Scientific Research Publishing

Open Journal of Blood Diseases, 2023, 13, 148-159
https://www.scirp.org/journal/ojbd
ISSN Online: 2164-3199
ISSN Print: 2164-3180

Characterization of Bleeding and Laboratory Phenotype in Hemophilia A Carriers: A Cross-Sectional Study in Benin

Tatiana Baglo Agbodandé[1,2*], Alban Zohoun[1,2], Abdel Aziz Ouabi[1], Edwige Araba[1], Bienvenu Houssou[1], Romaric Massi[1], Charlotte Orou Guiwa[1], Ludovic Anani[2], Dorothée Kindé Gazard[1,2], Awa Oumar Touré Fall[3,4]

[1]Hematology Laboratory, National Teaching Hospital Hubert KoutoukouMaga of Cotonou, Cotonou, Benin
[2]Faculty of Health Sciences, University of Abomey-Calavi, Cotonou, Benin
[3]Hematology Laboratory of The Aristide le Dantec Hospital, Dakar, Senegal
[4]Pharmacy and Odontostomatology, Faculty of Medicine, Cheikh Anta Diop University of Dakar, Dakar, Senegal
Email: *tatianabag@yahoo.fr

How to cite this paper: Agbodandé, T.B., Zohoun, A., Ouabi, A.A., Araba, E., Houssou, B., Massi, R., Guiwa, C.O., Anani, L., Gazard, D.K. and Fall, A.O.T. (2023) Characterization of Bleeding and Laboratory Phenotype in Hemophilia A Carriers: A Cross-Sectional Study in Benin. *Open Journal of Blood Diseases*, **13**, 148-159.
https://doi.org/10.4236/ojbd.2023.134017

Received: October 2, 2023
Accepted: December 11, 2023
Published: December 14, 2023

Abstract

Background: In Africa, hemophilia is underdiagnosed and carriers have long been considered free from bleeding symptoms. However, recent research has begun to reveal hemostatic abnormalities and bleeding manifestations in carriers of hemophilia A, particularly due to excessive inactivation of normal X chromosomes. **Objective:** To describe the bleeding symptoms and hemostatic abnormalities in carriers of hemophilia A (HA) in Benin. **Methods:** This study was conducted as a prospective cross-sectional investigation between April 2021 to March 2022. The study population consisted of identified through pedigrees of persons with hemophilia A being treated in various hospitals in Benin. Data were collected through interviews conducted by trained physician and each carrier underwent a biological workup. **Results:** A total of 71 hemophilia A carriers were included and 38 of whom were obligatory carriers. Thirty-one carriers (43.7%) reported abnormal bleeding symptoms. Menorrhagia has (71%) being the most important manifestation, followed by bleeding during or after childbirth (45.2%). Among the 71 carriers, 45 were of reproductive age. Of whom 22 (48.8%) had a Higham score exceeding 100. Activated partial thromboplastin time was prolonged in 7 carriers (9.9%). The mean activity factor VIII:C (FVIII:C) levels were 68.8 ± 34.9 IU/dL. The average FVIII:C level in obligatory carriers was 56.9% and among potential carriers, the average FVIII:C level was higher at 80.4%. However twelve female carriers (16.9%) had FVIII:C levels < 40%. The FVIII:C/FvWAg ratio was below 0.7 in 73.2% of female drivers. Obligatory carriers (p = 0.00003) and FVIII;

C/FvWAg ratio < 0.7 (p = 0.003) were statistically associated with abnormal bleeding symptoms, while blood group O (p = 0.0002) and FVIII/FvWAg ratio < 0.7 (p = 0.0016) were associated with a higher risk of menorrhagia. **Conclusion:** In Benin, carriers of haemophilia A present bleeding symptoms and haemostatic abnormalities. Further studies on a larger number of carriers are needed to better characterize and manage these patients.

Keywords

Carrriers of Hemophilia A, Bleeding Symptoms, APTT, Factor VIII, FVIII:C/FvW:Ag ratio

1. Introduction

Hemophilia A is hereditary leeding disorder caused by a mutation in the factor VIII genes, resulting in deficient and/or defective production of factor VIII (FVIII) [1]. As a recessive X-linked disease, the HA phenotype is manifested in hemizygous males, whereas heterozygous females (carriers) are usually asymptomatic [2]. Prevalence per 100 000 males was 17.1 cases for all severities of hemophilia A, and 24.6 case per 100 000 males at birth [3] with a similar incidence across ethnic populations [4]. According to most estimates, for each male with haemophilia, there are approximately 2.7 to 5 potential female carriers [5]. For many years, studies and recommendations did not specifically focus on carriers of hemophilia but on all women with von Willebrand disease. However the risk of bleeding in carriers of hemophilia is important. Some case series showed joint bleeds, prolonged bleeding after tonsillectomy, tooth extractions, or postpartum bleeding. [6] [7] [8]. In fact, in France, according to a study conducted at a regional university hospital, 35.9% of carriers experienced spontaneous bleeding (nosebleeds and/or bruises and/or gum bleeding), 29% had bleeding due to minor trauma and 30% had abnormal bleeding following surgery [7]. In Senegal, 18.1% of carriers of hemophilia had abnormal bleeding, and the most common being menorrhagia (13.6%), nose bleeds (9%), and gum bleeding (9%) [9]. It is the same in Côte d'Ivoire, where excessive or prolonged menstrual bleeding was found in 31% of carriers of hemophilia [10]. Furthermore, 3.5% to 4% of male newborns to carriers of hemophilia had intracranial bleeding [11]. So, determining the carrier status of hemophilia is an integral part of the overall management of hemophilia. Considering that Africa represents less than 3% of patients identified as having hemophilia, and only 2% of those use clotting factor concentrates (CFCs) for treatment [12], it is crucial to incorporate carrier screening into the practices of hemophilia treatment centers in order to prevent bleeding symptoms in these carriers of hemophilia, provide genetic counseling during pregnancy, and screen male newborns with hemophilia with intracranial haemorrhage or before their circumcision.

The aim of this study was screen for carriers of hemophilia A in Bénin and

describe the bleeding symptoms and hemostatic abnormalities

2. Material and Methods

2.1. Participants

The study population comprised mothers, sisters, daughters, cousins, and maternal aunts of persons with hemophilia A who were being monitored in various centers. They were identified as carriers after analyzing the family tree of each persons with hemophilia A under observation. Two types of carriers were distinguished: potential carriers and obligatory carriers. Obligatory carriers were defined as daughters of fathers with hemophilia, women who had multiple sons with hemophilia in separate births, or women who had a sick son and a confirmed hemophilic relative on their maternal side of the family. Potential carriers, on the other hand, were women with a hemophilic relative on the maternal side but had not yet given birth to a sick son or women who, despite the absence of a family history of hemophilia, had given birth to a son with hemophilia. Each pedigree was cross-verified with several family members to ensure its completeness. Excluded from the study were non-biological mothers of persons with hemophilia (PwH), sisters of PwH born to different fathers and mothers, women from families with acquired hemophilia or other constitutional bleeding disorders, women who use traditional reusable towels, carriers with jaundiced, hemolyzed, or lipemic plasma at the time of diagnosis, as well as those with a fibrinogen level between 0.6 g/L and 6 g/L The size of the study population was determined after systematic enrollment of all carriers of hemophilia A identified after review of the pedigrees of the 101 PwH followed in the hemophilia treatment center and after application of the study's inclusion and non-inclusion criteria.

2.2. Study Design

Between Avril 2021 and Mars 2022, we invited women identified as carriers of hemophilia A, to participate in this study conducted in three hospitals: in the South of Benin, at the University Clinic for Blood Disorders (CUMAS) located at the Hubert Koutoukou Maga National Hospital and University Center (CNHU-HKM) in Cotonou; in the Center, at the Zou-Collines Departmental Hospital Center (CHD) situated in the central region; and at the Borgou-Alibori Departmental University Hospital Center (CHUD) located in Parakou in the North of Benin. As for the laboratory tests, they were conducted at the hematology laboratory of CNHU-HKM in Cotonou. Candidates were recruited via pedigree of persons with hemophilia (PWHs) followed-up at the hospitals in Benin. A telephone directory was subsequently compiled, and the study participants were contacted via phone. Following the acquisition of their informed consent, these individuals were invited to visit one of the three aforementioned hospitals to take part in the study.

Data collected during interviews with the participants included socio-demo-

graphic information, medical history, surgical history, obstetric history, and details regarding bleeding episodes. The Higham score were employed during data collection to assess the risk of menorrhagia. It is an objective measure for quantifying menstrual blood loss in reproductive-age women. It assigns a score based on an evaluation of menstrual losses, taking into account the extent of staining on sanitary products used by the women and the number of sanitary products used. When the Higham score is sensitivity and specificity exceed 100 it used to identify menorrhagia.

2.3. Sampling and Biological Analysis

Following the completion of the data collection questionnaire, each carrier of hemophilia A was subjected to blood sampling. Samples collected into two tubes: one containing sodium citrate and the other containing ethylene diamine tetra acetic acid tripotassium. After double centrifugation of the citrated samples at 2500G for 15 minutes, with plasma decantation in between, the resulting platelet-poor plasmas were divided into cryotubes and frozen at −20˚C. These samples were then transported to the hematology laboratory of CNHU HKM in Cotonou using dry ice.

In hematology laboratory, the activated partial thromboplastin time (APTT) and the functional levels of factor VIII were determined using a chronometric method on a semi-automatic coagulometer with optical detection (CA 104 Sysmex). For each series of factor VIII assays, a calibration curve was constructed, and both normal and pathological control samples were processed under the same conditions as those applied to the carriers' plasma. Moreover, the von Willebrand factor antigen level was determined using an immunological method on the Mini Vidas automated system from Biomérieux, and blood grouping within the ABO and RH1 antigens was conducted through microfiltration technique.

Internal quality controls results were systematically validated and all results obtained biological validation

2.4. Data Processing and Statistical Analysis

All numerical data were reported as mean ± standard deviation along with the minimum and maximum values. Categorical data were expressed as percentages. Pearson's Chi-2 test was employed to compare different groups in the study. A significance level of $p < 0.05$ was considered as the threshold for statistical significance, indicating that results were considered statistically significant when the p-value was less than 0.05. The statistical analysis was conducted using a computer based statistical program Stata version 15.

2.5. Ethical Considerations

The study protocol received approval from the Local Ethics Committee for Biomedical Research at the University of Parakou (CLERB-UP) under the reference number N°464/CLERB-UP/P/SP/R/SA on August 9, 2021. The survey was con-

ducted in accordance with the ethical guidelines outlined by this committee, including voluntary participation, the ability for participants to withdraw from the study at any point, ensuring anonymity, and maintaining data confidentiality. Also the carriers provided written informed consent for participating in the study. In the case of carriers who were minors, consent from one of their parents or legal guardians was obtained before their inclusion.

3. Results

A total of 71 carriers of hemophilia A were included in the study.

3.1. Socio-Demographic Characteristics

All the carriers included in the study were aged between 1 and 73 years, with a median age of 23 years and a mean age of 23.2 ± 15 years. Approximately 63 carriers (88.7%) had some level of education, with 4.8% having attended nursery school, 34.9% having completed primary education, 44.4% having secondary education and 15.9% universary education. Regarding socio-professional categories, 8.5% were in the preschool age group, followed by students (39.4%), shopkeepers (21.1%), and employee (14.1%). It is worth noting that 11.3% of the carriers were artisans and 5.6% were homemakers. The distribution of carriers by ethnic groups revealed that 68.4% of the included women were Fon, followed by Adja (15.2%), Yoruba (10.1%) and Bariba (2.5%). The Dendi, Ottamari, and YoaLokpa ethnic groups were the least represented (1.3% each). Concerning the departments of Benin in which the carriers resided, 38% of 71 included carriers lived in the Littoral region of Benin. Other highly represented departments included Atlantique (18.3%) and Borgou (16.9%), while the department with the fewest recruited carriers in the study was Ouémé (12.7%), Zou (12.7%) and Collines (1.4%). Table 1 illustrates the socio-demographic characteristics of the study population.

3.2. Family History

During the study, family interviews and pedigree analysis allowed for the identification of 41 obligatory carriers and 30 potential carriers. Regarding the severity of hemophilia, 36 carriers (50.7%) had a family history of moderate hemophilia A, and 35 had a family history of severe hemophilia A (49.3%). No carriers of mild hemophilia were identified during the study.

Among the 71 carriers studied, 36 carriers (50.7%) reported having one or more brothers with hemophilia. The median number of brothers with hemophilia per carrier was 1, ranging from 1 and 3 brothers. Among these 36 carriers, 25 of them (69.4%) had a single brother with hemophilia, 10 carriers (27.8%) had two, and 1 carrier (2.8%) had 3 hemophilic brothers. Furthermore other than brothers, 21 of 71 carriers included (29.6%) had another family member with hemophilia, including cousins (76.2%), uncles (28.6%), nephews (47.6%), and fathers (33.3%). One carrier had grandfather with hemophilia, and another one

Table 1. Socio-demographic characteristics of carriers of hemophilia A.

Socio-demographic Characteristics		Number	Percentage
Socio-linguistic group	Fons	46	68.4%
	Adja	12	15.2%
	Yoruba	8	10.1%
	Bariba	2	2.5%
	Ottamari	1	1.3%
	YoaLokpa	1	1.3%
	Dendi	1	1.3%
Home department	Littoral	27	38.0%
	Atlantique	13	18.3%
	Borgou	12	16.9%
	Ouémé	9	12.7%
	Zou	9	12.7%
	Collines	1	1.4%
Socio-professional activity	Artisans	8	11.3%
	Employee	10	14.1%
	students	28	39.4%
	shopkeepers	15	21.1%
	Menagère	4	5.6%
	Preschool age group	6	8.5%
Level of education	Number of carriers instructed	63	
	Nursery school	3	4.8%
	Primary education	22	34.9%
	Secondary education	28	44.4%
	Universary education	10	15.9%

had grandchild with hemophilia. Among the 71 carriers included, 30 had children with hemophilia (42.3%). The mean number of children with hemophilia per carrier was 1.8 ± 1.00 children with extremes between 1 and 4.

3.3. Personal History

In the study population, 16 carriers (22.5%) had medical histories that included epigastric pain (31.3%), asthma (31.3%), and high blood pressure (31.3%). Hemorrhoidal disease (12.5%) and migraine (12.5%) were the least frequently reported medical histories among carriers. Long-term medication use was found in 6 carriers (8.5%), including three on hormonal contraception, two on antihypertensive medication, and one on bronchodilators.

3.4. Bleeding Symptoms

In the study population, 31 carriers (43.7%) reported having abnormal bleeding symptoms. The most frequently reported symptoms were menorrhagia (71%), postpartum hemorrhage (45.2%), gastrointestinal bleeding (19.4%), post-operative bleeding (12.9%) and gingivorragy (9.7%). The least common bleeding symptoms included epistaxis (3.2%), bleeding from wounds after minor trauma (3.2%), and hemarthrosis (3.2%). Hematuria, hematomas, and bleeding from the nervous system weren't observed in the carriers during this study. Among the 71 hemophilia A carriers, 45 were of reproductive age. Of whom 22 (48.8%) had a Higham score exceeding 100, indicating menorrhagia. The average Higham score in this study was 144.4 ± 143.3, with a median of 78.00 and a range from 2 to 603.

3.5. Laboratory Results

During the study, the activated partial thromboplastin time (APTT) was prolonged in 7 carriers, representing 9,9% of the study population. The average factor VIII:C level was 68.8 ± 34.9 IU/dL with ranging from 5.5 to 150.00 IU/dL. The average FVIII:C level in obligatory carriers was 56.9%, with extremes of 5.5% and 127.9%. Among potential carriers, the average FVIII:C level was higher at 80.4% with extremes of 11.5% and 132%. It is worth noting that out of the 71 carriers of hemophilia A, 12 had a factor VIII level < 40%, indicating a frequency of 16.9% for female hemophilia. Of these 12 female with hemophilia A, eight were obligatory carriers and four were potential carriers. The distribution of these female according to the severity of hemophilia revealed 11 cases of mild hemophilia and one case of moderate hemophilia.

Furthermore, the FVIII/FvWAg ratio was less than 0.7 in 52 carriers, accounting for a frequency of 73.2% of the study population. They include 32 obligatory carriers and 20 potential carriers. Regarding the distribution of carriers by ABO blood group, those with blood group O were the most common (53.5%), followed by blood group A (29.6%), B (14.1%), and AB (2.8%).

The study of factors favoring the occurrence of abnormal bleeding in carriers, regardless of the type, revealed that the status of being an obligatory carrier ($p = 0.00003$) and a FVIII/FvWAg ratio < 0.7 ($p = 0.003$) were associated with the occurrence of abnormal bleeding. Of the 19 womens with a FVIII:C/FvWAg ratio < 0.7, eight had abnormal bleeding symptoms without statistically significant relationship. However, prolonged APTT, a family history of hemophilia, the presence of a family history of severe hemophilia and blood group O were not statistically associated with the occurrence of abnormal bleeding in carriers. Furthermore, in this study, blood group O ($p = 0.000$) and a FVIII/FvWAg ratio < 0.7 ($p = 0.0016$) were associated with a higher risk of menorrhagia. **Table 2** and **Table 3** show the factors associated respectively with development of abnormal bleeding symptoms in carriers of haemophilia A in Benin and with hypermenorrhoea in these carriers.

Table 2. Factors associated with the occurrence of abnormal bleeding in carriers of hemophilia A in Benin.

	Abnormal bleeding symptoms		
	Oui	Non	
	N (%)	N (%)	Pvalue
Prolonged APTT	1 (14.3%)	6 (85.7%)	2.20
Obligatory carriers	23 (41.5%)	38 (56.5%)	15.21
Severe familial hemophilia A	16 (44.7%)	19 (55.3%)	1.14
Carriers who has children with hemophilia A	18 (61.3%)	12 (38.7%)	0.33
Family history of hemophilia	18 (46.2%)	16 (53.8)	4.98
Blood type O	16 (40.5%)	22 (59.5%)	0.25
Ratio FVIII:C/FVW:Ag < 0.7	20 (38.5%)	32 (61.5%)	**0.003**
FVIII:C < 40%	6 (50%)	6 (50%)	0.73

Table 3. Factors associated with the occurrence of menorrhagia in carriers of hemophilia A in Benin.

	Menorrhagia		
	Oui	Non	P value
	N (%)	N (%)	
Prolonged APTT	1 (33.3%)	2(66.7%)	0.344
Blood type O	11 (50.0%)	11 (50.0%)	**0.000**
Obligatory carriers	21 (65.6%)	11 (34.4%)	1.19
Severe familial hemophilia A	13 (52.0%)	12 (48.0%)	0.092
Ratio FVIII/FvW:Ag < 0.7	16 (50%)	16 (50%)	**0.00166**
FVIII:C < 40%	6 (66.7%)	3 (33.3%)	1.28

4. Discussion

During the study, carriers of hemophilia were recruited after analyzing the family trees of PwHs followed in Cotonou, Abomey and Parakou. This recruitment method has been used by several authors, making carrier screening more effective [9] [10]. In the absence of molecular diagnostic availability in developing countries, pedigrees become a cost-effective and useful tool for carrier screening in cases of familial hemophilia [10] [13] [14]. However, some pedigrees can be very large and complex to establish due to the African context where families are generally very large, and many deaths may have occurred without a specific cause, hence the importance of determining the FVIIIc/FvW:Ag ratio. When this ratio is less than 0.7, it is a good marker for screening carriers of hemophilia A, with a sensitivity of 82.8% and a specificity of 96.6%, according to Ki-Young Yoo [15]. In this study, 52 carriers of hemophilia A out of 71 had a ratio < 0.7, accounting for a frequency of 73.2% of carriers in this study population. However,

it isn't uncommon to see carriers with a ratio > 0.7.

Considering that the literature suggests there are approximately 2.7 to 5 potential female carriers for each male with haemophilia [5] [16] and considering that the number of PwH regularly monitored in Benin is 100 [17], the expected number of carriers in this study was between 270 and 500 carriers, but only 71 were included. This difference could be explained by the lack of financial means for many carriers, preventing them from traveling to the collection sites. Additionally, the lack of awareness of the hemorrhagic risks associated with carrier status and the benefits of knowing one's status could also explain the lack of interest among carriers in getting screened. This lack of information has been observed by several other authors in Africa and India.

Furthermore, approximately 43.7% of the included carriers had hemorrhagic symptoms, with menorrhagia (71%) being the most common. Other symptoms included postpartum hemorrhage (45.2%), gastrointestinal bleeding (19.4%) and post-operative bleeding (12.9%). These results are consistent with those found in many countries such as Côte d'Ivoire, Senegal or France [7] [9] [18]. However, despite the presence of these hemorrhagic manifestations, none of the included carriers, even those with a family history of hemophilia, had ever undergone factor assay to tailor their management. This indicates a lack of awareness among healthcare professionals regarding the management of carrier females.

The distribution of carriers based on the severity of hemophilia's family revealed that only carriers of severe and moderate hemophilia were represented in the study. This may be related to the difficulty in identifying mild hemophiliacs due to their often subtle, post-traumatic hemorrhagic symptoms. However, the severity of familial hemophilia doesn't influence the carrier's level of clotting factor VIII. In this study, 12 carriers of hemophilia A had factor VIII levels <40%, indicating a diagnosis of female hemophilia [19]. Hemophilia is transmitted by women, known as carriers, through a recessive X-linked mechanism. However, various mechanisms can explain the occurrence of hemophilia in women, such as lyonization of the dominant X chromosome over the normal X gene, Turner syndrome, X-autosome translocation, transmission of two X chromosomes carrying an anomaly, or maternal disomy of the X chromosome [8] [20] [21] [22].

The screening of carriers during this study has allowed for the establishment of a cohort at the hemophilia treatment center in Cotonou to follow these women. All of these women received genetic counseling and were informed about their carrier status and the associated risks that could occur [13]. However the small number of people included in the study can be explained by the specific context of African countries where hemophilia is under diagnosed. The means of diagnostic are difficult to access due to the cost of analysis.

5. Conclusion

The results of this study show that hemophilia carriers have increased bleeding

tendencies with low FVIII levels and a FVIIIC/FvW ratio < 0.7. It is therefore important to promote greater awareness of hemophilia carrier status through sensitization of family members of hemophiliacs and training of health workers. However, further studies on a larger study population will be needed to better characterize the female carriers of hemophilia in Benin, and among them, identify women living with hemophilia in order to adapt their care and monitoring.

Authors' Contributions

All authors contributed to the paper. All authors helped to conceptualise ideas, interpret the findings and contributed to the revision of the manuscript.

Acknowledgements

The authors are thankful whole-heartedly to Benin Hemophilia Association, Franco-African Alliance for Hemophilia Treatment (AFATH) and World Federation of Hemophilia (WFH).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Jayandharan, G., Srivastava, A. and Srivastava, A. (2012) Role of Molecular Genetics in Hemophilia: From Diagnosis to Therapy. *Seminars in Thrombosis and Hemostasis*, **38**, 64-78. https://doi.org/10.1055/s-0031-1300953

[2] Radic, C.P., Rossetti, L.C., Abelleyro, M.M., Tetzlaff, T., Candela, M., Neme, D., *et al*. (2015) Phenotype—Genotype Correlations in Hemophilia A Carriers Are Consistent with the Binary Role of the Phase between F8 and X-Chromosome Inactivation. *Journal of Thrombosis and Haemostasis*, **13**, 530-539. https://doi.org/10.1111/jth.12854

[3] Iorio, A., Stonebraker, J.S., Chambost, H., Makris, M., Coffin, D., Herr, C., *et al*. (2019) Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-Analytic Approach Using National Registries. *Annals of Internal Medicine*, **171**, 540-546. https://doi.org/10.7326/M19-1208

[4] Stonebraker, J.S., Bolton-Maggs, P.H., Soucie, J.M., Walker, I. and Brooker, M. (2010) A Study of Variations in the Reported Haemophilia a Prevalence around the World. *Haemophilia*, **16**, 20-32. https://doi.org/10.1111/j.1365-2516.2009.02127.x

[5] Hermans, C. and Kulkarni, R. (2018) Women with Bleeding Disorders. *Haemophilia*, **24**, 29-36. https://doi.org/10.1111/hae.13502

[6] Hirayama, A.B., Silva, A.K.C.D., Rocha, J.S. and Roberti, M.D.R.F. (2019) Prevalence of Symptoms in Hemophilia Carriers in Comparison with the General Population: A Systematic Review. *Hematology, Transfusion and Cell Therapy*, **41**, 349-355. https://doi.org/10.1016/j.htct.2019.02.006

[7] Sauguet, P., Aguilar-Martinez, P., Boulot, P., Escudié, J.B., Schved, J.F. and Biron-Andréani, C. (2015) Carriers of Haemophilia: Experience of a French University Hospital. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction*, **44**,

565-576. https://doi.org/10.1016/j.jgyn.2014.08.009

[8] Plug, I., Mauser-Bunschoten, E.P., Bröcker-Vriends, A.H., van Amstel, H.K., van der Bom, J.G., van Diemen-Homan, J.E., *et al*. (2006) Bleeding in Carriers of Hemophilia. *Blood*, **108**, 52-56. https://doi.org/10.1182/blood-2005-09-3879

[9] Seck, M., Faye, B.F., Sall, A., Sy, D., Touré, S.A., Dieng, N., *et al*. (2017) Bleeding Risk Assessment in Hemophilia A Carriers from Dakar, Senegal. *Blood Coagulation & Fibrinolysis*, **28**, 642-645. https://doi.org/10.1097/MBC.0000000000000653

[10] Lambert, C., Meité, N.D., Sanogo, I., Lobet, S., Adjambri, E., Eeckhoudt, S., *et al*. (2019) Hemophilia Carrier's Awareness, Diagnosis, and Management in Emerging Countries : A Cross-Sectional Study in Côte d'Ivoire (Ivory Coast). *Orphanet Journal of Rare Diseases*, **14**, Article No. 26. https://doi.org/10.1186/s13023-019-1005-9

[11] Street, A.M., Ljung, R. and Lavery, S.A. (2008) Management of Carriers and Babies with Haemophilia. *Haemophilia*, **14**, 181-187. https://doi.org/10.1111/j.1365-2516.2008.01721.x

[12] Diop, S., Haffar, A., Mahlangu, J., Chami, I., Kitchen, S. and Pierce, G. (2019) Improving Access to Hemophilia Care in Sub-Saharan Africa by Capacity Building. *Blood Advances*, **3**, 1-4. https://doi.org/10.1182/bloodadvances.2019GS121537

[13] Ljung, R. and Tedgård, U. (2003) Genetic Counseling of Hemophilia Carriers. *Seminars in Thrombosis and Hemostasis*, **29**, 31-36. https://doi.org/10.1055/s-2003-37937

[14] Mbanya, D.N., Diop, S., Ndoumba Mintya, A.N. and El Kiaby, M. (2021) Hemophilia Care in Africa: Status and Challenges. *Transfusion Clinique et Biologique*, **28**, 158-162. https://doi.org/10.1016/j.tracli.2021.01.008

[15] Yoo, K.Y., Jung, S.Y., Choi, J.Y., Park, H.R. and Park, Y.S. (2022) Clinical Application of Factor VIII: C to VWF: Ag Ratio for the Screening of Haemophilia A Carriers. *Journal of Clinical Medicine*, **11**, Article 1686. https://doi.org/10.3390/jcm11061686

[16] Naicker, T., Aldous, C. and Thejpal, R. (2016) Haemophilia: A Disease of Women as Well. *South African Journal of Child Health*, **10**, 29-32. https://doi.org/10.7196/SAJCH.2016.v10i1.961

[17] Baglo-Agbodandé, T., Zohoun, A., Agbeille, F., Abdelbakhit, D., Houssou, B., Massi, R., *et al*. (2022) Seroprevalence of HIV, HBV and HCV Viral Markers in Hemophiliacs in Benin. Les cahiers du CBRST Médecine et santé publique, **21**, 176-189.

[18] Bernard, W., Lambert, C., Henrard, S. and Hermans, C. (2018) Screening of Haemophilia Carriers in Moderate and Severe Haemophilia A and B: Prevalence and Determinants. *Haemophilia*, **24**, e142-e144. https://doi.org/10.1111/hae.13468

[19] Van Galen, K.P.M., d'Oiron, R., James, P., Abdul-Kadir, R., Kouides, P.A., Kulkarni Rand., *et al*. (2021) A New Hemophilia Carrier Nomenclature to Define Hemophilia in Women and Girls: Communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis*, **19**, 1883-1887. https://doi.org/10.1111/jth.15397

[20] Miesbach, W., Alesci, S., Geisen, C. and Oldenburg, J. (2011) Association between Phenotype and Genotype in Carriers of Haemophilia A. *Haemophilia*, **17**, 246-251. https://doi.org/10.1111/j.1365-2516.2010.02426.x

[21] Shoukat, H.M.H., Ghous, G., Tarar, Z.I., Shoukat, M.M. and Ajmal, N. (2020) Skewed Inactivation of X Chromosome : A Cause of Hemophilia Manifestation in Carrier Females. *Cureus*, **12**, e11216. https://doi.org/10.7759/cureus.11216

[22] Pavlova, A., Brondke, H., Müsebeck, J., Pollmann, H., Srivastava, A. and Oldenburg,

J. (2009) Molecular Mechanisms Underlying Hemophilia A Phenotype in Seven Females. *Journal of Thrombosis and Haemostasis*, **7**, 976-982.
https://doi.org/10.1111/j.1538-7836.2009.03346.x