectrum of the presentation of haemophilia helps in early diagnosis and planning of management. **Aims and Objectives:** This study aims to evaluate the socio-demographic profile of the patients, clinical presentations, epidemiological profiles, and the outcomes of the hemophilic patients in a tertiary care teaching hospital in West Bengal. **Materials and Methods:** This study was a prospective, observational, single center study conducted in the Pediatrics haemophilia treatment center at Midnapore Medical College, Paschim Medinipore from May 2020 to April 2021. Detailed history was taken and recorded in a predesigned pro forma Case Record Form. Analyses were done only after completion of CRF of the last patient. Statistical analyses were performed using SPSS version 20.0 software. Continuous variables were compared by Paired t-test. Dichotomous events were analyzed using the Fisher's exact test and Chi-squared Test. Statistical significance was defined as $P<0.05$. **Results:** Mean age of children was 93.64 months (SD 6.38). All children of haemophilia were male. This study noted that majority of patients of haemophilia were staying at rural area (67.19%) and rest at urban area (32.81%). BMI of majority children was within normal limit (51.56%), followed by underweight children (32.81%), overweight children (12.50%), and obese child (3.13%). Factor assay showed that 51 children (79.69%) had severe factor deficiency and 13 children (20.31%) had moderate factor deficiency. Positive family history was seen in 41 children (64.06%), and rest 23 children (35.94%) had no family history of haemophilia or any other bleeding disorder. Majority of patients (26 patients) came with their first bleed during infancy (40.63%), 21 children presented between the age of >12 months to ≤ 24 months (32.81%). Bruises were the most common presentation (37.50%), followed by joint bleeding (31.25%), muscle bleed (10.94%), and gum bleeding (7.81%). **Conclusion:** Facility of counseling for children of hemophilia is required at regular interval (trimester wise/semester wise) with the aim to enhance the knowledge of personal care, treatment, and to boost up themselves for their academics, activities, etc.

Key words: Bleeding disorder; Haemophilia; Hemarthrosis

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INTRODUCTION

Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the most common congenital coagulation factor deficiencies. The clinical findings in hemophilia A and hemophilia B are virtually identical. The inheritance is X-linked recessive, affecting the males; however, females are carriers.[1-3] The main defect lies with the impairment of body's ability to form clot that is a natural process which enables to stop bleeding after trivial trauma,

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easy bruisability with an increased risk of spontaneous intra particular and intracranial hemorrhage (ICH).[2] The overall prevalence is approximately 1 in 10000 individuals. The two most common forms are factor VIII deficiency or hemophilia-A, which comprises approximately 80% of cases and factor IX deficiency or hemophilia B, which comprises approximately 20% of cases.[4,5] The incidence of hemophilia A (Classical) is 1:5000 male births and that of hemophilia B (Christmas) disease is 1:25000.[6] Approximately 30% of the patients have no family history and are as a result of *de novo* mutations on chromosome 4.[7] The defective gene is inherited in autosomal recessive manner meaning that both males and females have the same risk of inheriting the condition. For the disease to develop, a faulty copy of the gene must be inherited from each parent. The reduced level or activity of factor XI is also known as hemophilia C or acquired hemophilia results in moderate bleeding symptoms usually occurring after trauma or surgery. The disorder can also occur if the body forms antibodies to own clotting factors in the blood that hampers the normal functioning of clot formation system.[8]

Depending on concentration levels of clotting factors disease are divided into: Mild that is more than 5% but <40% (>0.05–<0.40 IU/mL), moderate 1–5 (>0.01–<0.05 IU/mL), and severe <1% (<0.01–<1 IU/mL), respectively.[3,9] Severe and moderate hemophiliac might present at birth with prolonged bleeding from umbilical stump or ICH.[2,10] Serious ICH from trivial trauma endangers life of these severe hemophiliacs.[11] Patients with mild and moderate disease generally bleed after significant trauma or surgical procedure rarely leads into recurrent hemarthrosis and consequently arthropathy; however, patients with severe phenotype may bleed spontaneously or even after trivial trauma and consequently hemarthrosis and arthropathy.[12,13]

Before the availability of clotting factors concentrate most people with severe hemophilia developed crippling, musculoskeletal deformities and would have died due to hemorrhage.[14] In developing nations such as India, where patients with hemophilia have limited access to treatment and due to recurrent joint bleeds, there occur widespread disability and morbidity from joint impairment significantly with advancing age.[15] In literature minimum research, data are available with regard to hemophilia in children, which makes it very difficult to represent accurately the situation regarding epidemiology, clinical profile, and diagnosis.

Aims and objectives

By keeping in view this study was designed to evaluate the socio-demographic profile of the patients, clinical presentations, epidemiological profiles, and the outcomes of the hemophilic patients in a tertiary care teaching hospital in West Bengal.

MATERIALS AND METHODS

The prospective, observational, and single center study was conducted in pediatrics haemophilia treatment center, Department of Pediatrics, Midnapore Medical College (M.M.C), Paschim Medinipur. For each enrolled patient, the total duration of therapy and follow-up was 6 months. The entire study including recruitment, follow-ups, data capturing, and data analysis took about a year, starting from May 2020 to April 2021. The study was pre-approved by the Institutional Ethics Committee (IEC) for the final permission. After obtaining, the permission of IEC the study was conducted.

The study population were all children with haemophilia who attended pediatrics haemophilia treatment center, M.M.C, West Bengal. For the purpose of sample size calculation, α is consider 0.05, with 95% confidence level and 2% expected allowable error minimum sample size was 64. The computer software Win Pepiver 11.1 was used to calculate the sample size.

Inclusion criteria

Haemophilia patients of 0–18 years of age attended pediatrics haemophilia treatment center at M.M.C, Paschim Medinipur. Written consent of parents or legal guardian and assent of patients if applicable (7–18 years).

Exclusion criteria

The following criteria were excluded from the study:

- Patients with platelet and vascular disorders.
- Patients with clinically relevant coagulation disorders other than congenital haemophilia.
- Patients on currently active treatment for Hepatitis B Virus, Hepatitis C Virus, or Human Immune Deficiency Virus infections.
- Subjects with hepatic or renal impairment and patient having chronic illness or taking chronic medication.

Study tool

A detailed history was taken and recorded in a predesigned pro forma Case Record Form (CRF). The following information's were noted in CRFin detail.

Patients/Parents/legal guardian were instructed to attend pediatrics haemophilia treatment center on Monday and Thursday in every week after recruitment.

Method of statistical analysis

Data were processed and analyzed at the Department of Paediatrics, M.M.C, Paschim Medinipur with the help of statistician. Analyses were done only after completion of CRF of the last patient. Statistical analyses were performed using SPSS version 20.0 software. Continuous variables were compared by Paired t test. Dichotomous events were

analyzed using the Fisher's exact test and Chi-squared Test. Statistical significance was defined as P<0.05.

RESULTS

Sixty-four patients with haemophilia were included in this study from pediatrics haemophilia treatment center at M.M.C, since May 2020 to April, 2021.

In our study, children of haemophilia were commonly enrolled in the age group of >10 years followed by >4 years ≤10 years group. Mean age of children was 93.64 months (SD 6.38). All children of haemophilia were male (Table 1).

From Table 2, it was noted that majority population of patients of haemophilia belonged to the lower socio-economic Class V (45.31%) followed by the upper lower socio-economic class IV (23.44%), then lower middle socio-economic class (17.19%), and upper middle socio-economic class (14.06%) according to modified Kuppuswamy scale. The difference is statistically significant (P<0.0001), analyzed by Chi-square test.

This study noted that majority of patients of haemophilia were staying at rural area (67.19%), rest at urban area (32.81%) that was statistically significant (P<0.0001), analyzed by Chi-square test.

The mean weight of enrolled children was 22.52 kg (SEM 1.62), mean height/length was 115.52 cm (SEM 3.34), and the mean body mass index (BMI) was 15.62 (SEM 0.36) (Table 3).

In Table 4, it has been observed that BMI of majority children was within normal limit (51.56%), followed by underweight children (32.81%), overweight children (12.50%), and obese child (3.13%). The difference was statistically significant (P<0.0001), performed by Chi-square Test.

SD score = (observed value – expected value)/standard deviation of reference population. In our study, majority children had normal stature (64.06%), followed by stunting (26.56%) and severe stunting (9.38%). The difference was statistically significant (P<0.0001), statistical analysis performed by Chi-square Test.

In our study, factor VIII deficiency (haemophilia A) was observed in 52 patients (81.25%), while 12 (18.75%) patients were deficient in factor IX (haemophilia B). This difference was statistically significant (P<0.0001), the analysis was done by Fisher's Exact Test (Table 5).

In our study, the factor assay showed that 51 children (79.69%) had severe factor deficiency and 13 children (20.31%) had moderate factor deficiency. The difference was statistically significant (P value 0.0001). Fisher's Exact Test was used to analyze the data (Table 6).

Table 7 illustrates the family history of haemophilia. Positive family history was seen in 41 children (64.06%), and rest 23 children (35.94%) had no family history of haemophilia or any other bleeding disorder. Frequency of positive family history was significantly higher than the frequency of negative family history (P<0.0003), analysis was performed by Fisher's Exact Test.

Table 8 illustrates that majority of patients (26 patients) came with their first bleed during infancy (40.63%), 21 children presented between the age of >12 months to ≤24 months 32.81%), only 10 children (15.63%) presented between the age of >25 months to ≤60 months, and rest 7 children (10.94%) faced the first bleed after 60 months. Age wise these frequency were statistically significant (P value 0.001), this analyze was performed by Chi-square test.

Initial clinical presentation of children suffering from haemophilia. Bruises were the most common presentation (37.50%), followed by joint bleeding (31.25%), muscle bleed (10.94%), gum bleeding (7.81%), scalp hematomas, and prolong bleeding from wounds (6.25%) each. Initial presentation of haemophilia frequency was statistically significant (P=0.001), this analyze was performed by Chi-square Test.

Table 1: Age and gender distribution of haemophilia patients

Age	Haemophilia A	Haemophilia B	Total	Percentage
≤4 years	9	7	16	25.00
>4 years–≤10 years	15	6	21	32.81
>10 years	27	0	27	42.19
Total	51	13	64	100.00
Gender				
Male	49	15	64	100.00
Female	0	0	0	0.00
Total	49	15	64	100.00

Table 2: SES and residence of haemophilia patients (modified Kuppuswamy scale)

SES	Frequency	Percentage	P value
Lower class (V)	29	45.31	<0.0001
Upper lower class (IV)	15	23.44	
Lower middle class (III)	11	17.19	
Upper middle class (II)	9	14.06	
Upper class (I)	0	0	
Total	64	100	
Residence			
Urban	21	32.81	0.0001
Rural	43	67.19	
Total	64	100	

SES: Socioeconomic status

Table 3: Distribution of anthropometric parameters of children with haemophilia

Parameters	Mean±SEM	Median
Distribution of weight (kg) of the patients	22.52±1.62	24
Distribution of height/ length (cm) of the patients	115.52±3.34	119
Body mass index	15.62±0.36	15.3

Table 4: Distribution of body mass index and length/height of children with haemophilia

Weight for age	Frequency	Percentage	P value
Underweight (<5th centile)	21	32.81	<0.0001
Normal (5th to 85th centile)	33	51.56	
Overweight (>85th to<95th centile)	8	12.50	
Obese (>95th centile)	2	3.13	
Total	64	100.00	
Stature			
Normal	41	64.06	<0.0001
Stunting (SD score−2 to−3)	17	26.56	
Severe stunting (SD score <−3)	6	9.38	
Total	64	100.00	

Table 5: Distribution of type of haemophilia

Type	Frequency	Percentage	P value
Haemophilia A	52	81.25	<0.0001
Haemophilia B	12	18.75	
Total	51	100	

DISCUSSION

Haemophilia is an inherited x-linked recessive disorder in which the inherent clotting mechanism of the body is impaired. Depending on its severity, the disease may manifest as easy bruising, inadequate clotting after mild injury or even spontaneous hemorrhage. The disease occurs due to functional deficiency of Factor VIII and Factor IX which are classified as Haemophilia A and Haemophilia B, respectively.[16]

At present, India has the highest burden of haemophilia patients in the world.[17] To address the socio-demographic profile, clinical presentation and outcome of haemophilia patients. The study was conducted in the pediatrics haemophilia treatment center at M.M.C and Hospital, West Bengal, over a period of 1 year from May 2020 to April 2021. A total of 64 children of haemophilia were included in the study.

Age distribution

In our study, children with haemophilia were most commonly seen in the age group of >10 years (42.19%), followed by age of >4 years to ≤10 years (32.81%) and rest children were ≤4 years (25%). Mean age of children with haemophilia was 93.64 months (SD 6.38).

This type of frequency of the age distribution is also seen in previous studies. A study was conducted to find out the clinic-hematological profile among haemophilia children - the majority children (40.4%) had age between 11 and 20 = years, 28% children had age 5–10 years.[18] In another study conducted in South Kerala on children with haemophilia, it was observed that majority of children had the age group of above 9 years (46.67%), followed by 6–9 years (30%).[19]

Gender distribution

Since the mode of inheritance in hemophilia is X-linked recessive that typically affects males whereas females are the carriers. Accordingly, most of the existing literature report that the majority of the patients are males.[20,21] In our study, all the patients were males (100%).

However, haemophilia is rarely seen in females also, it may occur due to lyonization. In a study, five female patients presented with haemophilia A with moderate severity due to known mutation.[22] Haemophilia B has also been seen among female patients.[23] The underlying genetic mechanism behind the phenotypic expression of the disease in females has been studied by researchers.[24] In a study in Karnataka, it was observed that out of 50 hemophilic patients, 49 (98%) patients were male, and one was female. She was born out of consanguineous marriage.[25]

Socio-economic status

In our study, it was noted that majority patients of haemophilia belonged to the lower socio- economic Class V (45.31%), followed by the upper lower socio-economic Class IV (23.44%), then lower middle socio-economic class (17.19%) and upper middle

Table 6: Distribution of severity of haemophilia

Type	Severe	Moderate	Total (n=51)	Percentage	P value
Haemophilia A	39	12	51	79.69	<0.0001
Haemophilia B	11	2	13	20.31	
Total	50 (78.13)	14 (21.88)	64	100	

Table 7: Family history among haemophilia patients

Type	Yes	No	Total	Percentage	P value
Haemophilia A	33	17	50	78.13	<0.0003
Haemophilia B	8	6	14	21.88	
Total	41 (64.06)	23 (35.94)	64	100.00	

Table 8: Age distribution of first bleed and initial presentation of haemophilia

Variable	Age (months)	Haemophilia A	Haemophilia B	Total	Percentage (%)	P value
Age distribution of first bleed	≤12	21	5	26	40.63	0.0001
	>12–≤24	15	6	21	32.81	
	>25–≤60	8	2	10	15.63	
	>60	6	1	7	10.94	
	Total	50	14	64	100	
Features						
Bruises		17	7	24	37.50	<0.0001
Joints bleeding		16	4	20	31.25	
Muscle bleed		4	3	7	10.94	
Gum bleeding		5	0	5	7.81	
Scalp hematomas		4	0	4	6.25	
Prolonged bleeding from wounds		4	0	4	6.25	
Total		50	14	64	100	

socio-economic class (14.06%) according to modified Kuppuswamy scale.

In a previous study, similar results were observed that the haemophilia patients belonged predominantly to low socioeconomic status.[26] In another study on 'Disability in Indian Patients with Haemophilia,' it was observed that the socio-economic status is significantly associated with disability of haemophilia.[15]

The reason of higher prevalence of the disease in lower socio-economic class may be due to unavailability of antenatal screening in remote and economically backward areas. Although a significant association between socio-economic status and the disease has been observed in most studies, establishment of causation will need further research. People attend government, semi-government and private hospitals depending on their financial ability, accessibility to the facility, awareness, and personal choice. Unfortunately, there is no published literature on the clinico-epidemiological profile of the disease in non-government sector.

Distribution of residence

In our study, majority of children enrolled were living in rural area (67.19%). The remaining patients (32.81%) were residents of urban area. Our findings are in agreement with other studies.[27]

Distribution of BMI

In our study, it was seen that majority of children had weight within normal range (51.56%), followed by underweight children (32.81%), overweight (12.50%), and obese (3.13%) children. In affluent societies, obesity is commonly seen among hemophilic children due to lack of or restricted physical activities.[28-30] However, in our study and other studies from economically weaker regions, the proportion of underweight children suffering from the disease is much higher. Research have shown that low socioeconomic status, poor knowledge of food habits, hygiene, and personal care are primary reasons behind this problem.[31]

Distribution of type of haemophilia

In our study, haemophilia A (81.25%) was more common than haemophilia B (18.75%). Our results are congruent with other studies conducted in India. In a study in Northern India, it was seen that 90.74% children were diagnosed as haemophilia A and rest 9.26% were diagnosed as haemophilia B patients.[20] In another study, it was observed that 81% children had haemophilia A while 19% children were suffering from haemophilia B.[18] In a study in South Kerala, it was seen that 86.7% patients and 13.3% were suffering from haemophilia A and haemophilia B, respectively.[19] Worldwide, a similar pattern of distribution have been observed. The ratio of haemophilia A to

haemophilia B ratio has been reported between 78/22 to 87/13 in most studies.[29]

Severity of haemophilia

Depending on the concentration of deficient clotting factor, haemophilia is classified as mild (factor levels >5%), moderate (factor levels of 1–5%), and severe (factor levels of <1%) varieties. In our 50 children (78.13%) severe variety and 14 children (21.88%) had moderate variety without any mild variety.

This result correlated with the previous study also. In a study in South Kerala, 76.67% children were suffering from severe factor deficiency and 20% patients were suffering from moderate factor deficiency.[19] In other studies on Indian population of haemophilia, most common frequency was severe haemophilia.[16,18,30]

However, different frequency is also seen. In a study in Bhopal, it was observed that majority of children had moderate variety, followed by severe variety.[31]

Family history among haemophilia patients

In our study, positive family history of haemophilia was seen in 64.06% cases. No family history of haemophilia or any other bleeding disorder was seen in the remaining patients. It has been observed that 35.94% children with haemophilia have no family history and are suffering due to *de novo* mutation.[26] Similar result was reported in other clinical observations. In a study on haemophilia patients conducted in Kottayam, 60% children had positive family history.[16] In another study in western Uttar Pradesh, it was seen that 58.5% patients had positive family history.[32]

However, in study conducted in South Kerala, showed that majority had negative family history (77%).[19] This is in sharp contrast with our study and also other studies in India. This may be due to lack of screening and detection facilities.

Age distribution of first bleed

In our study, 40.63% (majority) patients came with their first bleed during infancy, 32.81% children presented their first bleeding between the age of >12 months to ≤24 months, only 15.63% children presented between the age of >25 months to ≤60 months, and rest 9.80% children faced the first bleed after 60 months. These results were also in agreement with previous studies. In a study in South Kerala, it was observed that majority children (48.3%) had first bleed during infancy.[19] However, in a study conducted at Kottayam, it was seen that majority children between the age group of 1–5 years presented with their first bleed (47.5%), then the infancy group (40%).[16] A study was conducted in Jodhpur region to find out the clinical profile of haemophilia and it was observed that majority of patients presented their first bleed during age of 1–5 years (51.74%), followed by infancy year (25%).[30]

Initial presentation of haemophilia

The most common initial presentation of the patients in our study was bruises (37.50%). Joint bleeding (31.25%), muscle bleed (10.94%), gum bleeding (7.81%), scalp hematomas (6.25%), and prolong bleeding from wounds (6.25%) were the initial presentation in the rest of the patients. We observed both similar and different results in other studies. A study was conducted in tertiary care center to find out the clinical profile of haemophilia concluded that bruises and ecchymosis were the most common (55%) initial presentation followed by hemarthrosis (30%).[16] In another study, it was seen that skin and subcutaneous bleed was the initial presentation (26.7%).[19] However, a study from Jodhpur region reported that the most common initial site of bleed was posttraumatic (35.7%), followed by gum bleed (30.35%).[30]

Limitations of the study

The study is, however, not without limitations. The sample size was small and also it was a single center study.

CONCLUSION

Bleeding disorders are the conditions when the blood cannot clot properly. Haemophilia is the commonest congenital bleeding disorder in clinical practice. Haemophilia is X-linked hereditary disorder typically affecting males whereas females are the carriers. In haemophilia, there is single gene mutation of factor VIII (FVIII) or factor IX (FIX) genes, resulting in deficiency of factor VIII, or factor IX respectively. Factors VIII and IX take part in the intrinsic pathway of coagulation process. Bruises were the most common initial presentation (37.50%), followed by joint bleeding (31.25%), and muscle bleed (10.94%). Incidence of gum bleeding, scalp hematomas and prolong bleeding from wounds were seen in very few cases.

Although it was seen that factor requirement was more in prophylactic therapy (in the past 6 months), overall clinical responses such as bleeding episodes, hemarthosis, hospital admission, requirement of orthopedic care and physiotherapy and quality of life were dramatically improved. Ultimately, cost of therapy is less in children with haemophilia on prophylactic treatment.

Facility of counseling for children of hemophilia is required at regular interval (trimester wise/semester wise) with the aim to enhance the knowledge of personal care, treatment, and to boost up themselves for their academics, activities, etc.

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ETHICAL APPROVAL

The study was approved by the institutional ethics committee.

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BKK- Concept and design of the study, prepared first draft of manuscript, **MS-** Interpreted the results; reviewed the literature and manuscript preparation; **KKP, KPM-** Concept, coordination, statistical analysis, and interpretation, preparation of manuscript, and revision of the manuscript

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