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Original Article

Clinicopsychological profile of children with bleeding disorders from a tertiary center in Karnataka

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ABSTRACT

Objectives: The aim of this study is to observe the clinical spectrum of presentation of hemophilia and other bleeding disorders in children. **Material and Methods:** This observational study was carried out in the Comprehensive Hemophilia Center at Bangalore Medical College and Research Institute from December 2015 to August 2016. Clinical profile of 126 diagnosed children of hemophilia and other bleeding disorders <18 years of age was analyzed. **Results**: Among the 126 cases of bleeding disorders, 123 were male and 3 were female. 101 (80.2%) cases were of hemophilia A, 15 (11.9%) cases were hemophilia B, and 3 (2.4%) were of Von Willebrand disease. Other rare deficiencies were seen in 7 (5.5%) cases. Mean age at diagnosis was 2.5 years (range-1 month to 8 years). Only 45.2% of cases had a family history of bleeding. Inhibitors were seen in 9 (7.14%) cases with hemophilia A. Joint bleeding (52.9%) either spontaneous or after trauma was the main forms of bleeds with hemarthrosis of knee joint being most common. Psoas muscle bleeds in 10 (33.3%) followed by hematemesis and melena in 7 (23.3%) were the most common critical bleed seen in our patients. Numerous psychosocial issues such as school absenteeism (68.25%), family dysfunction (50.8%), depression, low self-esteem, parental separation (21.4%), and divorce (2.4%) were noticed. Mothers were blamed for the disease and victimized in 10 (7.9%) cases. **Conclusion:** Joint bleeding was the most common bleed with hemarthrosis of knee joint being the major presentation. Psoas muscle bleeds were the most common critical bleed. Major life-threatening bleeds such as intracranial bleed and liver bleeds were seen only in patients with severe hemophilia A. Numerous psychosocial issues were noticed quite often and need equal attention as a medical treatment to optimize hemophilia care.

Key words: *Bleeding disorders, Children, Hemophilia, Karnataka*

Bleeding disorders are a group of conditions that result when the blood cannot clot properly. Hemophilia A and B are perhaps the most well-known inherited bleeding disorder, which are X-linked hereditary disorders caused by mutations in factor VIII (FVIII) and factor IX (FIX) genes, respectively. They are distributed worldwide affecting approximately 1 in 5000 male births for hemophilia A and 1 in 25,000 male births for hemophilia B and often under diagnosed. Many more people are affected by Von Willebrand disease, the most common inherited bleeding disorder which can affect both males and females. Rare clotting factor deficiencies are bleeding disorders in which one of the other clotting factors (i.e., factors I, II, V, V + VIII, VII, X, XI, or XIII) is missing or not working properly. Less is known about these disorders because they are diagnosed so rarely [1-3].

These factors take part in the intrinsic pathway of blood coagulation, and affected individuals have severe, moderate, and mild forms of the diseases, defined by factor plasma levels of 1% or less, 2-5%, and 6-40%, respectively [1-3]. Those with severe deficiency (<1% of normal) experience spontaneous bleeding without apparent trauma, whereas in moderate deficiency (1-5% of normal) there is no spontaneous bleed but may bleed excessively after minor trauma, surgery, or other invasive procedures. In mild deficiency (5-40% of normal), abnormal bleeding occurs only after significant trauma. Females are carriers for hemophilia and transmit the disease to their sons, while 30% of the patients have no family history and are a result of *de novo* mutations [4,5].

Although India has a very large population of patients with hemophilia and other bleeding disorders, there are very few studies on their epidemiology. Based on the 2008 Global Survey of the World Federation of hemophilia, nearly 149,000 individuals worldwide have hemophilia, hemophilia A being more common. 15,000-16,000 hemophiliacs are registered with the Hemophilia Federation of India [6-9]. Our study is one of the largest cohort studies on the epidemiology of bleeding disorders and associated from this region. A study leading to the knowledge of spectrum of presentation of hemophilia helps in the early diagnosis and effective management.

MATERIAL AND METHODS

This observational study was conducted on all children <18 years of age with bleeding disorders attending Comprehensive

Hemophilia Center from December 2015 to August 2016. It is also the Nodal Center for Hemophilia Care in Karnataka at Bangalore Medical College and Research Institute. Informed written consent was obtained for the use of patient information for research and studies. Patients with platelet and vascular disorders and those older than 18 years were excluded from the study. Detailed clinical history and a thorough clinical examination were performed on these patients. The questionnaire included details of past treatment and bleeding episodes, family history and pedigree analysis, mode of presentation, age of onset of the disease, associated symptoms, and drug history.

The blood sample was collected and subjected to fresh complete coagulation workup on all patients, which included complete blood count using automated hematology analyzer, bleeding time (modified Ivy's method), clot retraction time, platelet count, and platelet morphology. Hematological parameters obtained by 5 Part Beckman LH 780 analyzer for hemoglobin, hematocrit, white blood cells count (total leukocyte count), differential count, platelet count, blood grouping by slide method, and peripheral smear examination were done. These tests were followed by tests for prothrombin time, activated partial thromboplastin time (APTT), and thrombin time by Sysmex CA-620 coagulometer. Correction test was done using adsorbed plasma, aged serum, Factor VIII deficient plasma, Factor IX deficient plasma, and normal pooled plasma to know the factor deficiency followed by respective factor assay. Tests to identify inhibitors (Inhibitor screening and assay) were done as required as per established protocols.

A separate questionnaire was given and discussed with patients for ascertaining details pertaining to the social and psychological impact from their disease. A dysfunctional family was defined as one in which conflict, misbehavior, and often child neglect or abuse on the part of individual parents occur continually and regularly, leading other members to accommodate such actions. Children sometimes grow up in such families with the understanding that such an arrangement is normal [10]. Statistics were analyzed using Microsoft Excel sheet and presented as percentages.

RESULTS

Among the 126 cases of bleeding disorders, 123 (97.6%) were male and 3 (2.4 %) were female. Mean age at diagnosis was 2.5±2.55 years (range-1 month to 8 years), and there was a time lag between the first bleeding and diagnosis of 27 days. The APTT was prolonged in all the cases. The family history of hemophilia was seen in 45.2% (57/126) of cases. Of the 3 female patients, 2 had Von Willebrand disease and 1 had factor 5 deficiency. 101 (80.2%) cases had hemophilia A, and 15 (11.9%) cases had hemophilia B. A total of 3 (2.4%) cases had Von Willebrand disease. Other rare deficiencies 7 (5.5%) included 2 each with factor XIII deficiency and congenital fibrinogen deficiency and 1 each with factor X deficiency, factor VII deficiency, and Factor V deficiency, respectively.

Among the hemophilia A, 4 (4%) cases had mild, 23 (22.8%) had moderate, and 74 (73.2%) had severe hemophilia, and among the hemophilia B, 3 (20%) cases had moderate, and 12 (80%) cases had severe disease. 24 (19%) children were between 0 and 5 years, 29 (23%) were between 5 and 10 years, the majority 56 (44.4%) were 10-15 years old, and 17 (13.4%) were from 15 to 18 years of age. 34% of cases had initial bleeding episode before 1 year of age and by 5 years of age, and 80% of the cases were symptomatic. None of the children was diagnosed with bleeds during neonatal period. Inhibitors were seen in 9 (7.14%) of children with hemophilia A, with 6 (66.7%) having high-titer inhibitors and 3 (33.3%) had low-titer inhibitors. Only one child was positive for hepatitis C virus (HCV) infection, and none of them had human immunodeficiency virus (HIV) infection or hepatitis B infection.

There were totally 285 bleeding episodes in 126 patients. Joint bleeding (52.9%) either spontaneous or after trauma was the main forms of bleeds (Table 1), followed by bruises and skin hematomas, oral cavity bleeding, and muscle bleeds with majority being psoas muscle bleeds. Among the joint bleeds, the knee was the most commonly affected, followed by elbow, ankle, hip, metatarsophalangeal joints, and wrist and shoulder joints, respectively (Table 2). Among the major and life-threatening bleeds, intracranial bleeds were seen in 5 (16.7%) cases, hematemesis and melena in 7 (23.3%), liver hematoma in 1 (3.3%), forearm muscle bleed with compartment syndrome in 2 (6.7%), ophthalmic bleeds in 2 (6.7%), and severe epistaxis in 3 (10%) cases. Psoas muscle bleeds in 10 (33.3%) followed by hematemesis and melena in 7 (23.3%) were the most common

Table 1: Type of bleeds

Type of bleeds	Number (%)
Joint	151 (52.9)
Bruises and skin hematomas	45 (15.8)
Gum/oral	29 (10.2)
Hematuria	1 (0.35)
Epistaxis	14 (4.91)
Post-Circumcision	4 (1.40)
Muscle bleed	26 (9.12)
Intracranial bleed	5 (1.75)
GI (Hematemesis±melena)	7 (2.46)
Liver hematoma	1 (0.35)
Ophthalmic bleeds	2 (0.76)
Total	285 (100)

Table 2: Frequency of the joints involved

Joint affected	Number of bleeds (%)
Knee	53 (35)
Ankle	34 (22.5)
Elbow	40 (26.5)
Shoulder	3 (2)
Wrist	5 (3.6)
Toe	6 (4)
Hip	10 (6.6)
Total	151 (100)

critical bleed seen in our patients. 30% of those with hematemesis gave a history of over the counter non-steroidal anti-inflammatory drugs intake. Psoas muscle bleed and epistaxis were seen in patients of both hemophilia B and A, whereas other critical bleeds such as liver bleed and intracranial bleed were seen only in children with severe hemophilia A.

Children with hemophilia commonly face a number of psychosocial challenges. We observed school absenteeism in 86 (68.25%) cases, and an average of 5 days of schooling per month was missed. Family dysfunction was rampant with 64 (50.8%) affected cases. Parental separation was seen in 27 (21.4%) and parental divorce in 3 (2.4%) cases. Mothers were blamed for the disease and victimized in 10 (7.9%) cases. An interesting observation was mothers deserting the child and family in 2 families, one mother having left the family and another committed suicide without any pressure from the marital family.

DISCUSSION

Both hemophilia A and B are indistinguishable clinically from each other. The diagnosis of hemophilia is based on factor assays, bleeding patterns, and family history; although, about 30% of those diagnosed do not have a family history of the disorder and are a result of *de novo* mutations [5]. The mainstay of treatment is replacement of the deficient factor. The two main concerns with factor replacement are transmission of pathogenic viruses or prions and the development of inhibitors. One of the most important complications of hemophilia treatment is the development of antibodies or inhibitors, to the exogenous factor, inactivating the infused coagulation factor. Inhibitor development is much more common in hemophilia A than in hemophilia B and is reported in up to 38% of patients with hemophilia A [7-9]. Inhibitors were seen in 9 (7.14%) of the children with hemophilia A in our study. No patient of hemophilia B had inhibitors in our series. Perhaps, more vigilant screening and prolonged follow-up is needed to detect inhibitors.

Demographic profile of patients was similar to other studies [12-21], with severe hemophilia A being the most common, similar to the findings by Mishra et al. [14] and Sharma and Arya [15]. Some studies may show higher incidence of mild hemophilia as severe and moderate cases of hemophilia get misdiagnosed as mild hemophilia if tested after blood or blood product transfusion. There was no symptomatic patient with mild hemophilia B in our study. There was a mean time lag between first bleeding and diagnosis of 27 days, which shows a lack of awareness among doctors in the community.

Joint bleeds have been reported as the most common site of spontaneous bleeding [12-15]. Even in our series, joint bleeding was the main forms of bleeds with hemarthrosis of knee joint being the most common type, which is similar to the results of other studies by Sharma and Arya [15] and Parthiban et al. [13]. Psoas muscle bleeds followed by hematemesis and melena was the most common critical bleed seen in our patients. Major life-threatening bleeds were seen only in children with severe deficiency of the respective coagulation factor. Bleeds such as intracranial bleed and liver bleeds were seen only in patients with severe hemophilia A in our study.

Only one child was HCV positive and none of them had HIV or hepatitis B infection. Incidence of transfusion-transmitted infections in the pediatric age group (i.e., <18 years) who were born in the late 90s and 2000AD onward when safer factor concentrates were available and strict transfusion practices were followed was very low, as reported in literature [22-24]. The introduction of virus inactivated plasma-derived coagulation factors and then of recombinant products has revolutionized hemophilia care. The development and implementation of viral inactivation techniques for the production of plasma-derived factor concentrates, as well as the adoption of new methods to screen viruses in blood donation (i.e., nucleic acid testing), greatly improved the safety of plasma-derived products, as shown by the fact that blood-borne transmission of hepatitis viruses or HIV has no longer occurred in the past 25 years. However, the most important advance in this field was represented by the rapid progress in DNA technology (following the cloning in 1982 and 1984 of FVIII and FIX genes), which allowed the industrial production of recombinant FVIII (and subsequently of FIX), culminating with the use of recombinant factor products [22-24].

We observed a number of psychosocial challenges in our hemophiliacs such as school absenteeism, family dysfunction, depression, and low self-esteem. Parental separation and divorce were seen quite often. Thus, to provide optimal care, health-care professionals need to be able to identify issues and challenges related to having a bleeding disorder that may be affecting their patients' cognitive and emotional development. A bleeding disorder is a chronic condition that imposes limitations, but it can also represent an opportunity to bring about positive change through learning and self-awareness. There are different ways of experiencing and coping with pain and chronic illness. Some people with hemophilia may focus on the emotional challenges, while others find ways to better cope with their situation. Mothers of hemophiliacs face special challenges. Apart from the guilt feelings associated with the birth of a child with hemophilia, women who have a family history of hemophilia suffer torture in tradition-bound households at the hands of husband, relatives, and society. Greater is the misery when she is abandoned by husband as she is tainted, incapable of bearing normal children. She may seek refuge in her parents who may or may not be in a position to help. Moreover, bringing up the child with hemophilia all alone itself takes a heavy toll on her physical and mental health [10,11].

Short-term psychotherapy and psychosocial services can help individuals with hemophilia cope with symptoms and limitations and develop a healthy sense of self. Studies and data on psychosocial aspects of the hemophilia are lacking in the published literature, especially from developing countries. There is a need for more international, multifaceted research to explore and quantify the social and psychological aspects of life with hemophilia. Interventions by the multidisciplinary team to support the psychosocial needs of patients and their families, such

as offering information and assistance, clarifying doubts, and teaching coping strategies to minimize the impact of disabilities, may help to maximize patient outcomes and improve the quality of life for their families. The goals of intervention should be to maintain good physical function, prevent joint disease and chronic pain, and screen patients for early signs of mental health problems that can negatively impact the quality of life and adherence to treatment.

CONCLUSIONS

In our study, the majority had hemophilia A and were males. Joint bleeding was the most common bleed with hemarthrosis of knee joint being the major presentation. Psoas muscle bleeds were the most common critical bleed. Major life-threatening bleeds such as intracranial bleed and liver bleeds were seen only in patients with severe hemophilia A in our series. Incidence of transfusion-transmitted infections in the pediatric age group was very low. Psychosocial support is an important part of comprehensive care for people with hemophilia.

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