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A Clinico-Pathological Study of Hemophilia in Rural Set up of Karnataka

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Authors' contributions

This work was carried out in collaboration between all authors. All the authors designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author MS managed the literature searches, and author AK managed the experimental process and author RP identified the new aspects and cases of the disease. All authors read and approved the final manuscript.

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ABSTRACT

Haemophilia is the most common inherited coagulation disorders, with X linked recessive inheritance, affecting the males while females are the carriers of the disease. Haemophilia A and Haemophilia B are the commonest form of Haemophilia encountered and they result from defect in Factor VIII and Factor IX gene respectively. A clinico hematological study with suspected coagulation disorder was conducted over a period of two years, from June 2008 to July 2010. Of the 76 patients visited OPD, based on clinical presentation and family history, 50 cases were categorized as Hemophilia A or B after laboratory investigations. Majority (41) of the cases were categorized as Hemophilia A & only 7 cases were Hemophilia B. The mean age group of the patients was 2.87 years with an age of onset ranged between 3rd day to 5.6 years. All the cases were males and only a very rare case of female Hemophilia patient was noted. Thirty five (52.23%)

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patients had positive family history of bleeding. In 12 families (18.75%) there had been consanguineous marriage. Spontaneous bleeding was the predominant presenting symptom followed by Hemarthrosis and prolonged post traumatic bleeding. The knee joint was most commonly involved. Coagulation screening tests showed that 60% patients had prolonged activated partial thromboplastin time (APTT) with an average of 88 seconds. Mixing and substitution studies were very useful in distinguishing between Hemophilia A & B. Factor assays in both Hemophilia A & B showed 66% of cases with severe factor deficiency, 26% moderate and 8% with mild deficiency.

In the present study an effort is made to explore, elucidate and document the clinico haematological correlation of Hemophilia in this part of Karnataka.

Keywords: Haemophilia; hemarthrosis; bleeding disorder.

1. INTRODUCTION

Hemophilia is one of the oldest diseases known to mankind and encompasses a mysterious yet fascinating phenomenon through a 1800 year track. Hemophilia is a hereditary X-linked recessive disorder, characterized by the deficiency of factor VIII or IX coagulant activity [1]. It is the commonest congenital bleeding encountered in clinical practice affecting men, while females are carriers [2]. The incidence of haemophilia A and B is 1:10000 and 1:60000 males respectively, although its prevalence can vary [3]. It was estimated by WHO that there would be 5,50,000 patients with severe or moderately severe Hemophilia A and B by the year 2020 [4]. It carries a strong familial history but is noticed in about 30% of patients who have no family history; which presumably can be caused by a new mutation [5].

Hemophilia has affected some of the royal houses of Europe like Queen Victoria, who came to know about her status after the birth of her eighth child, who was Hemophilic. The term first haemophilia was first used by a student Friederick Hopf of University of Zurich in 1828 [6].

The percentage of the cases being diagnosed is only upto 12% in India [4]. Major advances have occurred over the last few decades in every aspect of care of the patients with Hemophilia. These include early recognition and accurate diagnosis, safe therapeutic products, carrier detection and antenatal diagnosis. But unfortunately these benefits are available to only 20% of patients who reside in developed countries and it continues to be a personal and social disaster in developing countries.

This study was carried out in rural population to determine the incidence of the hemophilia, clinical presentation, laboratory diagnosis of the disease.

2. MATERIALS AND METHODS

Known haemophiliacs or suspected cases with coagulation disorders referred to Bapuji Hospital, Chigateri Government General Hospital, Child Institute and Karnataka Hemophilia Society were picked for evaluation. After getting informed consent from the parents / guardians of the patients, detailed clinical history including family history, mode of presentation, age of onset of disease, symptoms like Hemarthrosis, post traumatic & superficial bleeding, hematoma, dental bleeding, epistaxis etc was taken into consideration. Pedigree analysis was done for each case to detect the obligate and possible carriers. Patients having coagulation disorders other than Hemophilia diagnosed after laboratory diagnosis were excluded, and the cases who had received coagulation factors, fresh frozen plasma or cryoprecipitate within the proceeding fortnight and ingestion of drugs like aspirin were not included for the study. After the clinical evaluation, patients are subjected to a battery of coagulation tests. Blood sample (citrate) was collected by venepuncture with necessary asceptic precautions. Routine haematological tests like hemoglobin estimation (Sahli method), platelet count (Rees-ecker manual method) and peripheral smear examination were done. These tests were followed by battery of coagulation tests namely bleeding time (BT) (modified Ivy's method), clotting time (CT) (Lee and White method), prothrombin time (PT), thrombin Time (TT), and activated partial thromboplastin time (aPTT). Correction studies using adsorbed plasma (factor V, VIII, XI, XII) and aged plasma (IX, X, XI, XII) were performed to evaluate the type of factor deficiency. Factor assay was performed to assess the severity of factor deficiency in diagnosed cases of Hemophilia.

Mild, moderate and severe haemophilia were defined as factor level of >5-30%, 1-5% and <1% of normal activity respectively.

3. RESULTS

The present clinico-pathological study of Hemophilia is a prospective study conducted over a period of two years. During the study period, 76 patents with suspected coagulation disorders were referred to the laboratory for thorough work up. Of these 76 patients, 50 patients were diagnosed as Hemophilic after laboratory investigations. Of the total 50 cases of Hemophilia, the majority (41) cases were classified as Hemophilia A and only 9 cases were confirmed as Hemophilia B.

For the 50 patients with Hemophilia, the age of onset for Hemophilia A ranged from 3rd day of neonatal period to 24 years, with an average of 3.56 years, and for Hemophilia B it was 2nd month to 5.6 years with an average of 2.18 years (Table 1).

Of the 50 cases, 49 (98%) patients were male, while a rare case of 12 year old hemophilic girl, born of consangionous marriage was encountered. Her father was a known Hemophilic and had married his niece (Fig 5). (Sister's daughter)

The first clinical symptom at the onset of the disease varied from spontaneous bleed either in the form of bruises or subcutaneous hematoma to post traumatic bleeding. Hemarthrosis was the next common symptom followed by surgical bleeds and dental bleeding (Figs. 1, 2, 3, 4, 6, 7 and 8). Rest of the patients manifested with bleeding from various other sites as shown in the Table 2.

Clotting time varied from 10 minutes to greater than 30 minutes with both Hemophilia A and B. Activated partial thromboplastin time ranged from 46 seconds to 130 seconds for patients with Hemophilia A and from 48 seconds to 174 seconds with Hemophilia B (Table 3). The prothrombin time and thrombin time were mildly increased.

The hemoglobin level of patients with Hemophilia A ranged from 7.8 g % to 14.6 g % and for Hemophilia B ranged from 9.6 g % to 12.8 g%. In Hemophilia A 12 patients were found to be O positive and 7 were B positive while in Hemophilia B, 5 were found to be O positive and 2 were B positive. For all the patents with prolonged APTT, correction studies were done with control plasma, aged serum and adsorbed plasma to identify the factor deficiency. Aged serum contains factors IX, X, XI, XII and absorbed plasma, contains factor V, VIII, XI, XII. The patient's plasma when mixed with adsorbed plasma with a known defect, to see, whether abnormal result on the known plasma is corrected. In 41 patients with APTT was corrected by adsorbed plasma and control plasma. In 9 patients, APTT was corrected by aged serum and control serum (Table 4). No inhibitors were detected in all 50 patients. Factor quantification by bioassay was done in all 50 cases to know the severity of the disease (Table 5).

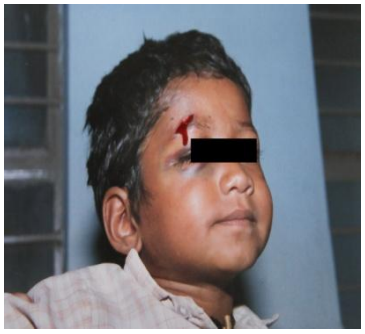

Fig. 1. Prolonged bleeding from a cut

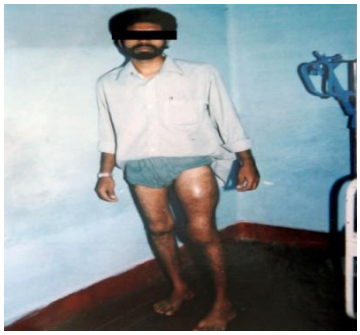

Fig. 2. Intramuscular bleed with hemarthrosis of the knee joint

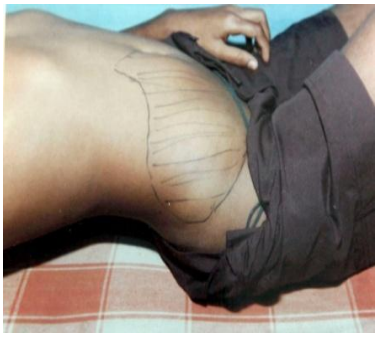

Fig. 3. Bleeding into the Ilio-Psoas muscle

Table 1. Age distribution of patients with hemophilia

Present age	Hemophilia A		Hemophilia B	
	No.	Percentage	No.	Percentage
Under 1	1	2.44	1	11.11
1-5	6	14.63	1	11.11
6-10	14	34.15	2	22.22
11-15	5	12.20	1	11.11
16-20	6	14.63	2	22.22
21-30	8	19.51	2	22.22
31-40	0	--	0	--
Above 40	1	2.44	0	--
Total	**41**	**100**	**9**	**100**
Mean age	13.94		12.79	

Table 2. First clinical symptom at the age of onset of disease

Symptoms	Hemophilia A		Hemophilia B		Total	
Prolonged post traumatic bleeding	5	12.20	5	55.56	10	20
Hemarthrosis	6	14.63	1	11.11	7	14
Superficial bleed	17	41.46	0	--	17	34
Dental bleed	5	12.20	1	11.11	6	12
Epistaxis	2	4.87	1	11.11	3	6
Intra cranial bleed	1	2.44	0	--	1	2
Surgical Bleed like circumscision, I & D	5	12.20	1	11.11	6	12
Total	41	100	9	17	50	100

Table 3. Clotting time and activated partial thromboplastin time in patients with hemophilia

		Clotting Time (min)				Total	Activated PTT (Sec)				Total
		8-10	**10-20**	**21-30**	**>30**		**40-60**	**61-80**	**81-100**	**>100**	
Hemophilia A	Mild	0	1	1	1	**3**	3	0	0	0	**3**
	Moderate	1	4	2	0	**7**	8	2	0	0	**10**
	Severe	0	12	10	10	**32**	0	2	11	15	**28**
Total		**1**	**17**	**13**	**11**	**42**	**11**	**4**	**11**	**15**	**41**
Hemophilia B	Mild	1	0	0	0	**1**	1	0	0	0	**1**
	Moderate	0	3	0	0	**3**	2	1	0	0	**3**
	Severe	0	1	2	2	**5**	0	1	3	1	**5**
Total		**1**	**4**	**2**	**2**	**9**	**3**	**2**	**3**	**1**	**9**

Table 4. Correction tests

Correction of APTT	No. of cases	Percentage
Correction with aged serum	9	18
Correction with adsorbed plasma	41	82
Total	50	100

Table 5. Factor level and severity of the disease in patients with hemophilia A & B

Severity & factor level	Hemophilia A		Hemophilia B		Total	
	No.	%	No.	%	No.	%
Mild (6-30%)	3	7.32	1	11.11	4	8
Moderate (1-5%)	10	24.39	3	33.33	13	26
Severe (<1%)	28	68.29	5	55.56	33	66
Total	41	100	9	100	50	100

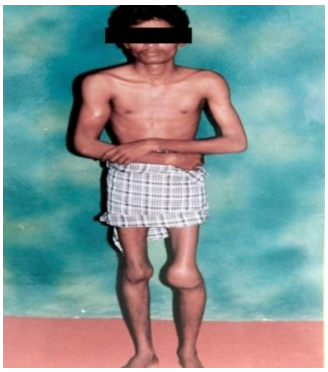

Fig. 4. Chronic hemophilic arthropathy

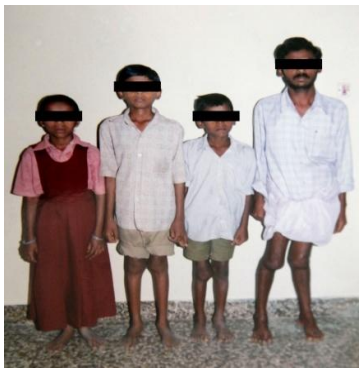

Fig. 5. A family of hemophilics including a female born of consanguineous marriage in the family

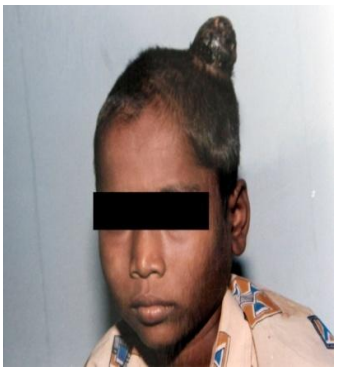

Fig. 6. Scalp hematoma

4. DISCUSSION

Hemophilia has been recognized in all parts of the world where adequate information is available [7]. The 50 hemophilia patients included for the present study constituted 0.96% of the total number of hemophilia cases registered in India and 0.13% of estimated hemophilia cases in India. Hemophilia constituted 88.15% of the hemorrhagic disorders investigated during the study period. This finding is consistent with various authors, who state that is one of the commonest hereditary bleeding disorders frequently encountered, accounting for 85% of these cases. [8,9] Of the 50 cases diagnosed with hemophilia based on the laboratory tests, majority 82% were hemophilia A and only 18% were hemophilia B, this is similar to the proportion of hemophilia A and B reported from Vellore, Delhi and Mumbai. (ICMR) [10].

Hemophilia A is the commonest type of hemophilia as compared to hemophilia B which is 1/5th less common. The ratio of hemophilia A/ hemophilia B seems to be constant throughout the world ranging from 78/22 to 87/13 (mean 83/17). No explanation for this consistent proportion has been proposed [11]. Hemophilia A accounted for 78.6% (236/300 cases) in a study by M.B. Agarwal and B.C. Mehta 1981, which is similar to the present study [12].

The youngest patient with hemophilia was 5 months old, while the oldest was 50 years old. The age range being similar to a study by Dube et al. [13] where the youngest patient was 7 months old while the oldest was 45 years.

Though hemophilia is solely a disease of males, a rare case of hemophilia was encountered in a female due to consanguineous marriage, where mother was a carrier and father was a patient of hemophilia. There are only rare case reports from India, Sitalakshmi et al. [14], have reported a case of hemophilia in a female who had a male sex chromosomal pattern. Of the total patients with Hemophilia, most (44.78%) were between 1-5 years of age at the onset of bleeding, followed by 34.32% who were less than one year old, at the time of first bleeding manifestation. 77.6% of patients with Hemophilia A were less than 5 years of age of onset of bleeding in a study by Agarwal et al. [12].

Spontaneous bleeding in the form of subcutaneous hematomas or bruises was the most common symptom in all patients with hemophilia irrespective of the type, which is in accordance with Agarwal et al. [12], Conway and Hilgartner [15] and Uddin [16] respectively. In the present study Hemarthrosis was one of the most common symptoms which was seen in 79.10% of all the hemophilics, 85.36% of patients with hemophilia A and 66.66% of patients with hemophilia. This feature correlated with Dube et al. [13] and Agarwal et al. [12] and Agarwal and Mehta [17]. Karim et al. [18] and Nigam et al. [19] has described Hemarthrosis as the most common symptom in his study. The joint most commonly was the knee point (40.32%) followed by elbow (28.22%). Wrist joint was the least commonly affected. These findings were similar to Alok Srivastava [13,20].

Though Whole Blood Clotting Time (WBCT) was prolonged in most cases of hemophilia A (97.56%) and hemophilia B (88.88%) there remained a small percentage of cases in which clotting time was within normal limits. These results were similar to Agarwal et al. [12] and Dube et al. [13]. This supports the view that the clotting time is not recommended as a reliable indicator of abnormal haemostasis and may be normal even in severe hemophilia as suggested by various authors [21]. The APTT is the main screening test used for the diagnosis of hemophilia. Since it is simple and more reproducible, the APTT has largely replaced other methods of exploration of the intrinsic coagulation system such as thromboplastin generation and thromboplastin screening tests [22]. APTT was prolonged in all cases (100%) of hemophilia A and B with an average of 88 sec, similar to the mean APTT value of 80 seconds reported by Horia et al. [23]. The Prolonged APTT values correlated with Dube et al. [13] and Criag S. Kitchens [24] and Uddin [16]. Prolonged APTT indicated that factor VIII or IX concentration is below 30 to 50% of normal [25].

Factor assay was useful to diagnose and to know the severity of hemophilia which is an essential for treating these patients, as the factor dosage is calculated based on the severity of factor deficiency. Majority of the patients with hemophilia belonged to the severe form. These findings are in correlation with Agarwal et al. [12], Hazewinke et al. [26] in South Africa and Kim et al. [27] in their study on Korean population showed more cases of severe Haemophilia (55.7%). Lusher in another study found 84% cases of severe haemophilia and 8% cases of moderate haemophilia to have spontaneous bleeding [28]. This was similar to the findings in this study (Table 6).

There was a preponderance of blood group O in the series of patients (51.57%) similar to that observed by CD Forbes et al. [29]. No circulating inhibitors of coagulation were identified in the present study though Thiam et al. [30] has reported 12% cases with circulating inhibitors. Inhibitor development is not predictable and can present at any time [22]. There was no significant difference between presence and absence of family history in the patients. 52.23% of the patients had family history of hemophilia. Women who know they are carriers may have options for prenatal diagnosis to obtain information on fetal status [22].

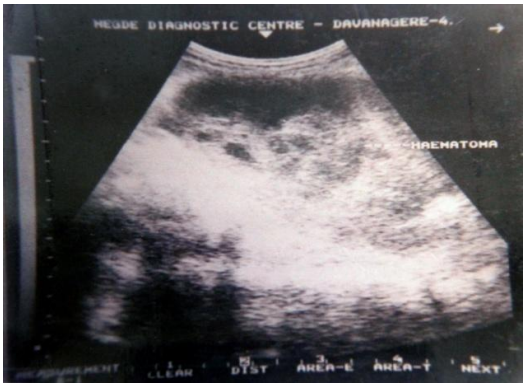

Fig. 7. Retroperitoneal Hematoma-ultrasound

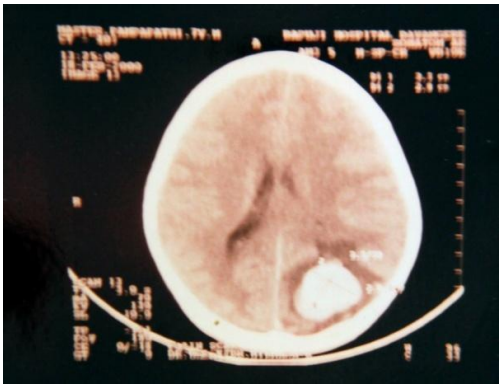

Fig. 8. CT scan view of intracerebral hematoma

Table 6. Factor level and severity in Hemophilia A & B Patients compared

Severity & factor %	Rodgers GM & Charles SG		Nigam et al (2014)		Present study (2014)	
Type	**A**	**B**	**A**	**B**	**A**	**B**
Mild (6-39%)	15	20	25.19	60	7.32	11.11
Moderate (1-5%)	15	30	38.84	26.67	24.39	33.33
Severe (<1%)	70	50	33.93	13.33	68.29	55.56

5. CONCLUSION

The present study made an effort to screen the patients with a probable diagnosis of hemophilia referred to our hospital set up. Spontaneous bleeding followed by hemarthrosis was the most common symptom. The most reliable screening test for the diagnosis of hemophilia was APTT. Correction studies and factor assays proved to be very effective for both qualitative and quantitative analysis.

Increased social awareness of bleeding disorders is necessary among public. Identification still remains a problem in our country because of lack of efficient coagulation laboratories, poor knowledge of coagulation disorders among the doctors in general and lack of emphasis on haematological diseases in the undergraduate and postgraduate medical training.

ETHICAL APPROVAL

It is stated to confirm that the authors have obtained all necessary ethical approval from both Institutional and State Committees. An informed consent, protection of privacy, and other human rights were taken into consideration before the study was initiated. This confirms either that this study is not against the public interest, or that the release of information is allowed by legislation.

No animal experiments were conducted in this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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