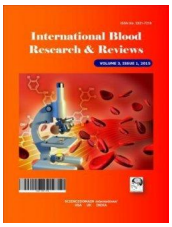

International Blood Research & Reviews

8(1): 1-7, 2018; Article no.IBRR.40474
ISSN: 2321–7219

Haemophilia B in Five Nigerian Siblings

Iragbogie Al-Mustapha Imoudu[1*] and Anas Abubakar[1]

[1]Department of Paediatrics, Federal Medical Centre PMB 005, Azare, 751101, Bauchi state, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Author IAMI conceptualized the report and wrote the draft of the manuscript. Author AA wrote the case summaries and drew the pedigree. Both authors read and approved the final draft of the manuscript.

Article Information

DOI: 10.9734/IBRR/2018/40474
Editor(s):
(1) Mehmet Sonmez, Professor, Department of Haematology, School of Medicine, Karadeniz Technical University, Turkey.
Reviewers:
(1) Rumena Dimitrova Petkova, Sofia University, Bulgaria.
(2) Vaddatti Tejeswini, NRI Medical College, India.
(3) Martin L. Nelwan, Nelwan Institution for Human Resource Development, Indonesia.
(4) Susumu Inoue, Hurley Children's Hospital, Michigan State University, College of Human Medicine, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history/24077

Case Study

Received 21st January 2018
Accepted 8th April 2018
Published 10th April 2018

ABSTRACT

Aim: To highlight the diagnosis of haemophilia B in 5 Nigerian brothers as well as the diagnostic and management challenges inherent in resource-poor settings.

Presentation of Cases: We report the cases of 5 brothers with ages ranging from 2 years to 13 years seen at the paediatric out-patient unit of the Federal Medical Centre Azare, Nigeria. They presented with complaints of abnormal and excessive bleeding since the neonatal period. Bleeding was often provoked by events ranging from traditional uvulectomies, dental exfoliation to circumcisions and was severe enough to require blood transfusions in some instances. Following diagnosis, genetic counseling was offered to the family and plans put in place to commence administration of prophylactic factor IX concentrate.

Discussion: The peculiarity in these cases is the large number of affected individuals in one family. This is made more remarkable by the fact that haemophilia B (HB) is extremely rare in Nigeria. The reason for the relative rarity of HB in Nigeria is not known. However, it is recognized that the genetic mutations associated with HB are diversely distributed and often show variations between and across ethnic groups. This may account for the spread and variability in clinical manifestations of the disease.

Conclusion: Haemophilia B though very rare may cluster in individual families. The unavailability, as well as the high cost of coagulation factor concentrates in resource-poor settings remains a significant challenge for physicians and patients alike.

**Corresponding author: E-mail: tomhe164@yahoo.com;*

Keywords: Haemophilia B; five siblings; traditional uvulectomy; circumcision; Azare; Nigeria.

1. INTRODUCTION

Haemophilia B (HB) and haemophilia A (HA) are bleeding disorders inherited corresponding to x-linked recessively inheritance pattern [1]. They result from a quantitative and/or a qualitative decrease in coagulation factors IX (FIX) and VIII (FVIII) respectively [1,2]. The diseases are consequences of mutations in the genes encoding for FIX or FVIII correspondingly located on the long arm of the X chromosome [1]. HB (Christmas disease) is considerably less common than HA and hence a rare disease. It was not recognized as a disease entity separate from HA before 1947 and to date it is estimated that there are no more than 29,712 global cases of HB [3,4,5].

Nigeria with a prevalence of 0.01 cases per 100,000 males has the lowest in the world. [6] As of 2016, 7 cases of HB had been diagnosed in Nigeria [4]. Under such circumstances most paediatric physicians practice for several years in Nigeria without coming across patients with HB. It was therefore extraordinarily astounding for us to have encountered this unique family. We present the interesting cases of five Nigerian siblings with HB disorder.

2. PRESENTATION OF CASES

In January 2018 five boys were brought to the Federal Medical Centre, Azare in North-Eastern Nigeria by their parents. They had complaints of excessive bleeding. Following diagnosis, genetic counseling was offered to the family, and prophylactic regime was outlined based on the expected availability of FIX concentrates. These boys are further discussed as Case 1, Case 2, Case 3, Case 4, and Case 5.

2.1 Case 1

A 2-year old boy presented with a complaint of bleeding excessively since the second week of life. His problems started on the 8th day of life after traditional uvulectomy when he bled continuously for about 12 hours. However, the bleeding did not flow fast, controlled at home, and required no blood transfusion. Subsequently, he had been noticed to bleed excessively from minor injuries, although none resulted in a presentation to the hospital. There was a history of excessive bleeding in 4 of his elder brothers and a maternal uncle (Fig 1). The patient never had joint swellings, joint pains or deformities. There was no spontaneous bleeding from bodily orifices and no history of jaundice or previous blood transfusions.

Physical examination findings were unremarkable. Laboratory investigation results which included a full blood count and differential (revealed normal findings), liver function tests (normal findings), and clotting profile with mixing studies (Table 1) showed features suggestive of haemophilia B. A regime was outlined to commence prophylactic administration of recombinant FIX before circumcision.

2.2 Case 2

A 5- year old boy, 1st of a set of fraternal twins who was being managed in the cardiology clinic for pulmonary stenosis presented with a 3-year history of excessive bleeding from minor injuries. Three years prior to presentation he bled spontaneously and excessively from the buccal mucosa which warranted a transfusion of fresh whole blood before haemostasis was achieved. About 18 months prior to presentation he sustained labial lacerations with dental avulsions following a fall, bled excessively and was again transfused by dental surgeons. He was transfused a 3rd time 2 months prior to presentation following a domestic accident with associated bleeding from the buccal mucosa. There was no history of abnormal bleeding or any chronic illness in his twin brother. However, 4 of his brothers and a maternal uncle had a history of excessive bleeding (Fig 1). He had never suffered joint swellings, pains or deformities. And no history of jaundice was elicited.

Examination findings were normal and laboratory investigation results which included a full blood count and differential (revealed normal findings including a normal platelet count), liver function tests (normal findings), and clotting profile with mixing studies (Table 1) showed features suggestive of haemophilia B. A regime was outlined to commence prophylactic administration of recombinant FIX before circumcision.

2.3 Case 3

A 7-year old boy presented with recurrent excessive bleeding from minor cuts since infancy. He was noticed to have been bleeding for prolonged periods from minor injuries since

the first few months of life. About a year prior to presentation he bled torrentially for 3 days following circumcision. He was subsequently admitted to the hospital and transfused before haemostasis was accomplished. There was a family history of abnormal bleeding in 4 of his brothers and a maternal uncle. No history suggestive of joint swellings, pains or deformities. There was also no history suggestive of jaundice.

Findings on clinical examination were normal. Laboratory investigation results which included a full blood count and differential (revealed normal findings including a normal platelet count), liver function tests (normal findings), and clotting profile with mixing studies (Table 1) revealed features suggestive of haemophilia B.

2.4 Case 4

A 10-year old boy who had been bleeding excessively from minor injuries since infancy was brought by his parents along with 4 of his brothers to the POPD. About 3 years prior to presentation he was transfused with 3 units of blood following a circumcision done at home. There was no history of a major bleeding episode since then. There was also no prior history of spontaneous bleeding from bodily orifices. No joint swellings, pains or deformities, and no history suggestive of jaundice. Four of his brothers, as well as a maternal uncle had recurrent abnormal bleeding episodes.

Physical examination findings were unremarkable. The laboratory investigations which included a full blood count and differential (revealed normal findings including a normal platelet count), liver function tests (normal findings), and clotting profile with mixing studies (Table 1) showed features suggestive of haemophilia B.

2.5 Case 5

A 13-year old boy presented with a complaint of recurrent excessive bleeding since the 17th day of life. He was said to have had abnormal bleeding from his traditional uvulectomy site with associated haematemesis noticed 2 weeks after the procedure. Vomiting was associated with passage of blood clots and dark stools but did not warrant a blood transfusion. He also bled excessively after vaccinations. At the age of 1 year he bled abnormally following a minor bruise. Five years prior to presentation he bled excessively for 2 days following circumcision. The last bleeding episode at the time of presentation had occurred 1 day earlier following exfoliation of a molar tooth. Bleeding was eventually controlled at home after several hours. He had never been transfused prior to presentation. There was a positive history of abnormal bleeding in 4 of his younger brothers and a maternal uncle (Fig. 1). However, neither had he ever bled spontaneously from bodily orifices, nor had joint pains/swellings or deformities. He also had never been jaundiced.

Clinical examination findings were normal. The laboratory investigations which included a full blood count and differential (revealed normal findings including a normal platelet count), liver function tests (normal findings), and clotting profile with mixing studies (Table 1) showed features suggestive of haemophilia B.

Table 1. Coagulation profile of subjects

Patient	PT(control = 16seconds. Normal range= 11-16seconds)	APTT (control = 35seconds. Normal range=25-35 seconds)	APTT (patient's plasma+ FVIII deficient plasma)	APTT(patient's plasma + normal plasma)
Case 1	16	> 2 minutes	35 seconds	35 seconds
Case 2	16	> 2 minutes	35 seconds	35 seconds
Case 3	16	> 2 minutes	35 seconds	35 seconds
Case 4	16	> 2 minutes	35 seconds	35 seconds
Case 5	16	> 2 minutes	35 seconds	35 seconds

PT = prothrombin time, APTT = activated partial thromboplastin time, FVIII = factor VIII

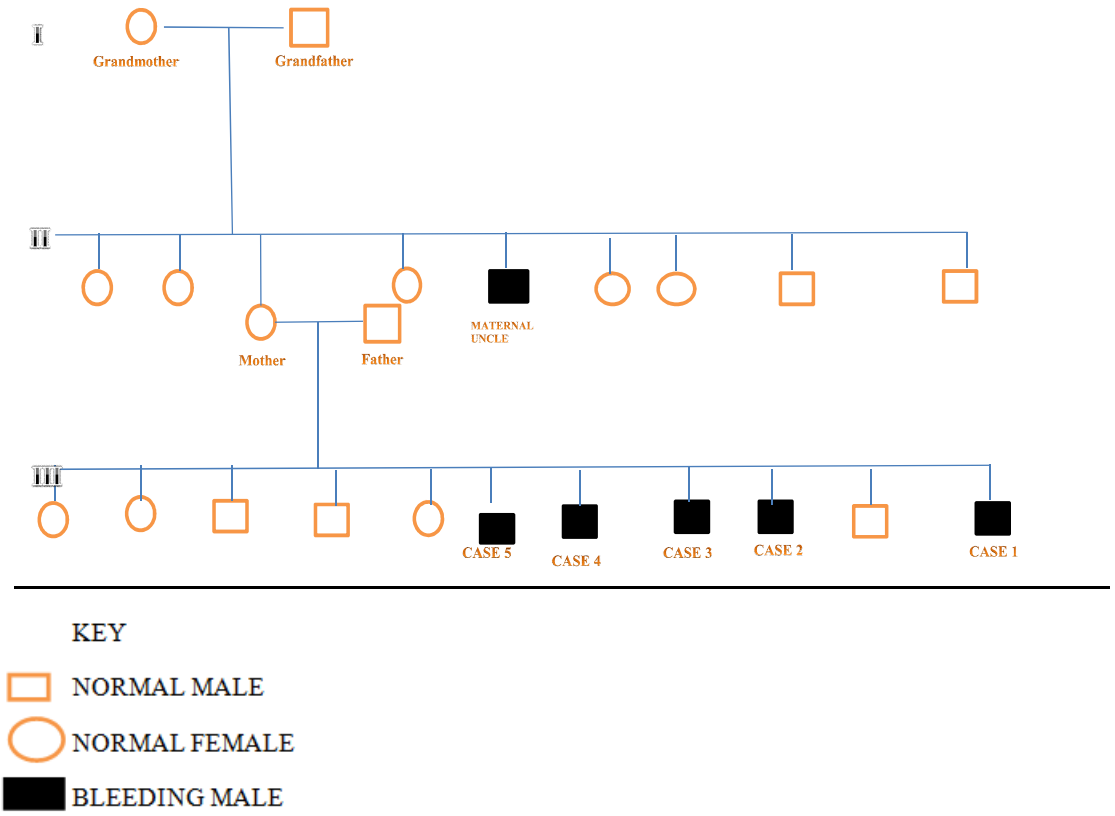

Fig. 1. Pedigree of the patients

3. DISCUSSION

The peculiarity in these cases is the large number of affected individuals in one family. This is made more remarkable by the fact that HB is extremely rare in Nigeria [6]. The reason for the relative rarity of HB in Nigeria is not known. However, it is recognized that the genetic mutations associated with HB are diversely distributed and often show variations between and across ethnic groups. This may account for the spread and unevenness in the clinical manifestations of the disease. [7] in HB missense mutations occur more often than null mutations providing biological proof that a less severe phenotype may be expected. Nonetheless, clinical evidence is often lacking in this regard as demonstrated in this family [8].

HB is inherited in an x-linked recessive fashion (acquired disease has been described) hence the 3 female siblings were not affected. Each female of a carrier mother has a 50% chance of being a carrier and the males a 50% chance of being affected [1]. In this family, it is highly probable that the maternal grandmother transmitted the genetic mutation to the mother of the index cases.

Laboratory diagnosis is made by demonstrating a prolongation of the activated partial thromboplastin time (APTT). The prothrombin time (PT), bleeding time (BT), and thrombin time (TT) are usually normal as demonstrated in these cases [1]. Full blood counts including platelet counts were also normal for all the patients. In the current report APTT was more than 3 times longer than the reference range in all the patients. This is often indicative of severe disease. Mixing studies conducted showed correction with both normal and FVIII deficient plasma in all the patients. This is highly suggestive of HB given that an x-linked transmission is highly likely here (Fig. 1). [1] Confirmation of diagnosis would require conduction of FIX assay. Assay levels are compared with that of a normal-pooled plasma standard regarded as having 100% activity. This corresponds to FIX U/ml. Values > 5% FIX activity are classified as mild disease, 1-5% as moderate and < 1% as severe disease [1]. The facilities for undertaking these investigations

were however not available to us. Other tests that may be done include, serum levels for other clotting factors as well as von Willebrand factor levels if FVIII and FIX are normal. Prenatal diagnosis is possible with chromosomal analysis of cells obtained by amniocentesis or chorionic villus sampling. This is not routinely done. On the other hand, identification of an affected male foetus of a carrier mother may present the rare opportunity for genetic counselling [2].

The differential diagnoses include other factor deficiencies (VIII, VII, V, X, XI and fibrinogen), platelet disorders and von Willebrand disease (VWD). VWD is autosomally inherited, mainly presents with mucocutaneous bleeding and may manifest with abnormal BT [9,10]. Platelet disorders often present with prolonged BT as well as abnormal platelet counts and/or function tests but they often have normal APTT [11]. Factor XI deficiency (haemophilia C) is a very rare autosomal recessively inherited coagulation disorder that seldom causes spontaneous bleeding. Yet in extremely severe cases may bleed into the mouth, nose and genitourinary tract post-surgery or injury. It may also present with menorrhagia [12,13]. Factor V deficiency is also autosomal recessive in inheritance and is frequently brought to notice by bleeding into the skin, epistaxis and intracranial haemorrhage. Affected persons may also exhibit prolonged PT and BT [14]. Factor VII deficiency is autosomal recessive in inheritance and very rare [15,16]. HA is hard to differentiate from HB on clinical

Table 2. Recommended doses for treatment of bleeding episodes in resource-limited settings [17]

Type of hemorrhage	Desired factor IX level (IU/DL)	Duration (days)
Joint	10–20	1–2, may be longer if response is inadequate
Superficial muscle/no neurovascular compromise (except iliopsoas)	10-20	2–3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with neurovascular injury, or substantial blood loss		
Initial	15-30	
Maintenance	10-20	3–5, sometimes longer as secondary prophylaxis during physiotherapy
CNS/head		
Initial	50–80	1-3
Maintenance	30–50	4–7
	20–40	8–14
Throat and neck		
Initial	30-50	1-3
Maintenance	10-20	4-7
Gastrointestinal		
Initial	30-50	1-3
Maintenance	10-20	4-7
Renal	15-30	3-5
Deep laceration	15-30	5-7
Major surgery		
Pre-op	50-70	
Post-op	30–40	1–3
	20–30	4–6
	10–20	7–14
Pre-op (minor surgery)	40-80	
Post-op (minor surgery)	20-50	1–5, depending on type of procedure

grounds only. However, mixing studies (as was done in these cases) and factor assays may help in making the distinction. [2]

The principal purpose of treatment of HB is to prevent and treat bleeding with the appropriate coagulation factor concentrate. [1,2,17] Hence we outlined a regimen for prophylaxis in these cases. Coagulation factor concentrates are high-priced and hence out of the reach of most Nigerians. Thus it was impracticable for this family to fund any form of treatment for these children. The managing team however, made contacts with a Non-Governmental Organization (whose primary mission is to support, educate and advocate for persons with bleeding disorders in Nigeria) to sustain a regimen of intermittent prophylaxis for the patients.

The recommended prophylactic dose for HB is 25-40IU/kg (Malmo protocol) or 15-30IU/kg (Utrecht protocol) given twice weekly intravenously. [17] The recommended doses for treatment of bleeding episodes in resource-limited settings are shown in Table 2. [17]

Other therapeutic agents that may be useful in the management of HB include fresh frozen plasma and cryoprecipitate. These are however, associated with infection-related complications. Tranexamic acid and epsilon aminocaproic acid may be valuable as adjunctive therapy. [2,17] Gene therapy is a prospective therapeutic option that has shown some success in clinical trials. [2]

4. CONCLUSION

HB though very rare may cluster in certain families. This underscores the need for genetic counseling and testing of relatives of affected individuals. The diagnostic challenges, unavailability as well as the high cost of coagulation factor concentrates in resource-poor settings remain significant obstacles for physicians and patients alike. This is more so since early commencement of prophylaxis has a positive impact on long-term prognosis.

CONSENT

Consent was obtained from the parents before writing this report.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

The authors are thankful to all those involved in the management of these patients.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zimmerman B, Valentino LA. Haemophilia: In Review. Pediatrics in Review. 2013; 34(7):289-95.
Available:http://pedsinreview.appublications.org
(Accessed 19 February 2018)
2. Dolan G, Benson G, Duffy A, Hermans C, Jimenez-Yuste V, Lambert T, et al. Haemophilia B: Where are we now and what does the future hold? Blood Reviews. 2018;32:52-60.
3. World Federation of Haemophilia. Report on annual global survey 2014: WFH Montreal; 2015.
Available:http://www1.wfh.org/publications/files/pdf.1627.pdf
(Accessed 20 February 2018)
4. World Federation of Haemophilia. Report on annual global survey 2016: WFH Montreal; 2017.
Available:http://www1.wfh.org/publications/files/pdf-1690.pdf
(Accessed 26 February 2018)
5. Biggs R, Douglas AS, macfarlane RG, Dacie JV, Pitney WR, Merskey C, et al. Christmas disease: A condition previously mistaken for haemophilia. Br Med J. 1952; 2:1378-82.
6. Stonebraker JS, Bolton-Maggs PH, Michael Soucie J, Walker I, Brooker M. A study of variations in the reported haemophilia B Prevalence around the World. Haemophilia. 2011;18:1-4.
7. Nawaz N, Hussain R, Masood K, Niazi G. Molecular basis of hemophilia B in Pakistan: Identification of two novel mutations. World J Med Sci. 2008;3(2):50-3.
8. Goodeve AC. Hemophilia B: molecular pathogenesis and mutation analysis. J Thromb Haemost. 2015;13(7): 1184-95.
9. Bowman M, Hopman WM, Rapson D, Lillicrap D, James P. The prevalence of symptomatic von Willebrand disease in

primary care practice. J Thromb Haemost. 2010;8(1):213-6.
10. Saders YV, Fijnvandraat K, Boender J, Mauser-Bunschoten EP, van der Bom JG, de Maris J, et al. Bleeding spectrum in children with moderate or severe von Willebrand disease: Relevance of pediatric-specific bleeding. Am J Hematol. 2015;90(12):1142-8.
11. Amesse LS, Pfaff-Amesse T, Gunning WT, Duff N, French II JA. Clinical and laboratory characteristics of adolescents with platelet-function disorders and heavy menstrual bleeding. Experimental Hematology & Oncology. 2013;2:3. Available:http://doi.org/10.1186/2162-3619-2-3.
(Accessed 22 February 2018)
12. Seligsohn U. Factor XI deficiency in humans. J Thromb Haemost. 2009;7(1): 84-7.
13. Asakai R, Chung DW, Davie EW, Seligsohn U. Factor XI deficiency in Ashkenazi Jews in Israel. N Engl J Med. 1991;325:153-8.
14. Delev D, Pavlova A, Heinz S, Seifried E, Oldenburg J. Factor 5 mutation profile in German patients with homozygous and heterozygous factor V deficiency. Haemophilia. 2009;15(5):1143-53.
15. Sacco S, Dragani A, Davi G, Carolei A. Four recurrent intracerebral haemorrhages. Cerebrovasc Dis. 2003; 16(4):435-6.
16. Alexander B, Goldstein R, Landwehr G, Cook CD. Congenital SPCA deficiency: A hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions. J Clin Invest. 1951;6:596-608.
17. World Federation of Haemophilia. Guidelines for the management of hemophilia. 2nd Ed. WFH Montreal; 2012. Available:http://www1.wfh.org/publications/files/pdf-1512.pdf.
(Accessed 26 February 2018)

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/24077