An experience of single centre at C S M Medical University, Lucknow, for the prevalence of hemophilia in Uttar Pradesh

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Abstract

Objective To evaluate the incidence of hereditary bleeding disorders, registered at our centre from all over Uttar Pradesh over an extended period of 10 years.

Material and methods A complete coagulation profile of 240 cases conducted, followed by clinical history of the patient. The frequency and type of bleeding, age of onset, treatment taken, consanguinity and the blood transfusion if any, are little information collected from the patient.

Results The complete scenario of bleeders indicated maximum number (92%) of hemophilia 'A' from northern UP as compared from other zones ($76.5\% \pm 3$). Contrarily, hemophilia 'B' registered maximum from eastern zone (26%) and minimum from the northern zone (8%). The age diversity at diagnosis ranged between 1–32 years. The reasons for difference are all speculative. Definite cause needs extensive research.

Conclusions The study showed that elderly patients with hemophilia had significantly more impairments in physical functioning and depression than younger ones.

Keywords Hemophilia · Prevalence · Uttar Pradesh · India

Introduction

Coagulation disorders deal with disruption of the body ability to control blood clotting. The most commonly known coagulation disorder is hemophilia, a condition in which patients bleed for long periods before clotting. There are other coagulation disorders with a variety of causes. Coagulation, or clotting, occurs as a complex process involving several components of the blood. Plasma, the fluid component of the blood, carries a number of proteins and coagulation factors that regulate bleeding. Platelets (small colorless fragments in the blood), initiate contraction of damaged blood vessels to prevent excess blood loss. They also help in plugging the damaged blood vessels and work with plasma to accelerate blood clotting. A disorder affecting platelet production or one of the many steps in the entire process can disrupt clotting. Coagulation disorders arise from different causes and produce different complications. Two common inherited coagulation disorders are Hemophilia A and B, carried by females but affect males. The incidence of hemophilia A (FVIII) is nearly 1 in 5,000 male live births whereas, that of hemophilia B (FIX) is 1 in 30,000 live births transmitted by females who are asymptomatic carriers [1]. Some signs of hemophilia 'A' are numerous large, deep bruises, pain, and swelling of joints caused by internal bleeding. Patients with hemophilia do not bleed faster, just longer. A person with

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mild hemophilia may first discover the disorder with prolonged bleeding following a surgical procedure. If there is bleeding into the neck, head, or digestive tract, or bleeding from an injury, emergency measures may be required.

Mild and severe hemophilia 'A' are inherited through a complex genetic system that passes a recessive gene on the female chromosome. Women usually do not show signs of hemophilia but are carriers of the disease. The recessive X-chromosome inheritance pattern, affects mostly men while their female relatives may be heterozygous for the mutation, often referred to as carriers of hemophilia [2]. The genes for hemophilia which lie on X- chromosome at Xq28 and Xq27 position is responsible for causing hemophilia A (FVIII deficiency) and hemophilia B (FIX deficiency) respectively [3]. Each male child of the carrier has a 50% chance of having hemophilia, and each female child has a 50% chance of passing the gene.

Christmas disease, or hemophilia B, is also hereditary but less common than hemophilia A. The severity of Christmas disease varies from mild to severe. The severity depends on the degree of deficiency of the clotting factor. Hemophilia B symptoms are similar to those of hemophilia A, including numerous, large deep bruises and prolonged bleeding. The more dangerous symptoms are those that represent internal bleeding, such as swelling of joints or bleeding into internal organs upon trauma. Hemophilia most often occurs in families with a known history of the disease, but occasionally, new cases will occur in families with no apparent history. Approximately, 1500 new cases are born every year in India and there are nearly 50,000 patients with severe hemophilia A [3]. The severity is categorized according to the clinical and hematological bleeding status of the patient, as 5–30% to be mild, 1–5% moderate & <1% to be the severe one [4]. The present study is an experience with patients of inherited bleeding disorders in the frame of 10 years at C S M Medical University, Lucknow (Uttar Pradesh).

Materials and methods

In all 240 bleeders registered as hemophilic from all over UP during the last 10 years of study at Pathology Department, C S M Medical University Lucknow, Uttar Pradesh, India. A thorough past history including nature of bleeding, physical disability if any, and family history with complete family pedigree was prepared. Hemostatic tests included platelet count, bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (aPTT) and clot retraction (CR). Specific tests performed in groups with prolonged activated partial thromboplastin time included mixing study with normal and deficient plasma in the ratio

of 1:1. Assay of coagulation factors included aPTT of test plasma, and normal control in variable dilutions mixing with severe deficient plasma. Bleeding time conducted by Ivy's method [5]. The normal value ranges from 2–7 minutes. Prothrombin time by one stage Quick's method [6] and Kaolin cephalin clotting time method [7, 8] used for Activated partial thromboplastin time using Dade Behring reagent kit with 1.00 ISI value. Clot retraction conducted using 2 ml whole blood kept at 37°C in water bath. Normal value ranges from 30 to 50%.

Result

Cases registered at our centre were from not only Uttar Pradesh alone but also we received cases from Nepal, South India and Madhya Pradesh. In the present study, we opted to compile hemophilic cases registered at our Institute only from all over Uttar Pradesh. Bar diagram (Fig 1), shows that maximum number of hemophilia 'A' cases diagnosed at our centre from northern zone (92%) while minimum number of cases identified from central, eastern, southern and western zones ($76.5\% \pm 3$). Hemophilia 'B' cases on the contrary, registered maximum from the eastern zone (26%), and minimum (8%) approximately 1/3rd from the north zone. From rest of the zones, south, west and central, cases identified in-between eastern and northern zones ($22.5\% \pm 2$). Of the total 240 cases, 185 cases (77.1%) were of hemophilia 'A' and 55 cases (22.9%) were of hemophilia 'B'. Of these 185 cases, 106 cases (57.3%) were mild, 59 cases (31.9%) were severe, and only 20 cases (10.8%) were moderately suffering from factor VIII deficiency. However, compared to hemophilia 'A', of the 55 cases of hemophilia 'B', 30 cases (54.5%) were mild, 18 cases (32.7%) were severe and only 7 cases (12.7%) were moderately suffering from factor IX deficiency. Test run for vWD ruled out the suspected cases. Any such case diagnosed as vWD was excluded. The age group of patients enrolled in the study varied between 1 year and 32 years inclusive of 3 female hemophilic 'B'. Clinically patients presented with hemarthrosis, epistaxis, gum bleeding, prolonged bleeding after minor trauma, bruises, stump bleeding in few cases. In young children easy bruising, gum bleeding and epistaxis were the early symptoms for which they attended the OPD of pediatric department at our centre. Complete coagulation profile and mixing assay revealed the factor deficiency.

Discussion

Hemophilia is a low incidence, high cost disease that is of low health care priority in developing countries with

Fig. 1 Bar diagram showing zone wise distribution of hemophilic

economic constraints. The incidence of hereditary hemorrhagic disorders may vary according to the country and ethnic origin. Hemophilia A remains the most common bleeding disorder in the Indian population, followed by platelet function defects in India. In the industrial world, von Willibrand disease has emerged as the most common hereditary hemorrhagic disease [9]. The ratio between hemophilia 'A' and hemophilia 'B' from the Northern Zone is 11.5:1 (92%: 8%) which shows maximum difference between the two whereas, the ratio from Central, Eastern, Southern and Western Zones are 3.35:1 (75%:23%), 2.85:1 (74%:26%), 4:1 (80%:20%) and 3:1 (75%:25%) respectively revealing comparatively 3–5% less from Northern zone. Ghosh et al (2001) worked out the prevalence of inhibitors in India and found 7.3% of patients of hemophilia 'A' and 2.4% of hemophilia 'B' to have developed inhibitor. Gupta et al (2005) reported the prevalence of hemophilia 'A' to be 42.4% followed by 39.4% of platelet function defect. The Netherlands has approximately 500 children under the age of 18, with severe hemophilia, of which 90% receive regular treatment [11]. Of the 600 registered cases from western India 598 patients diagnosed as suffering from coagulation

disorder and the rest of the 32 patients suffered from platelet function disorder [12]. Ahmed et al attempted to correlate the prevalence of hemophilia and platelet function disorder and found hemophilia A to be 52.31% whereas that of PFD to be 27.77%.

Internationally the worldwide incidence of hemophilia A is approximately 1 case per 5000 male individuals, with approximately one third of affected individuals not having any family history. Comparatively hemophilia B occurs in 1 case per 25,000 male individuals and represents one fourth of all patients with hemophilia. In Europe and North America, the annual incidence of hemophilia A is approximately 1 case per 5000 male births and of hemophilia B approximately 1 case per 30,000 male births. About 200 people are reported to be hemophilics (HA and HB) from Singapore [14]. Although hemophilia is a well-known bleeding disorder in men, it seldom recognized that female carriers of hemophilia might not only have an increased bleeding tendency but that the symptoms may be frequent and severe [15]. Female carriers expected to have a plasma concentration of factor VIII or IX corresponding to half the concentration found in healthy individuals, which is generally sufficient for nor-

mal hemostasis. However, in carriers a wide range in clotting factor levels seen varying from very low, resembling affected males, to the upper limit of normal [16]. This is the phenomenon of lyonization, random X-chromosome inactivation, which takes place in the early embryonic life [17]. Other genetic factors, such as ABO blood group, may also affect factor VIII and IX plasma concentrations in carriers as well as non-carriers, in whom a wide distribution also is observed [18]. The hallmark of hemophilia is hemarthrosis leading to a painful inflammation and deterioration of the joint. The ultimate result is permanent deformities, misalignment, loss of mobility, and extremities of unequal lengths if not taken proper and timely treatment. Severity of bleeding depends on the range of activity of factor VIII or factor IX, clinical bleeding symptoms or plasma pro-coagulant levels. About 3,50,000 people are affected by severe hemophilia A. These are the most widely used criteria indicating less than 1% normal factor (<0.01 IU/ml) to be severe, 1–5% normal

factor (0.01–0.05 IU/ml) to be moderate and more than 5% but less than 40% normal factor (>0.05–<0.40 IU/ml) to be mild hemophilia. Clinically bleeding symptoms criteria may confuse because patients with factor VIII or factor IX levels < 1% occasionally have little or no spontaneous bleeding and appear to have clinically moderate or mild hemophilia. Further, the reverse is also true for patients with pro-coagulant activities of 1–5%, who may present with symptoms of clinically severe disease.

The results demonstrate that children of age group 1–6 years presented with mild hemophilia A (57.3%) and hemophilia B (54.5%), and those of age group 7–15 years revealed moderate hemophilia A (10.8%) and hemophilia B (12.7%) while adults of age group 16–32 affected severely with hemophilia A (31.9%) and hemophilia B (22.9%) (Fig. 2). Higher incidence of FVIII deficiency as compared to FIX deficiency seems to be due to the genetically high mutation rate in FVIII than in FIX deficiency [19].

Fig. 2 Percentage severity of 240 hemophilic

In conclusion, it is clear that no two countries or states have the same percentage of prevalence of hemophilia. It varies from place to place and needs detailed study accordingly.

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