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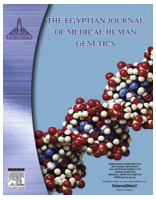

Determinants and modifiers of bleeding phenotypes in haemophilia-A: General and tropical perspectives

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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 derminants 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

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