Pattern Of Bleeding In Nigerian Haemophilliacs Seen In A Tertiary Hospital

[1,2]W.A. Shokunbi, [1,2]F.A Fasola, [2]K.B. Shonde-Adebola, [2]H.A. Odebiyi, [2]O.A. Adeoye

1. Department of Haematology, College of Medicine, University of Ibadan, Ibadan, Nigeria
2. Department of Haematology, University College Hospital, Ibadan Nigeria.

Abstract:

Haemophilia A and B are X-chromosome linked bleeding disorders, due to defective synthesis of factor VIII or IX respectively, and are characterised by delayed and sustained bleeding. Bleeding into the joints (Haemarthrosis) is the most common presentation. Recurrent haemarthrosis leads to crippling haemarthropathy and flexion deformities, typically in the hinge and socket joints. This study determined the pattern of bleeds in the Nigerian haemophiliacs in order to locate the usual sites and influence their care in emergencies. We reviewed the records of 28 haemophiliacs who were seen at the Haematology Day Care Unit over a 2-year period for emergency care of acute bleeds. The patients were aged between 16 months and 42 years with a median age of 12.5 years. Twenty-six of these patients had Haemophilia A (93%) and Haemophilia B constituted 7%. The coagulation factor levels ranged between 0.4% and 8%. The commonest bleeding site was the joint which constituted 41% of cases followed by soft tissue involvement, observed in 25% of patients and gastrointestinal tract, in 16% of cases. All 28 (100%) patients received fresh frozen plasma either given alone or in combination with other therapeutic options. Ten (36%) patients received cryoprecipitate; 6(21%) got recombinant factor VIII, 5(18%) received fresh whole blood and 3(11%) patients were given antifibrinolytic agents for the management of acute bleeding episodes. We concluded that the joints are the commonest site of bleeding in our hospital with knee joint involvement being the most frequent. This may result in physical disability. Patients experiencing bleeding episodes might require a more personalized approach to treatment in which case, there might be the need to consider prophylaxis for some of our patients.

Key words: Bleeding Pattern, Haemophilia, Emergency Care.

Correspondence to:

Prof WA Shokunbi
Department of Haematology,
College of Medicine, University College Hospital,
Ibadan Nigeria;
email: wuraolashokunbi@yahoo.co.uk;
telephone number 08022903245.

Introduction

Haemophilia A and B are X-chromosome linked bleeding disorders, in which there is defective synthesis of factor VIII or IX respectively, and are characterised by delayed and sustained bleeding involving various sites in the body (figure 1). Bleeding into the joints (Haemarthrosis) is the most common presentation accounting for about 75% of bleeding episodes in patients with severe disease. Haemarthrosis is characterised by joint discomfort, progressive joint pain, swelling and limitation of movement of the affected joint. The consequences of bleeding into the joints can be debilitating depending on the joint. The weight-bearing, hinge joints (knees and ankles) are more susceptible. However studies on the most frequently affected joint has not been consistent. Complication of bleeding into the joint includes arthropathy which can lead to a decline in patient autonomy and quality of life.

Another mode of presentation is Soft-tissue hematomas such as haemorrhage into subcutaneous connective tissues or into muscles. This may occur with or without a known trauma (i.e spontaneous). There are several other modes of presentation including, mucous membrane bleeding, Intracranial haemorrhage (one of the most dangerous haemorrhagic events in haemophilic patients), pseudotumours (blood cysts) and post-operative bleeding. Post-surgical bleeding is characterized by prolonged bleeding and delayed wound healing because of poor clot formation. Bleeding may persist for several hours or, occasionally, for several days. The frequency of bleeding has been reported to change with age. Bleeding was associated with increased absence from school, decreased levels of physical activity and decreased rates of household task performance. Relatively high rates of bleeding associated with trauma suggest the need for preventive interventions.

Replacement of the deficient factor is the main stay of haemophilia management. Replacement therapy is aimed at achieving haemostatically adequate levels of coagulation factor when bleeding has occurred or is suspected. It should be initiated at the onset of symptoms to reduce bleeding and to prevent damage to the surrounding tissues. This therapy was achieved in the past, by using cryoprecipitate (for haemophilia A) and fresh frozen plasma. However specific factor concentrate replacement is now the gold standard. Factor concentrates may be derived from pooled plasma or genetically engineered through

recombinant technology. Other adjunct therapies include the use of antifibrinolytic agents (such as epsilon aminocaproic acid- EACA) and topical haemostatic agents like fibrin sealant. For patients with haemarthrosis, resting, elevating the joint and use of ice or cold compression on the affected joint as well as the avoidance of contact sports and prevention of aspirin use and other non-steroidal anti-inflammatory agents are also important supportive measures. The cost and the duration of treatment would depend on the site of bleeding. Therefore, information on bleeding pattern in haemophilia patients is useful for clinical care, transfusion support and policy development in the management of inherited bleeding disorders.

This study investigated the pattern of bleeds in the Nigerian haemophiliacs so as to prioritize and ensure prompt haemostatic support in emergencies.

Methodology

This was a retrospective study carried out at the Department of Haematology, University College Hospital, Ibadan. We reviewed the records of 28 patients with haemophilia who were seen and managed at the Haematology Day Care Unit over a 2-year period for emergency care of acute bleeds. Information on socio - demographic characteristics and clinical data were retrieved. The treatment of the patient included on demand administration of blood product and antifibrinolytic agents as required. None of the patients was on prophylaxis. The statistical analysis employed, expressed categorical variables as frequencies and percentages.

Results

The patients were aged between 16 months and 42 years with a median age of 12.5 years. The age distribution of the patients is as shown in table 1 with majority (39%) of the patients within the age group 1 to 9 years. Twenty-six of these patients had Haemophilia A (93%) while the other two patients had Haemophilia B (7%). The coagulation factor levels ranged between 0.4% and 8% implying severe to moderately severe disease (table 2). Bleeding into the joints (haemarthrosis) was the commonest site of bleeding

Table1: Age distribution of patients

Age	Frequency	% (n=28)
1 – 9	11	39
10 – 19	7	25
20 – 29	5	18
30 – 39	4	14
40 – 44	1	4

Table 3: The sites/pattern of bleeding and their frequencies

Site of bleed	Frequency (N=44)	(%)
Haemathrosis	**18**	**41**
Left knee	7	16
Right knee	3	7
Left elbow	2	4.5
Right elbow	2	4.5
Left ankle	2	4.5
Right ankle	1	2.3
Right hip	1	2.3
Muscle/soft tissue haematoma	**11**	**25**
Gastrointestinal	**7**	**16**
Tongue	3	7
Gastritis/melena	3	7
Oral mucosa/gum	1	2.3
Others	**10**	**22.7**
Bone fracture	2	4.5
Post-circumcision	2	4.5
Post-operative	1	2.3
Epistaxis	1	2.3
Pseudo-tumour (left iliac fossa)	1	2.3
Central nervous system	1	2.3

Table 2: Disease severity among the Haemophiliac patients

Severity	Factor level (%)	frequency	% (n=28)
Mild	6 – 10	10	36
Moderate	1-5	12	43
Severe	0 - <1	6	21

Table4: Treatment options used alone or in combination and the frequency of use

Treatment option	Frequency	%	Haemophilia A	Haemophilia B
FFP	28	100	26	2
Cryoprecipitate	10	36	10	-
rFVIII	6	21	6	-
Fresh Whole Blood	5	18	5	-
Antifibrinolytic agents	3	11	3	-
FFP alone	13	46	11	2
FFP, CRYO, rFVIII, and FWB	2	7	2	-
FFP and CRYO only	7	25	25	-
FFP and rFVIII only	3	11	3	-
FFP and FWB only	3	11	3	-

Key: FFP= fresh frozen plasma; CRYO = cryoprecipitate; rFVIII = recombinant factor VIII; FWB = fresh whole blood;

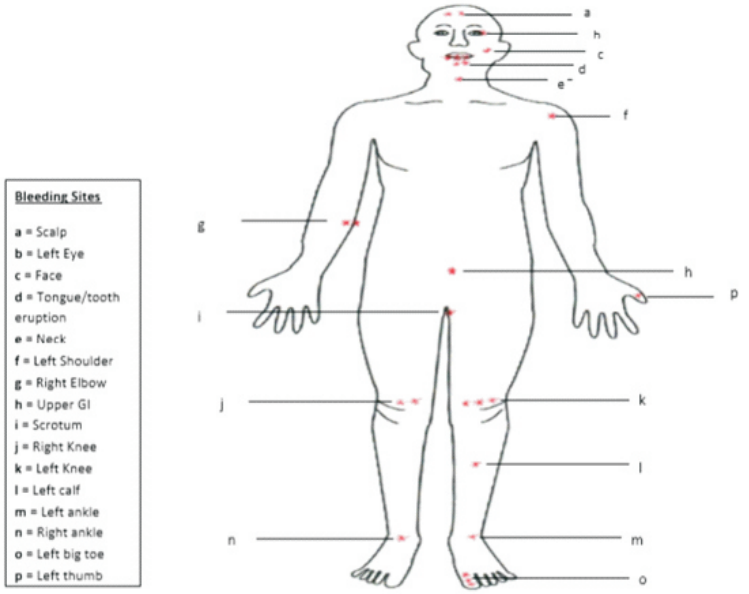

Figure 1: sites of bleeding in Nigerian Haemophiliacs seen at a tertiary Hospital over a two-year period

constituting 41%. The knee joint was the commonest site as a target joint (23%) mostly involving the left knee (16%). Soft tissue haematoma was next in frequency to haemarthrosis observed in 25% of patients, greater percentage of which occurred following a trauma. Gastro-intestinal (GIT) bleeding constituted 16% of all cases with bleeding into the tongue accounting for 7% of cases and gastritis with passage of melena accounting for another 7%. Tongue bleeding was usually self-inflicted while chewing food, meat or fish bone. Other patterns of bleeding experienced in these haemophilic patients included post-surgical, post circumcision, bone fracture, epistaxis, central nervous system (CNS) bleeding and left iliac fossa pseudotumor all together constituting 22.7%. The least commonly observed bleeding sites were hip joint, right ankle, epistaxis, CNS bleeding and pseudotumor each constituting about 2.3% (n=1) each (table 3).

The acute bleeds were managed with fresh frozen plasma (FFP), sometimes cryoprecipitate, and in recent times, recombinant factor VIII concentrate (Elocate). Fresh whole blood (screened for transfusion transmissible infections) was given in addition to factor replacement therapy, for correction of severe anaemia in patients with severe bleeding. The tongue bleeds required anti-fibrinolytic agent such as tranexamic acid or epsilon aminocaproic acid (EACA) in addition to the factor replacement therapy. Some patients received various combinations of these treatment options to achieve haemostasis (table 4). Overall, all 28 (100%) patients received FFP either given alone or in combination with other therapeutic options. Ten (36%) of patients received cryoprecipitate; 6(21%) got recombinant factor VIII, 5(18%) received fresh whole blood and 3(11%) patients were given antifibrinolytic agents [one of whom had EACA and remaining 2 got tranexamic acid] see (table 4). The two patients with haemophilia B received only FFP as recombinant factor IX was not available when they presented.

Discussion

Haemophilia A is commoner than haemophilia B with worldwide prevalence of 1/5000 and 1/40000 live male births respectively. Higher prevalence of haemophilia A was also observed among our patients with 93% (n=26) of our patients being haemophilia A and 7% haemophilia B. The pattern of bleeding observed in our patients is similar to what has been documented in the literature as observed by Srivastava who reported joint bleed as being the commonest (70-80%), followed by haematoma in (10-20%) and CNS bleed being the least (<5%).

Bleeding into the joints (haemarthrosis) is the commonest (41%) presentation in our patients involving mainly the knees followed by the elbows, then the ankles and thigh (knee>elbow>ankle>thigh). Studies have reported other sites such as elbow in adolescents by Aronstam et al and ankles being the commonest site in a more varied population across 21 countries as reported by K. Khair et al. Aronstam et al reported that the elbow being the most frequent site of bleeds occurred in age group 15-17 years, while the knee was the commonest site in ages 10-14 years. The difference was attributed to the adolescent using the arm more frequently as they become less physically active with inclination to academic work or due to a relative decrease in the use of leg because of the predominance of leg bleeds in earlier life.

Stephensen D et al also reported that the ankle joint has replaced the knee joint as the most common joint affected. However, our study showed that the traditional pattern of joint bleed is retained in our patients. This emphasises the need for early prevention

and treatment of haemarthrosis so as to restore function of the affected joints. Subsequent crippling haemarthropathy and flexion deformities in affected limb could impair quality of life and increase expenditure on health.

Haemorrhage into muscle (haematoma) and soft tissue was next in frequency after haemarthrosis. It was observed in 25% of patients similar to what has been documented in the literature. Sorensen B. et al also reported that 10 -25% and Srivastava et al 10-20%, of the bleeding in haemophilia involves the muscles. Hematomas and other soft tissue bleeding may occur spontaneously, but this is most often preceded by trauma. Haematomas once formed, may stabilize and later slowly resolve. However, in moderately and severely affected patients, hematomas have a tendency to enlarge progressively and to dissect in all directions, unless appropriately treated.

Gastrointestinal bleed was the next in frequency, constituting 16% with equal frequencies of tongue bleed and NSAID induced gastric bleeding occurring in 7% of cases each. Peptic ulcer disease has been found to be more frequent in the adult haemophiliacs than in the general male population. Ingestion of anti-inflammatory drugs for relief of pain is a frequent cause of upper gastrointestinal haemorrhage. The tongue bleeds were severe enough to cause anaemia requiring red cell transfusion in addition to factor replacement therapies. There was also the need to administer anti-fibrinolytic agent such as tranexamic acid at 1g orally every 8 hours or epsilon aminocaproic acid (EACA) at 25mg/kg orally every 8 hours, so as to reduce the digestion of fibrin by ptyalin, the digestive enzyme in the oral cavity.

Other forms of bleeding observed among few of our patients included CNS bleeding, pseudocysts, bone fracture, post-surgical, and epistaxis. Spontaneous intracranial haemorrhage is a rare complication of haemophilia with frequency of about 2.2 – 7.8% and a mortality rate of 34%. CNS bleeding was found in 2.3% of our patients similar to the above incidence of 2.2-7.8%. This rarity of CNS bleeding in haemophiliacs has been reported to be due to the high level of tissue factor in the brain providing additional haemostatic protection to this vital organ. Haemophilic pseudotumours are blood cysts that occur in soft tissues or bone. They are rare but dangerous complications of haemophilia. Pseudotumors often develop in the lower half of the body, usually in the thigh, buttock, or pelvis, but they can occur anywhere, including the temporal bone. Only 2.3% of our patients had a pseudotumor which was located in the left iliac fossa. Surgery in patients with haemophilia is characterized by delayed wound healing because of poor clot formation. Prolonged bleeding and subsequent infection of the wound hematoma may further complicate healing. The management of post-surgical bleeding in haemophiliacs has been made possible with the availability of factor concentrate. The factor concentrate should be commenced preoperatively after ruling out presence of antibodies in the patient. Factor replacement therapy is continued until about 1 to 2 weeks postoperatively so as to ensure adequate healing of surgical site. There is controversy on the frequency of bone fractures in haemophilic patients. Some authors believe that fractures are infrequent due to the fact that patients understanding of the gravity of their illness makes most haemophilic patients reduce their levels of activities thereby posing a risk to their physical well-being. Abreu et al are opposed to this argument in that they believe haemophiliacs suffer higher frequency of fractures than the general population as a result of loss of movement caused by haemophilic arthropathy, reduced muscular function, osteoporosis and increased number of traumas suffered by them because preventive treatments enables them to engage in sports, consequently leading to accidents. Pattern of fracture sites in haemophiliacs was reported to show a reversal from being previously commoner in the lower limbs, but now being more frequently found to involve the upper limbs, however overall frequency of fractures was reported to be less. In our study only one (2.3%) patient had a femoral mid shaft fracture, which was managed conservatively. Haematoma at fracture site was minimised by the use of FFP and Infusion of recombinant FVIII concentrate.

Conclusion

Bleeding into the joint is the commonest complication in haemophilia patients in our hospital. The knee joint was the commonest site of joint bleed. This may result in physical disability. Patients experiencing bleeding episodes might require a more personalized approach to treatment in which case, there might be the need to consider prophylaxis for some of our patients.

All efforts should be made to adequately treat haemarthrosis, as this is the most frequent type of acute bleed in haemophiliacs, so as to prevent flexion deformities. Oral bleeds tend to be relentless if anti-fibrinolytic agent is not added to the haemostatic support.

References

1. Basravi S, Shastry PP, Cynthia H, Zia SK, Chan RY. Delayed bleeding in a Toddler. Paediatric Annals. 2016;45(1):e10-e2. Epub 19 January 2016.
2. Lobet S, Hermans C, Lambert C. Optimal management of Hemophilic arthropathy and hematomas. J blood Med. 2014;5:207-18.
3. Knobe K, Berntop E. Haemophilia and joint disease: Pathophysiology, evaluation and management. J Comorb. 2011;1:51-9.
4. Soucie JM, Monohan PE, Kulkarni R, Konkle

BA, Mazepa MA. The Frequency of joint haemorrhages and procedures in non-severe Haemophilia A Vs B. Blood Adv. 2018 Aug 28;2(16):2136-44.
5. Reinke C, Spodeck A, Schildhauer TA, Swol J. Haemophilia A in a major trauma patient. BMJ Case Rep. 2015. Pubmed Central PMCID: PMC4691853. PMID: 26677147. Epub Dec 16, 2015.
6. Prasant J, et al. Recent trends and advances in Haemophilia, its management and therapeutic outcomes. Indian J pharm Biol Res. 2014;2(4):68-76.
7. Guidelines for the management of Haemophilia 2nd ed. [Internet]. Blackwell publishing. 2012. Available from: www.wfh.org.
8. Franchini M, Mannucci PM. Haemophilia B is clinically less severe than Haemophilia A: further evidence. Blood Transfus. March 2018;16(2):121-2.
9. Srivastava A, et al. Guidelines for the management of Haemophilia. Haemophilia. 2013;19(1):e1-47. Epub 2012,July 6.
10. Aronstam A, Ranfor SG, Painter MJ. Pattern of bleeding in adolescents with severe haemophilia A. BMJ. 1979;1:469.
11. Khair K, Mazzucconi MG, Parra R, Santagostino E, Tsakiris DA, Hermans C, et al. Pattern of bleeding in a large prospective cohort of haemophilia A patients: A three-year follow-up of the AHEAD (Advate i HaEmophilia A outcome Database) study. Haemophilia. 2018;24(1):85-95.
12. Stephensen D, Tait RC, Brodie N, Collins P, Cheal R, Keeling D, et al. Changing Patterrns of bleeding in patients with severe haemophilia A. Haemophilia. 2009;15(6):1210-4. Epub 2009 Jul 29.
13. Sorensen B, Benson GM, Bladen M, Classey S, Keeling DM, McLaughlin P, et al. Management of muscle haematomas in patients with severe haemophilia in an evidence-poor world. Haemophilia. Jul 2012;18(4):598-606.
14. Pettersson H, Gilbert MS, editors. Soft tissue bleeding, In: diagnostic Imaging in Haemophilia. 1st ed. London: Springer; 2017.
15. Eyester ME, Asaad SM, Gold BD, Cohn SE, Goedert JJ. Upper gastrointestinal bleeding in hemophilics: incidence and relation to use of non-steroidal anti-inflammatory drugs (second multicenter hemophilia study group. Hemophilia. 2007;13(3):279-86.
16. Shokunbi WA, Shonde-Adebola KB, Fowodu FO, Ogundeji PS, Busari OE. Gastrointestinal Bleeding in a patient with Haemophilia A. Nigerian Society For Haematology and Blood Transfusion, 40th Annual general Meeting and Scientific conference; Benin. Benin Nigeria 2013. p. 19-20.
17. Hegde A, Nair R, Upadhyaya S. spontaneous intracerebral hemorrhage in hemophilics- A treatment dilemma. Int J Surg Case Rep. 2016;29:17-9.
18. Mackman N. the role of tissue factor and factor VIIIa in Haemostasis. Anesth Analg. May 2009; 108 (5):1447 -52.
19. Lewis TR, Webb HR, Bell JP, Beall DP, Fish JR. Hemophilic Pseudotumor. J Okla State Med Assoc. 2005; 98(10):485-7.
20. Rodriguez-Merchan EC. Surgical wound healing in bleeding disorders. Haemophilia. 2012. Epub 15 February.
21. Sethi M. perioperative management of patient with Hemophilia A for major abdominal surgery. Indian J Anaesth. 2017;61(4):354-5.
22. Fell F, Bentley C, Rizza CR. Fracture management in patients with haemophilia. J Bone Joint Surg (Br). 1974; 56B:643-9.
23. Abreu A, etal. Tratamento ortopedico de urgencia no hemofilico. Tratamiento ortopedico de las lesiones Hemofilicos des Aparato locomotor. New York: Schattauer Verlag; 1981.
24. Caviglia H, Landro ME, Galatro G, Candela M, Neme D. Epidemiology of fractures in patients with Haemophilia. Injury. 2015 Oct;46(10):1885-90