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Inhibitor epidemiology and genetic-related risk factors in people with haemophilia from Côte d'Ivoire

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Abstract

Introduction: In Sub-Saharan Africa, inhibitor prevalence data in people with haemophilia (PWH) are scarce, as are data on genetic or treatment-related risk factors.

Aims and methods: We performed a prospective study on PWH from Côte d'Ivoire to collect data into inhibitor prevalence, create a database of haemophilia genotypes, establish correlations between inhibitor presence and genetic variants identified amongst Ivoirian PWHs and evaluate exposure to CFCs.

Results: The study included 54 unrelated participants (43 severe, four moderate, two mild haemophilia A and five severe haemophilia B). PWH were treated on-demand with various product types for short periods, non-intensively, and using low-dose regimens. We reported similar distributions of intron 22 inversions (39.5%), point pathogenic variants (32.6%) and rearrangements in Ivoirian severe haemophilia A patients versus non-African ethnic groups. The haplotypes H1 (29.6%), H2 (36.3%) and H3 (34.1%) frequencies in haemophilia A were consistent with results published on African populations. We identified eight new causal variants. An inhibitor was found in 12% of haemophilia A patients previously exposed to replacement therapies. Among PWH with inhibitors, 66.7% had a positive intron 22 inversion and 50% the H1 haplotype.

Conclusion: This study provides original data on molecular diagnosis of haemophilia, inhibitor prevalence and risk factors for inhibitor development previously associated with inhibitors in Côte d'Ivoire. The low inhibitor prevalence likely reflects the limited exposure to replacement therapy in Côte d'Ivoire. Further larger, multicentric and international studies are needed to gain more insight on inhibitor incidence and risk factors in African PWH.

KEYWORDS

Côte d'Ivoire, haemophilia, inhibitor, Sub-Saharan African country

1 | INTRODUCTION

Despite tremendous improvements in haemophilia treatment over the last decades, the development of an inhibitor remains the greatest complication for people with haemophilia (PWH)[1] who are treated with clotting factor concentrates (CFC). The management of inhibitors is even more challenging in resources-constrained countries due to limited access to CFC, no regular access to prophylaxis treatment, immune tolerance therapy or bypassing agents.[2]

The onset of inhibitors remains complex, modulated by genetic and environmental factors that are not yet fully understood. This phenomenon has primarily been studied in Caucasian populations from developed countries. In haemophilia A [HA] patients, an important predictor of inhibitor development is the F*8* gene pathogenic variant, followed by disease severity and positive family history.[1] Intron 22 inversion, the most common F*8* variant, displays an inhibitor incidence of 21% in severe HA, while large deletions involving multiple domains shown to exhibit an 88% proportion of inhibitor formation.[3] PWH of African heritage in North America bear an increased risk of inhibitor development, up to twice that of Causasians.[4-6] The mechanisms accounting for these ethnic differences remain unclear. As the haemophilia genetic causing variant spectrum does not differ among ethnic groups, other explanations for the higher incidence of inhibitors in black PWH may be related to genetic variations on immunoregulatory genes or environmental factor related to the modalities of replacement treatment.[4,7] Although Viel and colleagues found that differences in Factor VIII (FVIII) haplotype among black patients and recombinant FVIII products could explain this difference,[5] findings from other large cohort studies did not support this hypothesis.[8,9]

Treatment-related risk factors for inhibitor development were extensively studied in previously untreated patients,[10-12] and along with the number of exposure days (ED), the concept of danger days has recently been introduced in the pathophysiology of inhibitors.[13] Several environmental factors influence the risk of inhibitor development, such as age and reason for the first infusion, the treatment intensity (dose of FVIII) and the setting (bleeding, trauma or surgery).[10,13] As access to CFCs widely varies worldwide with no or extremely limited access in most developing countries,[2,14] the impact of treatment-related factors in resource-constraints countries could differ but this was not well studied so far.

In Sub-Saharan African countries, data on inhibitor prevalence and causal haemophilia variants are scarce.[15-18] In 2015, a World Federation of Hemophilia (WFH) twinning programme was established between the Yopougon Hemophilia Treatment Center (HTC) in Abidjan, Côte d'Ivoire, and the international HTC of the *Cliniques universitaires Saint-Luc* in Brussels, Belgium. In this setting, we studied genotypes, inhibitor prevalence, genetic-related risk factors and exposition to CFCs among Ivoirian PWHs. The study was conducted to determine the background inhibitor prevalence just prior to initiating a low-dose prophylaxis programme in children with haemophilia, rendered possible by improved access to CFC through WFH donation programmes.

2 | STUDY OBJECTIVES

We initiated a prospective study in Ivoirian PWHs designed to (I) assess the inhibitor prevalence; (II) create a database (including haplotypes) of haemophilia genotypes; (III) examine the correlation between inhibitor prevalence and causal haemophilia variants/haplotypes; (IV) collect data on exposure to CFCs.

3 | PATIENTS AND METHODS

3.1 | Patients

The study was conducted from January to December 2017 at the HTC of Yopougon, located in Abidjan. This is the unique HTC in Côte d'Ivoire, and the only place where PWHs are provided with CFCs, exclusively issued from humanitarian aid. We invited all identified 81 PWHs belonging to 57 different families, registered and regularly followed at the Yopougon HTC, to participate. It is worth noting that this cohort represents the entire Ivoirian haemophilia population identified and reported by the WFH at the time of the initiation of the study.[14] The study protocol was approved by the Ivoirian Ethics Committee (*Comité National d'Ethique de la Recherche)* and registered at ClinicalTrials.gov (NCT03054662). In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants and their parents or legal guardians.

3.2 | Data collection

Of note is that prior to 2016, there were no data available on either inhibitors or ED in Ivoirian PWH. Since January 2016, a locally adapted logbook has been provided to each PWH (or their parents) to record data on annual bleeding rate including treated and untreated bleeds, ED and CFC consumption.[19] Demographics on the Ivoirian PWH were collected for the first time in 2017, as reported elsewhere.[20] It was, thus, impossible to obtain data on cumulative life-long ED, with the collection of objective data on ED limited to the 2016-2017 evaluation period. CFC consumption and ED were calculated using systematic analysis, based on a combination of the data recorded in the PWH logbooks, on regular follow-up consultations, and in CFC donation registry.

3.3 | Methods

FVIII and FIX activities were measured on site with the one-stage assay method on a semi-automated coagulometer (Option 4 Plus; Biomerieux) using human plasma immunodepleted of FVIII and FIX (HemosIL, Werfen). A systematic inhibitor screening was performed on site with oversight from the Belgian partner by mixing studies (at two different occasions, within 3 months-during twinning visits) and, if appropriate, with an inhibitor titration through the Nijmegen-Bethesda method.[21]

Genomic DNA extraction was performed using a QIAamp DNA Blood Midi Kit (Qiagen), following the manufacturer's instructions. Molecular analysis was performed in the Genetic and Molecular Biology Laboratory, Cochin Hospital, Paris, France. F*8* intron 22 inversion was detected by performing long-range polymerase chain reaction (PCR) in a two-tube PCR assay according to the Liu et al method, along with some modifications such as optimized the PCR conditions (initial denaturing step at 95°C for 10 minutes followed

by 30 cycles of denaturing at 95°C for 30 seconds, annealing at 57°C for 1 minutes, extension at 72°C for 1.5 minutes and a final extension step at 72°C for 10 minutes.[22] F*8* intron 1 was detected using a PCR protocol described by Bagnall et al.[23] All known functional *F8* and *F9* coding regions, including their immediate 5′ and 3′ flanking splice junctions, promotor and 3′-genomic DNA sequences, were sequenced through next-generation sequencing (NGS) using an Ion PGM System (ThermoFisher Scientific). Two detection tools, a variant caller, Polydiag and Nextgene were used to detect variants (point variants and copy-number variations). The nomenclature of the *F8* and *F9* gene variants relied on cDNA reference sequences NM_000132.3 and NM_000133.3 and protein reference sequences NP_000123.1 and NP_000124.1, respectively, in accordance with the recommendations of the Human Genome Variation Society (http://www.hgvs.org/mutnomen/). Variants were identified by searching against the Human Gene Mutation professional database and haemophilia A/B locus-specific variant databases (http://www.factorviii-db.org/, http://hemobase.com, and http://www.cdc.gov/ncbddd/hemophilia/champs.html). Structural impacts on protein function and potential splice effects of novel missense variants were evaluated by different bioinformatics tools (Table 1).[24] Data from non-synonymous single nucleotide polymorphisms (SNPs)—rs35383156 (c.1508G > A; Arg503/484His) in exon 10, both rs2228152 (c.2383A > G; Arg795/776Gly) and rs1800291 (c.3780C > G; Asp1260/1241Glu) in exon 14, and rs1800297 (c.6769A > G; Met2257/2238Val) in exon 25—were collected during exon sequencing to draw F*8* haplotypes named H1 through H6, as described by Viel.[5] All variants were interpreted according to the consensus guidelines of both the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[25]

Finally, we compared our results on prevalence of inhibitor and genetic-related risk factors for inhibitor development (if available with those obtained from other Sub-Saharan African countries (Cameroon,[18] Senegal[15,17] and South Africa[16]) and reported in peer-reviewed journals.

4 | RESULTS

Overall, 57 PWH were included in the study, though we analysed complete data from only 54 unrelated PWH, as DNA could not be extracted from three samples. The cohort comprised 49 PWH with HA (43 severe, four moderate and two mild) and five PWH with severe haemophilia B [HB]. The median [range] age at evaluation was 12 [1-64] years. Spontaneous cases, defined as cases with no other PWH (alive or deceased) within the family, were reported in 33.3% (n = 18) of participants. Participants were geographically clustered (50.0%) around Abidjan, where the HTC is located, but half of them were also living in remote areas of the country.

Results of the F*8* and F*9* genetic PWH analyses were summarized in Table 1. In severe HA patients, intron 22 inversion was the most recurrent variant (39.5%; n = 17), followed by a single nucleotide variant (nonsense (16.2%; n = 7), missense (14.0%; n = 6), nonsense and splicing variant (2.3%; n = 1)) identified in 32.6% (n = 14). Frameshift causal variants and large rearrangements (deletion/duplication) were found in 14.0% (n = 6) and 7.0% (n = 3), respectively, while one 9pb in-frame deletion was identified in 2.3% (n = 1) of the severe HA patients. SNPs analysis results (haplotypes H1 to H6) were available in 44 HA PWHs, with a frequency of 36.3% (n = 16) for H2, 34.1% (n = 15) for H3 and 29.6% (n = 13) for H1. No participant exhibited H4, H5 or H6 haplotypes. Of the 28 unique variants identified in our HA cohort, seven new variants were previously unreported. In the HB patients, only one variant was still unreported. According to both the guidelines and in silico pathogenicity prediction, these variants were predicted to affect FVIII and FIX protein function.

We obtained detailed data on self-reported CFC consumption and indication for infusion in 85% of PWH in 2016 and 98% of PWH in 2017, as logbook completion improved over time since its introduction. In 2016, 24% (n = 13) of PWH, with a median [range] age of 10 [1-63] years, had never been exposed to CFC in their lifetime, and the rest were treated on-demand. At the time of inclusion in 2017, 7.4% (n = 4) of PWH had still never been treated with CFC (median [range] age of 5.5 [1-17] years). Of the PWH without exposure to CFCs, 53% were living in the Abidjan district. PWH were provided with CFCs at the HTC and infused either at the HTC or in a clinic located close to their living area. The median [range] and mean ± SD ED were 4 [0-35] days and 6.5 ± 8.0 days in 2016, and 5 [0-27] days and 6.5 ± 6.6 days in 2017, respectively. Indication for CFC administration was exclusively on-demand therapy, with one infusion per bleed on average in 84%. The CFC amount was usually low (10-20 IU/Kg). No surgery was performed during the 2016-2017 period. Based on these findings, we considered our population as having a low rate of danger days. Substitutive hemostatic treatment included recombinant standard, extended half-life products and plasma-derived concentrates from different manufacturers. The CFCs were often used alternately, depending on the donations' availability and supply.

An inhibitor against FVIII was detected in 12% (n = 6) of the 50 previously exposed PWH (five severe forms and one moderate). Their median age [range] was 16 years [7-23 years]; one patient exhibited a high-titre inhibitor (6.8 BU/mL) and another one a transient inhibitor, while another patient had a sibling with an inhibitor history. With regard to the genetics of the PWH with inhibitors, 66.7% (n = 4) had a positive intron 22 inversion, with the following haplotype distribution: 50% (n = 3) had H1, 33% (n = 2) had H3 and 17% (n = 1) had H2.

The prevalence result comparison with other Sub-Saharan African countries is detailed in Table 2. To better reflect the haemophilia context of each country, we added data from the 2016 WFH Report on Annual Hemophilia Survey (RAGS) indicating the number of PWH and the annual consumption of FVIII (IU per capita) among those countries.

5 | DISCUSSION

Data on inhibitors and molecular diagnosis in PWH are scarce in Sub-Saharan Africa.[15,16] This is the first prospective study in

TABLE 1 Distribution of F8 and F9 haemophilia causing variants among the 54 Ivoirian people with haemophilia

	Mutation					
Phenotype	Exon/intron	Observed cDNA change (HGVS notation)	Predicted protein change (HGVS notation)	Mutation Effect	Haplotype	Inhibitor
Haemophilia A						
Severe	2	c.209_212delTTGT	p.Phe70*	Frameshift	H2	
Severe	2-10	c.144-?_1537+?dup	**	Large duplication	UNK	
Severe	**3-26**	**c.266-?_*1788+?dup**	**	**Large duplication**	H2	
Severe	4	c.536C > T	p.Ser179Phe	Missense	H3	
Severe	7	c.788+?_1009-?del	**	Large deletion	H2	YES
Severe	8	c.1172G > A	p.Arg391His	Missense	H1	
Severe	9	c.1336C > T	p.Arg446*	Nonsense	H1	
Mild	13	c.1930T > G	p.Leu644Val	Missense	H2	
Severe	**13**	**c.1921T > G**	**p.Phe641Val**	**Missense**	H1	
Mild	**13**	**c.2027C > A**	**p.Thr676Asn**	**Missense**	UNK	
Severe	**14**	**c.[4738_4753del;4754_4771dup]**	**p.Leu158fs*41**	**Frameshift**	H1	
Severe	14	c.4825dup	p.Thr1609Asnfs*4	Frameshift	H3	
Severe	14	c.4382delA	p.Asn1461Thrfs*4	Frameshift	H2	
Severe	14	c.4379dupA	p.Asn1460Lysfs*2	Frameshift	H1	
Severe	14	c.2702C > G (n = 2)	p.Ser901*	Nonsense	H2	
Severe	14	c.2933C > A	p.Ser978*	Nonsense	UNK	
Severe	**15**	**c.5322_5330del9**	**p.Leu1777_Gly1779del**	**In-Frame**	UNK	
Severe	16	c.5409_5412delCTTC	p.Phe1804Ilefs*66	Frameshift	H3	
Severe	16	c.5575G > C	p.Asp1859His	Missense	H3	
Moderate	Intron 16	c.5587-2A > G	**	Splicing	H1	YES
Severe	17	c.5766C > A	p.Cys1922*	Nonsense	H1	
Severe	18	c.5825G > T	p.Gly1942Val	Missense	H2	
Moderate	**18**	**c.5852T > C**	**p.Leu1951Ser**	**Missense**	UNK	
Severe	18	c.5953C > T	p.Arg1985*	Nonsense	H3	
Severe	**Intron 19**	**c.6115 + 2T>A**	**	**Splicing**	H2	
Severe	22	c.6403C > T	p.Arg2135*	Nonsense	H2	
Severe	Intron 22	Inv 22 (n = 17)		Inversion	H2 (n = 5) H3 (n = 7) H1 (n = 5)	YES (n = 4)
Moderate	23	c.6506G > A	p.Arg2169His	Missense	H1	
Severe	23	c.6544C > T	p.Arg2182Cys	Missense	H3	
Moderate	26	c.7021G > A	p.Glu2341Lys	Missense	H3	
Severe	NO mutation	NA (n = 2)	NA	NA	H3 (n = 1) H2 (n = 1)	
Haemophilia B						
Severe	5	c.423C > A	p.Cys141*	Nonsense		
Severe	**7**	**c.779_780insTAGAG**	**p.Lys260Asnfs*6**	**Frameshift**		
Severe	8	c.1135C > G	p.Arg379Gly	Missense		
Severe	All exons	c.-29-?_*1437+?del	NA	Deletion		
Severe	No material	NA	NA	NA		

New mutations are in bold.

NA, not applicable, UNK, unknown, HGVS, Human Genome Variation Society.

**RNA supplementary analysis required.

TABLE 2 Comparison of results obtained from the literature on the prevalence of inhibitors and genetic-related risk factors (if available) in other Sub-Saharan countries

Country	Cameroon[14]	Côte d'Ivoire	Senegal[11]	Senegal[15]	South Africa[12]
Type of haemophilia	HA + HB	HA + HB	HA	HA	HA
Number of PWH	42	54	22	50	116 Black[a]
Number of severe HA	25	44	21	NR	108
Prevalence of inhibitors	19%	12%	22.7%	20%	18%
Identified variants	NR	51/54	21/22	NR	100%
Inversion intron22[b]	NR	38.6%	38%	NR	40%
New variants	NR	8	5	NR	UNK
Study of haplotypes available	NO	YES	NO	NO	YES
Number of PWH identified in the country[c]	176	81	193	193	2206
Mean use of FVIII in IU per capita[c]	0.052	0.032	0.118	0.118	1.049
Year of NMO creation	2008	2008	1996	1996	1970

Abbreviations: HA, Hemophilia A; HB, haemophilia B; NMO, National Member Organization recognized by the World Federation of Hemophilia; NR, Not reported; PWH, people with Hemophilia; UNK, Unknown.

[a]The study also included white PWH, with a prevalence of inhibitors of 13% among the total population, but we only considered the results of the black PWH.

[b]Among severe HA patients.

[c]Data from the 2016 World Federation of Hemophilia Report on Annual Global Survey.[14]

Côte d'Ivoire, providing data on inhibitor prevalence, molecular diagnosis (including haplotypes) and exposure to CFCs. Despite a population of over 23 million inhabitants,[26] only 81 PWH were reported in 2016 by the WFH RAGS in Côte d'Ivoire.[14] Although small in size, our cohort was thus representative, with data obtained from 95% of the 57 Ivoirian PWH families identified at the time of the study and participants coming from various regions of the country. Age and severity distributions were in line with other African countries with low economic income and restricted access to haemophilia care.[17,18]

We reported a similar distribution of intron 22 inversions, point variants and rearrangements compared to non-African ethnic groups. This distribution had previously been reported in studies from Senegal and South Africa.[15,16] The frequency of H1-H3 haplotypes in our patients was consistent with data published from African populations.[5,16] We identified eight new variants, which were registered into the EAHAD Variant Database. No haemophilia causing variant was found in 3.7% (n = 2) of participants. This is consistent with the 2%-4% sensitivity in detecting causal variants, reported in the literature.[27] These results support the view that the molecular diagnostic algorithms applied in Europe and North America are applicable in Africa.

The prevalence of inhibitors in our study was slightly lower than that in studies performed in Senegal,[15,17] Cameroon[18] and Black PWH from South Africa.[16] This difference should be interpreted with caution and take into account the small size of the study cohorts, the variable recruitment methodology and the limited number of publications. Little is actually known on inhibitors in Sub-Saharan Africa that represents 48 countries and with only 19 of those having established national member organizations reporting to the Annual Global WFH Survey in 2017. One could assume that the difference in inhibitors prevalence is related to variations of CFC consumption. However, CFC consumption (IU per capita) in Cameroon and Senegal is very low and comparable to Côte d'Ivoire.[14] Another hypothesis could be a longer standing experience in haemophilia care in some of these countries resulting in a larger number of PWH identified and more PWH exposed to CFCs.[14]

We investigated the association between the causal variants, haplotypes and presence of an inhibitor. According to published data, intron 22 inversion is an intermediate risk factor for inhibitor development.[3] In our population, intron 22 inversion was present in two-thirds of PWH, whereas only one participant had a high-risk inhibitor haemophilia causing variant (large deletion). Fifty percent (n = 3) of PWH with an inhibitor displayed the H1 haplotype. While absent in Caucasian and Chinese populations, the H3 haplotype was initially suggested to be associated with a higher risk for inhibitor development.[5] This hypothesis has however not been confirmed in subsequent work performed in Afro-American PWHs.[8,9] Lochan et al examined F*8* gene haplotypes, ethnicity and inhibitor development in black and white intron 22 positive PWH from South Africa. Although results suggested that the H3/H5 haplotype group had a higher inhibitor incidence than the H1/H2 haplotype group, the size sample was too small to reach statistical significance. On the other hand, the authors found a significant association between inhibitor development and ethnicity as well as with F*8* gene variant type.[16] The haplotype distribution among Ivoirian PWH with inhibitors was discrepant with the black South African PWH, but this cannot be interpreted because of the small number of inhibitors positive participants in both studies. Based on these data, ethnicity and F*8* pathogenic variant type actually emerge as the strongest genetic risk factor in the onset of inhibitors.

Regarding the environmental risk factors likely to impact inhibitor development, several aspects should be considered when interpreting our findings. First, in Côte d'Ivoire, the 2016 WFH Global Survey reported a mean per capita FVIII and FIX use of 0.032 and 0.005, respectively,[14] with CFC supplied exclusively by humanitarian aid since 2008. This accounts for the very low ED number in our population, with an important proportion of previously untreated patients (PUPs) having a 'zero' risk of developing inhibitors, with the remaining majority composed of minimally treated patients (MTPs). Decrease in number and age of PUPs between 2016 and 2017 can be explained by the progressive increase in WFH donation programmes. Secondly, we observed an extremely low rate of danger days that could trigger the inhibitor development (*eg* neither surgery nor prolonged or intensive treatments), as well as the use of low-dose regimens of CFCs. However, as CFCs are supplied exclusively by humanitarian aid, a higher inhibitor level could have been expected, given the variations of product types and sources used, which are dependent on the availability and manufacturers' supply of the donation programmes. From the Sippet study, little is known about the influence of the product source in African PWH, as only four participants from South Africa were randomized in this study.[12]

Our study has several limitations. First, the number of PWH with inhibitors was very small. Secondly, there are only data on the inhibitor prevalence and exposure data over a limited period, with no point of comparison available in Côte d'Ivoire, and only little data from other African countries. We have no data on cumulative exposure since birth and on inhibitor incidence, as this was impossible to assess. However, with the systematic use of logbooks and regular screening for inhibitors, we plan to better assess inhibitor incidence and treatment-related risk factors in Ivoirian PWH in the future. Finally, information on the familial history of inhibitors is still lacking, as regular screening only started in 2016 in Côte d'Ivoire. Therefore, further larger studies and participation to international registries are needed in the upcoming years to confirm these data and improve knowledge on inhibitors in Côte d'Ivoire and by extension to other Sub-Saharan African countries.

6 | CONCLUSIONS

Our study displays original data on molecular diagnosis of haemophilia, inhibitor prevalence and prevalence of risk factors associated with inhibitors in Côte d'Ivoire. The background inhibitor prevalence in Côte d'Ivoire is still low, possibly but not only reflecting the limited exposure to available replacement therapies in PWH, who predominantly harbour the intron 22 inversion and H1 haplotype. Yet, these data are critical to evaluate the impact on inhibitor incidence/prevalence of improved replacement therapy access through donations in Ivoirian PWHs. In the future, pooling data from other African countries and participation to large, multicentric and international studies would be of great value to gain more insight on inhibitor incidence and risk factor development in African PWH.

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DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict of interest or bias.

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