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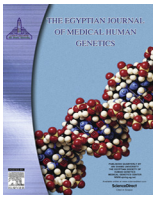

Review

Determinants and modifiers of bleeding phenotypes in haemophilia-A: General and tropical perspectives

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ABSTRACT

Haemophilia-A is an X-linked recessive bleeding disorder characterized by deficiency of FVIII. Although severity of haemophilia is largely determined by the extent to which different mutations abolish FVIII production, the overall phenotypic variations among haemophiliacs is determined by a combination of several other factors, which range from general to tropical factors on the one hand, and from genetic to immunologic and infective factors on the other hand. Determinants and modifiers of haemophilic bleeding phenotypes are important predictors of prognosis. However, tropical determinants of haemophilic bleeding phenotypes are virtually ignored because majority of haemophilia research originated from developed non-tropical countries. The aim of this paper is to present a balanced review of the haemophilic bleeding phenotypes from general and tropical perspectives. Hence, we present a concisely updated comprehensive review of the pathophysiologic and clinical significance of general vis-à-vis tropical determinants and modifiers of haemophilic bleeding phenotypes from genetic, immunologic and infective perspectives. Understanding of general phenotypic determinants such as FVIII gene mutations, immunological (inhibitors) and infective (e.g. hepatitis and HIV) complications, classical thrombophilias (e.g. FV-Leiden) and non-classical thrombophilias (e.g. non-O blood groups) will throw more light into the mechanisms by which some tropical prothrombotic gene mutations (such as sickle β-globin gene) and certain chronic tropical pro-haemorrhagic parasitic infections (such as urinary and gastrointestinal helminthiasis) may modify frequency, intensity and pattern of bleeding among haemophiliacs in the tropics. The clinical significance of iron deficiency within the context of helminthiasis and haemophilia is also reviewed. More research is needed to determine the precise effect of non-classical thrombophilias such as sickling disorders and ABO blood groups on haemophilic bleeding phenotypes. Meanwhile, tropical healthcare workers should incorporate regular screening and treatment for common pro-haemorrhagic parasitic diseases and iron deficiency into standard of care for management of haemophilia.

Contents

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1. Introduction

Haemophilia-A is an X-linked recessive disorder characterized by deficiency of clotting factor VIII (FVIII) [1]. Inadequate FVIII levels result in insufficient formation of the intrinsic tenase complex (FIXa, FVIIIa, Ca^{2+} and Phospholipids) which subsequently leads to reduced generation of thrombin with impaired fibrin deposition and clot formation [1]. However, the bleeding disorder in haemophilia-A is not merely a reflection of reduced clot formation due to low FVIII activity. The pathophysiology of the bleeding diathesis in haemophilia-A is in fact the result of an interplay between a defective procoagulant process and a deregulated fibrinolytic process. Bleeding is triggered either by identifiable trauma (referred to as trauma-induced bleeding) or unidentifiable trauma (referred to as spontaneous bleeding), noting that these so-called 'spontaneous bleeds' are usually caused by some form of trivial unrecognizable trauma [2]. As expected from physiological perspective, the local tissue damage and vascular endothelial injury at the site of bleeding would simultaneously activate the intrinsic pathway (via contact activation) [3], the extrinsic pathway (via release of tissue factor) [3] and the fibrinolytic pathway (via release of tissue plasminogen activator) [4]. Moreover, the activity of fibrinolytic pathway, which is triggered by contact-activated FXIIa [5] as well as the tissue plasminogen activator [4], proceeds normally. In contradistinction to the fibrinolytic pathway, the procoagulant pathways are hindered by the summation of a series of haemostatic anomalies, which is initiated by the low FVIII activity followed by reduced initial thrombin generation via the intrinsic pathway [6]. The next haemostatic anomaly is the failure of the extrinsic pathway to adequately compensate for the insufficient thrombin generation by intrinsic pathway [6]. The inadequate compensation by the extrinsic pathway leads to the absence of sufficient burst of thrombin, which is necessary for activation of thrombin activable fibrinolysis inhibitor (TAFI) [6]. This persistent lack of sufficient thrombin burst ultimately leads to sub-optimal activation of TAFI with a resultant defective down regulation of fibrinolysis [6]. Therefore, the haemostatic failure in haemophilia-A can be viewed as a vicious combination of poor fibrin clot formation on the one hand and an up-regulated fibrinolysis on the other hand [6]. Moreover, the production of tissue factor pathway inhibitor (TFPI) by synovial cells and chondrocytes leads to localized intra-articular attenuation of the extrinsic pathway, which consequently aggravates bleeding tendency within the joints [7]. Other local aggravators of haemophilic bleeding include plasminogen activators produced by the kidneys [8] and the prostate [9], which aggravate urinary tract bleeding; and the fibrinolytic effect of saliva, which aggravate bleeding within the oral cavity [10].

Although the overall severity of haemophilia is largely determined by the extent to which different mutations abolish functional FVIII production, the overall phenotypic variations among haemophiliacs is determined by additional confounding effects of several other factors, which range from general to tropical factors on one hand, and from genetic to immunologic and infective factors on the other hand. Determinants and modifiers of haemophilic bleeding phenotypes are important predictors of bleeding rates and clotting factor consumption, both of which are vital indices in the clinical process of individual patient prognostication. Hence, a thorough understanding and identification of these determinants and modifiers are paramount for clinicians and other medical personnel that are involved in the management of haemophilia. However, tropical determinants of haemophilic bleeding phenotypes are virtually ignored in the literature because the majority of haemophilia research originated from developed non-tropical countries. Because of the high prevalence of poverty, malnutrition and infectious diseases in tropical countries, haemophiliacs living in the tropics face peculiar challenges that are not present in the developed regions of the world. Therefore, the aimed of this paper is to present a balanced review of the haemophilic bleeding phenotypes from general and tropical perspectives in order to highlight the peculiarities of the tropical haemophiliacs. In this paper we present a concisely updated comprehensive review of the pathophysiologic and clinical significance of general vis-à-vis tropical determinants and modifiers of bleeding phenotypes in haemophilia-A from genetic, immunologic and infective perspectives. The clinical significance of iron deficiency and its treatment within the context of haemophilia is also reviewed.

2. General determinants and modifiers of haemophilic bleeding phenotypes

Several factors are known to be important determinants and modifiers of bleeding phenotypes of patients with haemophilia-A. These factors include FVIII gene mutations and inhibitors, as well as classical and non-classical thrombophilic conditions as outlined in Table 1.

2.1. FVIII gene mutation

The severity of haemophilia is largely determined by the extent to which different mutations abolish functional FVIII production. The clinical severity of the disease and bleeding rates significantly correlate with residual FVIII levels, which is classified as severe (FVIII level <1%), moderate (FVIII level 1–5%) or mild (FVIII level 6–40%) [11]. Severe haemophilia, which is characterized by high bleeding rates and frequent occurrence of apparently spontaneous bleeding episodes, is typically associated with the null mutations due to inversions, insertions, deletions, non-sense and mis-sense mutations [11]. Whereas mild and moderate haemophilia, characterized by lower rates of bleeding that is usually provoked by recognizable traumatic events, are usually associated with non-null mutations due to less severe forms of mis-sense, single-nucleotide deletions or splicing error mutations [11]. There is a direct correlation between disease severity, bleeding rate and the risk of iron deficiency among haemophiliacs [12]. A previous study from Nigeria revealed that in comparison with non-severe haemophiliacs, severe haemophiliacs had higher frequency and relative risk of iron deficiency, a finding that was attributable to the higher bleeding rates among severe haemophiliacs [12]. There is no doubt that the FVIII gene mutation is the most important determinant of disease severity and bleeding phenotype in patients with haemophilia-A [11]. However, the phenotypic heterogeneity of haemophilia-A is multi-factorial, which includes

Table 1
General determinants and modifiers of haemophilic bleeding phenotypes.

Determinant/modifier	Basic pathophysiology	Predictable effect on bleeding phenotype
FVIII gene mutation	(a) Null mutations: Lack of FVIII production (b) Non-null mutations: Reduced production of FVIII	(a) Null mutations: severe haemophilia (b) Non-null mutations: non-severe haemophilia
Treatment Related Complications	(a) FVIII Inhibitor: Neutralization of FVIII (b) Viral Chronic Liver Disease: Multiple Coagulation Factor deficiency (c) HIV: Thrombocytopenia	Higher Risk of all types of bleeding
FV-Leiden G1691A mutation	Reduced inactivation of FVa-Leiden by Protein-C: Enhanced PROTHOMBINASE activity with greater thrombin generation	Lower Risk of all types of bleeding
Protein-C gene mutation (Protein-C deficiency)	Reduced inactivation of FVa and FVIIIa: Enhanced PROTHOMBINASE and TENASE activity with greater thrombin generation.	Lower Risk of all types of bleeding
Protein-S gene mutation (Protein-S deficiency)	Reduced inactivation of FVa and FVIIIa: Enhanced PROTHOMBINASE and TENASE activity with greater thrombin generation.	Lower Risk of all types of bleeding
Antithrombin-III gene mutation (Antithrombin-III deficiency)	Reduced inactivation of thrombin: Enhanced thrombin generation.	Lower Risk of all types of bleeding
Prothrombin G20210A mutation	Hyper-prothrombinemia: Enhanced thrombin generation	Lower Risk of all types of bleeding
Methylenetetrahydrofolate reductase gene C677T mutation	Hyper-homocysteinemia: Global activation of coagulation pathways	Lower Risk of all types of bleeding
PAI-1 mutation	Decreased Plasminogen Activation: Hypo-fibrinolysis with decreased fibrin degradation	Lower Risk of all types of bleeding
ABO Blood Group Genes	(a) Non-O Blood Group: Higher vWF levels with higher baseline FVIII level. (b) Blood Group-O: Lower vWF levels with lower baseline FVIII level.	(a) Non-O Blood Group: Lower risk of all types of bleeding (b) Blood Group-O: Higher risk of all types of bleeding

not only the type of FVIII gene mutation but also the coinheritance of several other genetic factors that can potentially aggravate or ameliorate the bleeding tendency as outlined in the subsequent sections of this review.

2.2. Treatment related complications

Because haemophilia is a lifelong bleeding diathesis, patients are repeatedly exposed to blood and blood products. Consequently, patients may be further burdened with immunological and infective complications of product transfusion, which may include the development of FVIII inhibitor and the acquisition of transfusion transmissible infections such hepatitis and HIV.

2.2.1. Immunological complication: FVIII inhibitors

The clinical significance of FVIII inhibitors is linked to their ability to neutralize FVIII as a result of which affected patients have increased risk, frequency and severity of bleeding, with a concomitant sub-optimal response to factor replacement and a corresponding increase in the demand for factor concentrate that ultimately raises the intensity and cost of treatment [13]. The risk of developing FVIII Inhibitor is mainly related to the type of FVIII mutation [11]. It has been demonstrated that FVIII gene mutations that are associated with the absence of the gene product (null mutations) confer higher risk for inhibitor development, while mutations that are associated with the presence of the gene product (non-null mutations), even at very low level, confer a lower risk for inhibitor development [11]. Interestingly, the type of FVIII mutation also significantly influences the therapeutic response to Immune tolerance induction (ITI) [14]. It appears that there is an inverse correlation between the risk of inhibitor development and success rate of ITI [14]. This is because it has been demonstrated that FVIII mutations that confer higher risk of inhibitor development were also significantly associated with lower success rates of ITI therapy than that seen in patients with lower-risk FVIII mutations [14]. Apart from FVIII gene mutations, other genetic factors also contribute to the risk of developing inhibitors (Table 2). These factors include a positive family history of inhibitors, ethnicity, and certain polymorphisms in immune modulatory genes that may increase (eg IL-10 and TNF-alpha) or decrease (eg CTLA-4) the risk of developing inhibitor [11,15]. The relatively higher incidence of polymorphisms in the immune modulatory genes for IL-10 and TNF-alpha may partly explain the higher risk of inhibitor development in blacks and other non-Caucasian haemophiliacs [16]. Moreover, the role of ethnicity and FVIII haplotype variation between donor and recipient in the development of FVIII inhibitors has been studied among black haemophiliacs living in Caucasian communities [17]. The study suggested that mismatched factor VIII replacement therapy is a risk factor for the development of FVIII antibodies in black patients receiving human FVIII derived from Caucasian plasma or rFVIII derived from genetic template obtained from Caucasian genomes [17]. Moreover, the ABO blood groups play important roles in the risk of inhibitor development as the inheritance of non-O blood groups appear to confer a higher relative risk of developing FVIII inhibitor as detailed in subsequent section (section A3b).

Table 2
Risk Factors for FVIII Inhibitors Among Patients with Haemophilia-A.

Genetic risk factors
Type of FVIII Gene Mutation
Ethnic and Racial Mismatch
FVIII Haplotype Variation
Family History of Inhibitor in Siblings
Inheritance of Non-O Blood Group
Non-genetic risk factors
Non-Genetic Immune Modulators
(a) Infections and Vaccinations
(b) Accidental and Surgical Trauma
Age at onset of FVIII Therapy/Prophylaxis
Modality of FVIII administration: Continuous Infusions
Intensity of FVIII Therapy/Prophylaxis
Type of FVIII product and its Immunogenicity

The observation of discordance in inhibitor risks among hemophilic monozygotic twins [18] suggest the existence of non-genetic factors in the development of FVIII inhibitors (Table 2). It has been suggested that exposure to FVIII in the presence of non-genetic immune modulators such as active infections or vaccinations, as well as tissue damage due to accidental or surgical trauma have the potential to generate signals that would activate the antigen-presenting cells and increase the risk of developing FVIII inhibitors

[11,19]. Moreover, treatment-related cofactors, such as early age at first exposure to FVIII, type of FVIII product and its inherent immunogenicity, as well as the intensity of treatment, especially when administered by continuous infusion may significantly increase the risk of inhibitor development [18,20,21].

2.2.2. Infective complications: viral hepatitis and HIV

Transfusion of blood or blood products is associated with the risks of contracting blood born infections such as hepatitis (B and C) and HIV. The risks of acquiring these infections in the developed countries have been greatly minimized as a result of modernization of blood safety protocols with efficient donor screening procedures, effective viral inactivation techniques and production of recombinant blood products [22]. However, infection risks are particularly high in the tropics where the prevalence of blood born infections is high, donor screening procedures are inadequate, viral inactivation techniques are virtually absent, and recombinant blood products are unavailable [23]. Both chronic viral hepatitis and HIV infections can negatively affect the bleeding rates and clinical phenotypes of infected haemophiliacs by causing chronic liver disease with multiple coagulation factor deficiencies [24] and HIV-associated thrombocytopenia [25]. In view of their prothrombotic side effects, HIV protease inhibitors [26] may be particularly advantageous for HIV-infected haemophiliacs. This is because the protease inhibitors will certainly treat the HIV infection and also predictably reduce the haemophilic bleeding rate as a paradoxical 'benefit' of their prothrombotic side effects [26]. Hence, physicians involved in the management of HIV infections may consider taking this point into perspective when 'tailoring' drug regimen for HIV-infected haemophiliacs especially for cases that are complicated by thrombocytopenia.

2.3. Coinheritance of thrombophilia genes

Coinheritance of a number of prothrombotic gene mutations resulting in milder bleeding phenotypes in severe haemophiliacs have been described. These mutations include a wide spectrum of genetic polymorphisms, including classical thrombophilias such as the FV-Leiden G1691A, Protein-C, Protein-S, Antithrombin-III, Prothrombin G20210A, Methylenetetrahydrofolate reductase (MTHFR) C677T and Plasminogen Activator Inhibitor-1 (PAI-1) mutations, as well as the non-classical thrombophilias such as the non-O blood groups [11].

2.3.1. Coinheritance of classical thrombophilia

From pathophysiologic perspectives, coinheritance of thrombophilic genes would modify the haemophilic thrombo-haemorrhagic balance by reducing bleeding tendencies and positively influencing the phenotypic expression of haemophilia. A classical example of this scenario is the coinheritance of FV-Leiden mutation. Under normal physiological conditions, the intrinsic anticoagulant Protein-C pathway (encompassing Protein-C, Protein-S and Thrombomodulin) inactivates excess FVa and FVIIIa in order to maintain a normal thrombo-haemorrhagic balance [27]. However, the mutant FVa-Leiden is resistant to inactivation by the Protein-C pathway [28]. Hence, coinheritance of FV-Leiden with haemophilia leads to relatively high FVa-Leiden activity, which enhances the prothrombinase complex, and subsequently shifts the thrombo-haemorrhagic balance in favour of greater thrombin generation with a significant reduction in bleeding rates [28]. Moreover, it should be appreciated that mutations that affect any component (eg Protein-C or protein-S deficiency) of the intrinsic anticoagulant Protein-C pathway would lead to impaired inactivation of even normal FVa and FVIIIa [27]. Consequently, such mutations (eg Protein-C or protein-S deficiency) enhance both the tenase and prothrombinase complexes, which would subsequently increase thrombin generation and predictably reduce bleeding rates in haemophiliacs [29,30]. Animal haemostatic model suggests that Antithrombin-III deficiency mutation, which causes reduction in thrombin neutralization, is also associated with lower haemophilic bleeding rates [31]. Other thrombophilic mutations that are associated with increase in thrombin generation (eg prothrombin G20210A mutation), decrease in fibrin degradation (eg PAI-1 mutation) or global increase in activation of coagulation pathways (eg MTHFR C677T mutation) would also reduce bleeding rates in haemophilia patients [32].

2.3.2. Coinheritance of non-classical thrombophilia: non-O blood groups

The ABO-related differences in glycosylation patterns of vWF strongly influence its clearance. Consequently, vWF levels are 25–30% higher in non-O plasma than in group-O plasma [33]. The high levels of vWF in non-O plasma are linearly correlated with parallel elevations of FVIII levels [34] due to the physiological role of vWF as the carrier of FVIII and its protector from proteolysis [35]. These normal variations in vWF and FVIII levels between ABO groups are of triple clinical significance. First, higher levels of vWF enhance platelet adhesion in the primary haemostatic pathway leading to faster platelet aggregation [36] and shorter bleeding time [37] in normal persons with non-O blood groups. Second, higher levels of FVIII level enhance the tenase complex in the secondary haemostatic pathway leading to faster generation of fibrin thrombi [38] and shorter clotting time [37] in normal persons with non-O blood groups. Third, a meta-analysis had revealed that the non-O blood type is the commonest genetic risk factor for venous thromboembolism [39], which implies that the non-O blood group is a genetic marker of thrombophilia (albeit non-classical). These strong linkages between ABO blood groups and haemostasis in normal (non-haemophilic) persons underscore the potential significance of the ABO blood groups as modifiers of haemophilic bleeding phenotypes. It is therefore not surprising that ABO blood groups have been shown to contribute to the inter-individual variations in the half-life of infused FVIII [40] and its in vivo immunogenicity [41] in recipient haemophiliacs. For example, it has been demonstrated that in comparison to haemophiliacs with non-O blood group, haemophiliacs with blood group-O have lower vWF antigen level with corresponding lower half-life of infused FVIII and a commensurate higher annual clotting factor consumption [40,42], which imply higher bleeding rates. Moreover, haemophiliacs with blood group-O had higher risk of peri-operative bleeding despite factor supplementation [43]. In contradistinction to the aforementioned disadvantages of blood group-O, a recent study revealed that blood group-O appears to be a negative regulator of in vivo immunogenicity of infused FVIII and hence a protector against the development of inhibitors, a finding that is potentially highly advantageous for haemophiliacs with blood group-O [41].

3. Tropical determinants and modifiers of haemophilic bleeding phenotypes

The tropical environment is characterized by certain geographical, microbiological and socio-economic peculiarities that influence the pattern of genetic mutations and infectious diseases. However, the vast majority of the literature on haemophilia originate from the developed temperate countries devoid of these peculiarities. Consequently, the impact of tropical modifiers on clinical phenotypes of haemophilia are not adequately investigated and documented. Nonetheless, it is pertinent to study and understand the mechanisms by which some prothrombotic tropical gene mutations (such as the sickle β-globin gene mutation) and certain

Table 3
Tropical Determinants and Modifiers of Bleeding Phenotypes in Haemophiliacs.

Determinant/modifier	Basic pathophysiology	Predictable effect on bleeding phenotype
HbS Gene Mutation (SCT and SCD)	Sickle cell associated hypercoagulability due to red cell sickling, release of membrane phospholipids and increased monocyte-tissue factor expression	Lower Risk of all types of bleeding
Helminthic Infection of Gastrointestinal Tract	Parasite-induced mucosal injury with or without parasite-associated anticoagulant production (e.g. ancylostomal anti-FX and anti-FXI production)	Higher Risk of Gastrointestinal Tract Bleeding
Urinary Schistosomiasis	Parasite-induced mucosal injury and parasite-associated anticoagulant production (S. haematobium anti-thrombin production)	Higher Risk of Urinary Tract Bleeding

chronic pro-haemorrhagic tropical parasitic infections (such as urinary and gastrointestinal helminthiasis) may modify the frequency, intensity and pattern of bleeding among haemophiliacs living in the tropics as outlined in Table 3.

3.1. Tropical prothrombotic mutation: HbS gene mutation

Haemoglobin S (HbS) is a structural variant of the normal haemoglobin (HbA) [44]. HbS arose as a result of a genetic mutation in the β globin gene where thymidine replaced adenine resulting in the substitution of glutamic acid by valine in position-6 of the β globin chain [44]. This sickle β-gene mutation confers relative protection against falciparum malaria among individuals who inherited the sickle cell trait (SCT) [45]. Therefore, natural selection by malaria is the single most important driver for the perpetuation and high prevalence of SCT, which subsequently leads to high rates of inter-marriages with significant incidence of sickle cell disease (SCD) in black Africa and other tropical regions of the world [46]. For example, Nigeria has the largest back population of over 170 m with SCT prevalence of 25–30% and SCD prevalence 1–3% [47]. Hence, Nigeria is thought to carry the heaviest burden of SCD in the world [47]. Both SCT and SCD are strongly associated with increased risks of venous thrombo-embolism [48,49] due to the combined hypercoagulable effects of red cell sickling [50] with resultant scrambling and asymmetry of red cell membrane phospholipids [51] and the release of procoagulant red cell membrane phospholipids [52]. Moreover, both SCT and SCD are associated with relative elevation of monocyte count with increased expression of monocyte-derived tissue factor [50], which is thought to aggravate the prothrombotic hypercoagulability due to the aforementioned red cell sickling-induced membrane phospholipid changes [50–52]. These studies [48–52] strongly suggest that the sickling disorders are essentially thrombophilic. Hence, coinheritance of the either SCT or SCD should predictably ameliorate haemophilic bleeding phenotypes. However, research in this area is very scanty and probably consists of only two reports in the literature at the moment. The first study is a case report from India, which revealed lower incidence of bleeding complications in a patient with coinheritance of severe haemophilia-A and SCD [53]. The second study is a small retrospective study from Nigeria, which revealed lower frequencies of spontaneous bleeding in patients with coinheritance of severe haemophilia-A and SCT [54]. These two studies preliminarily suggest that SCT and SCD are positive modifiers of bleeding phenotypes in haemophiliacs. However, more research is needed in this area of study.

3.2. Tropical pro-haemorrhagic parasitic infections: intestinal and urinary helminths

Developing tropical countries are often associated with low resources, poor environmental sanitation and high prevalence of intestinal helminths, which contribute to high incidence of iron deficiency within the local populations, especially among children [55]. Intestinal helminths cause iron deficiency by inducing malabsorption and gastrointestinal haemorrhage (GIH) even in haemostatically normal persons [55]. Intestinal helminths may cause GIH by inducing mucosal injuries leading to a wide spectrum of chronic or intermittent blood losses that range from occult bleeding to melena and frank bleeding on the one hand, and from upper to lower gastrointestinal bleeding episodes on the other hand [56–60]. In addition to mucosal injuries, some intestinal helminths have the capacity to manipulate the host haemostatic system by actively producing anti-coagulants such as anti- FX and anti-FIX in the case of hook worms [61]. Therefore, intestinal helminthiasis is an important risk factor for GIH even in haemostatically normal individuals. Hence, it is easy to infer that the haemostatic abnormality associated with haemophilia would create a highly pro-haemorrhagic host-parasite relationship, which would make the haemophiliacs particularly vulnerable to the haemorrhagic effects of intestinal helminths. However, this potentially significant vulnerability have not been adequately studied because the vast majority of publications on haemophilia arose from developed nations where parasitic diseases are not prevalent. A single study conducted in Nigeria on the subject matter revealed that haemophiliacs with intestinal helminthiasis had significantly higher frequency of GIH and iron deficiency than their counterparts without helminthiasis [62]. This solitary study preliminarily suggests that intestinal helminthiasis is a negative modifier of gastrointestinal bleeding rate and phenotype in infected haemophiliacs. Therefore, healthcare givers in the tropics should ensure that all haemophiliacs are regularly screened and de-wormed as appropriate.

Urinary schistosomiasis, caused by *Schistosoma haematobium*, is yet another tropical pro-haemorrhagic parasitic disease. The adult *Schistosoma haematobium* parasites preferentially settle in the vesical plexus wherein they reproduce and produce eggs. Oviposition by the adult female parasites is characterized by continuing egg deposition in the vesical sub-mucosa leading to extensive inflammation, epithelial damage and haematuria [63]. In addition to epithelial injuries, *S. haematobium* parasite is known to secrete serine protease inhibitors with anti-thrombin properties that manipulate the host haemostatic system and escalate the severity of the haematuria [64]. Consequently, urinary schistosomiasis is an important cause of haematuria and iron deficiency even in haemostatically normal persons in the tropics [65]. It can therefore be easily deduced that the haemostatic abnormality associated with haemophilia would create a highly pro-haemorrhagic host-parasite relationship, which would make the haemophiliacs particularly vulnerable to the haemorrhagic effects of urinary schistosomiasis. In similarity with intestinal helminthiasis, the significance of urinary schistosomiasis is not adequately studied because the vast majority of publications on haemophilia originated from developed countries in which parasitic diseases are not prevalent. However, a solitary study from Nigeria found out that although haematuria is not uncommon in haemophiliacs, it is mainly caused by spontaneous haemorrhage or trauma (blunt abdominal trauma) while schistosomiasis was responsible for about 20% of cases [66]. Moreover, the study revealed that schistosomal haematuria was severer and caused significant anaemia in contradistinction to spontaneous and traumatic haematuria that were milder and did

not cause significant anaemia [66]. The findings of this solitary study suggest that urinary schistosomiasis is a potential negative modifier of frequency and severity of urinary tract bleeding in haemophiliacs infected by the parasite. Therefore, healthcare givers in the tropics should ensure that all haemophiliacs presenting with haematuria in schistosomiasis endemic countries should be properly investigated by urinalysis for early detection and treatment. In particular, haemophiliacs who present with haematuria in association with eosinophilia should evoke the strongest clinical suspicion for urinary schistosomiasis [66].

3.3. Tropical pro-haemorrhagic parasitic infections: iron deficiency and its clinical implications for the haemophilia patient

The combined effect of poverty, malnutrition and frequent bleeding are sufficient to cause anaemia among haemophiliacs in the tropics [12]. Moreover, the acquisition of any tropical pro-haemorrhagic infections, especially the soil-transmitted helminths and schistosomiasis, which are notorious for causing blood loss and iron deficiency even in haemostatically normal persons [67], would considerably increase the risks of blood loss and iron deficiency among haemophiliacs living in tropical countries [62,66]. It is intriguing to note that iron deficiency is a potentially pro-thrombotic state as it is associated with increased blood viscosity [68] and thrombocytosis [69], and is thus reported to be an important risk factor for venous thromboembolism in haemostatically normal persons [70]. For the aforementioned reasons, iron deficiency may predictably reduce bleeding rates in haemophiliacs. However, this potential benefit is outweighed by a myriad of potentially adverse effects of iron deficiency that are highly undesirable in the haemophiliac *viz* cognitive retardation [71], impairment of wound healing [72] and immune dysfunction [73]. It is therefore highly desirable that even the mildest iron deficiency must be treated with vigor especially in the school-age haemophilic children in whom it may cause cognitive dysfunction with poor intellectual performance, as well as predispose to wound infection and delayed wound healing that would result in undue school absenteeism. Nonetheless, there are important challenges in the treatment of iron deficiency in the setting of haemophilia.

The major therapeutic challenges arise from the fact that one of the side effects of iron therapy is erosive gastritis, which is commonly associated with iron pills, but not with liquid iron preparations [74]. Erosive gastritis can increase the risk of gastric bleeding, which is not uncommon in haemophiliacs, especially in those infected by *Helicobacter pylori* [75]. The risk of iron-induced erosive gastritis would be higher in iron-deficient older children and adult haemophiliacs as these age groups are more likely to be treated with iron pills rather than liquid iron preparations. Therefore, haemophiliacs taking iron pills must be closely monitored for clinical features of gastritis and bleeding such as epigastric pain and passage of melena stool [76]. However, the dilemma in this perspective is the fact that iron preparations may by themselves also cause blackish discoloration of the stool (in the absence of any bleeding), which may be physically and chemically indistinguishable from true melena [77]. In view of these eventualities, we recommend that iron-deficient haemophiliacs, irrespective of their ages, should preferably be treated with liquid iron preparations as they are less toxic to the gastrointestinal tract [74]. Iron deficient haemophiliacs who develop intolerable gastritis and/or gastric bleeding due to oral iron may be cautiously treated with intravenous preparation under close supervision in view of the possible risks of anaphylaxis [78] and extravasation, which can cause localized inflammation, skin pigmentation and sensory deficit [79]. Nonetheless, we believe that the safest and the most convenient way of treating iron deficiency in haemophiliacs is by optimal dietary supplementation with iron-rich food items such as liver and red meat in conjunction with iron-fortified cereal-based meals, all of which are devoid of the side effects of conventional pharmaceutical iron preparations [80].

4. Conclusion

Disease severity as determined by the extent to which different mutations abolish FVIII production remains the most important determinant of haemophilic bleeding phenotypes. However, the overall phenotypic variation among haemophiliacs is determined by the interactions between the haemophilic pathophysiologic processes and effect of several other factors, which range from general to tropical factors on the one hand, and genetic to immunologic and infective factors on the other hand. While the roles of classical thrombophilias such as FV-Leiden is fairly well established within the context of clinical phenotyping of haemophiliacs, there is the need for more research to elucidate the clinical significance of non-classical thrombophilias such as the non-O blood groups and the sickle β-globin gene mutation, and also to further investigate the diametrically opposed roles of blood group-O, which is associated with relative increase in bleeding rates on the one hands, and a protector against development of FVIII inhibitor on the other hand. It is pertinent to screen every haemophiliac for the presence of co-existing bleeding modifiers at the time of diagnosis in order to predict individual patient prognosis and clotting factor requirement. Meanwhile, healthcare workers in the tropics should incorporate mandatory and regular screening and treatment for common pro-haemorrhagic parasitic diseases and iron deficiency into the standard of care for the management of haemophilia patients living in the tropical environment.

Authorship contributions

SGA: Conceptualized the study and gave intellectual interpretation of literature and citations accrued from web search; UAI: Conducted web search, collected and collated relevant citations from the literature on the web, and synchronized the literature and citations for each section of the manuscript; SGA and UAI: Conducted clerical formatting and verified the intellectual accuracy of all citations within the manuscript.

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