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Review Article

Hemophilia an Inhibitors Prevalence and Risk Factors: A Review Article

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Abstract

Introduction: Hemophilia A is a bleeding disorder results from genetic mutation in the coagulation factor synthesis process, which is critical for maintaining hemostasis. Hemophilia A, an X-linked disorder that affects males at a prevalence of 1:5000–10,00000, is the most frequent type and is caused by a deficiency of factor VIII (FVIII).

Replacement therapy for FVIII is still the cornerstone for treatment of hemophilia A. The main side effect of replacement therapy is the development of antibodies, which significantly reduces the therapeutic effectiveness by blocking FVIII activity. FVIII Inhibitors might be high or low titer. Risk factors, both genetic and non-genetic, influence the development of FVIII inhibitors. The types, prevalence, and risk factors of FVIII inhibitors are summarized in the current review.

Conclusions: Hemophilia A is an inherited disease due to decrease in FVIII synthesis. Accordingly,normal homeostasis is affected leading to bleeding according to the level FVIII and the site of bleeding. Meanwhile, treatment of hemophilia A by replacement factor may lead to inhibitor formation which is a major challenge.

Keywords: Hemophilia; Inhibitors; Risk factors.

INTRODUCTION

Hemophilia A is an X-linked recessive bleeding disorder caused by decrease in VIII synthesis, which interferes with normal hemostasis. The prevalence of this disease is 1 in 5000 male births. [1] Hemophilia A is thought to affect about 5,295 people, according to a global survey on the Egyptian population carried out by the World Federation of Hemophilia (WFH).

The normal intrinsic coagulation cascade is impaired by FVIII deficiency, which results in spontaneous bleeding or bleeding after trauma. Potential sites of bleeding include joints (such as the knee, ankle, or elbow), muscles, the genitourinary system, the cardiovascular system (CVS), the gastrointestinal (GIT) system, the pulmonary system, and the central nervous system (CNS).

Replacing the deficient factor is the cornerstone of hemophilia treatment. There are two distinct types of factor concentrates that are linked to varying rates of inhibitor formation: recombinant (rFVIII) and plasma derived (pdFVIII). With a significant financial burden, the most difficult and dangerous side effect of treating hemophilia is the development of inhibitors. [2]. Factor VIII inhibitors are Immunoglobulin IgG (IgG1 and IgG4) antibodies that block the procoagulant's ability to function in plasma. Generally, inhibitors are categorized as "high-titer" inhibitors if their levels in plasma are greater than 5 Bethesda Units (BU)/ml or as "low-titer" inhibitors if they are less than 5 BU. Thirty percent are low titer inhibitors and between sixty and seventy percent are high titer inhibitors in hemophilia A. Certain patients experience the development of transitory inhibitors, which are typically modest titers that never surpass 5 BU/ml and also fade away on their own over time[3]. The formation of inhibitors alters clinical presentation, which has a significant impact on bleeding control, the state of arthropathy, and

overall quality of life. Due to an increase in factor clearance, those with mild or moderate hemophilia may develop severe clinical behavior. Patients with inhibitors require either higher doses of FVIII in patients with low titre inhibitors or alternate therapy with bypassing agents in patients with high titre inhibitors since they do not respond to replacement medication, making it difficult to control their bleeding symptoms.[4]

Types of factor inhibitors

Inhibitors of coagulation factors are divided to neutralizing antibodies that result in inactivation of the factor and non-neutralizing (i.e. non-inhibitory antibodies that target non-functional epitopes on FVIII. These non-neutralizing antibodies become clinically relevant if they result in accelerated clearance of the transfused clotting factor [4].

Most FVIII alloantibodies target epitopes in the A2 and A3-C1 domains of FVIII. These antibodies are developed in hemophiliac patients exposed to exogenous FVIII. The binding of FVIII to phospholipid and Von Willebrand factor (VWF) is impacted by antibodies against the C2 domain, which also prevents thrombin and FXa from cleaving FVIII. Factor VIII inactivation in vitro is dependent on pH, temperature, and duration [5]

Prevalence of inhibitor formation

The overall prevalence of inhibitors is up to 30% in patients with hemophilia A [6]

703 people were found to have current FVIII inhibitors. WFH 2021

People with severe hemophilia A (overall lifetime risk of 25–40%) are more likely to develop inhibitors than those with moderate or mild hemophilia A (overall lifetime risk of 5–15%). It should be mentioned that while the majority of mutations causing mild to moderate hemophilia A have a very low likelihood of developing an inhibitor (>5%), some have a greater risk (up to 15%). When individuals have mild to moderate hemophilia, their inhibitors frequently behave differently from those with severe hemophilia A. [8]

A population's prevalence of inhibitors at any given time is influenced by a number of factors, including the rate at which inhibitors develop, the natural disappearance of temporary LTIs, the active removal of inhibitors through immune tolerance induction (ITI) therapy, and the mortality rate among inhibitor-using patients. The factor least likely to affect the prevalence of inhibitors is inhibitor patient deaths, which are uncommon in countries where bypassing agent are widely available.[8]

Earlier studies reported that the incidence of inhibitor in the range of 25%-32%, although the prevalence eventually fell to approximately 12% as some antibodies disappeared by time [9]

Risk factors for inhibitors:

The etiology of the appearance of FVIII inhibitors in certain patients while others remain unaffected is unclear. The development of inhibitors is a multifaceted and complicated process that involves interactions between genetic (unchangeable) and nongenetic (changeable) factors [10]

I-Genetic predisposition for inhibitors

- (a) Family history

The likelihood of developing an inhibitor is three times higher in families with a positive history of inhibitors. Additionally, the inhibitor status concordance of identical monozygotic twins is 90%, which is higher than that of non-twin siblings. It indicates that the fraction of antibody concordant families is higher than expected even when considering the overall antibody response, which includes both neutralizing and non-neutralizing antibodies. Lastly, differences in inhibitor risk between racial and ethnic groups emphasize the importance of genetic variables. [11]

- (b) Human Leucocyte Antigen Genotype

Human leukocyte antigen (HLA) class II molecules are integral membrane proteins that have a significant function in presenting extracellular antigens, such as infused FVIII peptides, to naïve T helper cells. These molecules exhibit significant heterogeneity among patients and different racial groups. These cells will assume a role in the ensuing immunological response. The findings of many studies have indicated that there are weak associations between certain HLA class I alleles (A3, B7, and C7) and HLA class II alleles (DQB0602, DQA0102, and DR15) with an increased opportunity to inhibitor development. On the other hand, it was observed that the HLA C2, DQA0103, DQB0603, and DR13 alleles had a protective effect against the formation of inhibitors.[12]

- (c) Ethnicity

It has been found that patients of African descent experience twice as many inhibitors as patients of Caucasian descent. Nevertheless, the cause of this discrepancy is still unknown. There are six distinct F8 haplotypes known as H1 through H6. H1 and H2 are found in all racial and ethnic groups, whereas

H3, H4, and H5 are only found in the black community. H6 is also present in people who are Chinese in origin. Patients exposed to FVIII concentrates may be at risk for inhibitors because to a mismatch between their F8 haplotype and the infused FVIII molecule, particularly if it contains H1 and H2. This mismatch affects both recombinant forms of FVIII and plasma derived FVIII. [12]. In the HIGS study Hemophilia Inhibitor Genetics Study, the association did not remain significant after adjustment for the F8 mutation type and HLA class II alleles. Hence, at present, it is not feasible to clearly state that a discrepancy in FVIII haplotypes alone would be linked to the risk of inhibitors. However, the inclusion of supplementary indicators such as HLA and immune regulatory molecules may yield more conclusive outcomes.[13]

- (d) Factor VIII genotype

The causative F8 mutation has been the most thoroughly studied risk factor for inhibitors because intron 22 inversion is the most significant risk factor for severe illness and has a major impact on the development of FVIII inhibitors. Patients with severe disease who carry the Inv22 mutation have a higher prevalence rate of inhibitors than patients who are similarly affected but do not carry the mutation. Regardless of the severity of the disease, this evidence confirms the direct involvement of the Inv22 mutation in inhibitor production.. [14] Several mutations have also been connected to the lack of a particular gene product, including splicing site mutations, big deletions, nonsense mutations, non-A-run minor deletions, and intron 1 inversion. Patients who have these mutations are more likely to develop inhibitors and experience a severe form of hemophilia. Notably, the mutation profile indicates that in approximately 17–41% of hemophilia A patients, over 80% of genetic anomalies in FVIII are linked to a propensity to impede development. Given the importance of gene mutation detection in guiding future treatment therapies, it is therefore strongly recommended that gene mutation detection be carried out for all recently discovered patients with HA. [15]

II non-genetic causes of inhibitors

- (a) Timing of inhibitor development

Fifty % of inhibitors are present after 14 to 15 exposure days (EDs) to FVIII, with the majority appearing over the first 50 EDs. After 50 EDs, inhibitor development is rare. PTPs (previously treated patients) and PUPs (previously untreated patients) are the two groups of patients based on FVIII exposure. The patient must not have previously been exposed to factor concentrate in order to be classified as a PUP. However, several studies pair PUPs with patients receiving minimal treatment (MTPs). Patients classified as MTPs have received four ED doses of factor concentrate or blood products. It is more typical for PUPs who are intolerant to exogenous FVIII to develop inhibitors. [16]

PTPs are usually defined as people who have received more than 75 to 150 Eds of FVIII concentrate treatment previously. Nonetheless, PTPs are also referred to as individuals who, following more than 150 administrations, have grown tolerant to exogenous FVIII products. [17]

- (b) Factor VIII protein

A prospective randomized study called the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study revealed a considerably greater inhibitor formation rate in the PUPs receiving one of four recombinant FVIII concentrates as opposed to those receiving one of four concentrates derived from plasma that contained FVIII/von Willebrand factor (VWF) (44.5% vs. 26.7% for all inhibitors, 28.4% vs. 18.5% for HTIs [18]. The relative risk of a number of more recent recombinant products and high-purity plasma-derived products cannot be determined because neither set of products has undergone this kind of studies. In September 2017, the European Medicines Agency (EMA) released a statement based on a review of available data, which was prompted by the SIPPET study. The statement pointed out that there is no consistent and clear evidence of a difference in the incidence of inhibitor development between the two classes of FVIII: plasma-derived and recombinant. [19]. There has been ongoing debate on whether all recombinant FVIII concentrates have the same chance of developing inhibitors or if some are more likely to do so than others due to variations in glycosylation and sulfation, for example. There was worry that B-domain deleted rFVIII concentrate might be more likely to produce an inhibitor than full-length factor concentrates when it was first presented. The European Medicines Agency and the U.S. Food and Drug Administration (FDA) regulators have concluded that there is insufficient evidence to substantiate these worries. Research employing PTPs alternating between various recombinant factor concentrations has not revealed any indications of heightened inhibitor development. [20]. The incidence of inhibitor formation was observed to be greater with one

second generation full-length BHK rFVIII concentrate compared to a third generation full-length CHO rFVIII concentrate (hazard ratio: 1.6–1.75) in recent investigations, including the large prospective cohort RODIN research. [21].

- (c) The gut microbiota and FVIII inhibitor

The gut microbiota undergoes significant changes throughout the first two years of life, during which the risk of inhibitor development is highest in cases with severe HA. The composition of the gut microbiota is influenced by several factors, including nursing, medications like antibiotics, and delivery methods like cesarean sections. [22]

The way that systemic immunity to FVIII is modified may be influenced by the gut flora. Foods that provide digestion-resistant fibers and other carbohydrates that are accessible to the gut microbiota enter the large intestine where they ferment to produce short-chain fatty acids that inhibit the immune system. Other dietary sources, like tryptophan, can also be catabolized by bacteria to produce indole-associated compounds that have immunosuppressive properties. These substances enter the body and can significantly impact immune cells involved in the FVIII inhibitor response. [23]

To further understand how the gut microbiota contributes to the formation of inhibitors in clinical settings, more research is required. Retrospective studies conducted in the past have shown that factors that can influence the composition of the gut microbiota, like breastfeeding or the way of delivery, do not appear to affect the prevalence of inhibitors. Lastly, immunomodulatory pathways linked to the gut microbiota may form the basis of treatments aimed at reducing the likelihood of the production of inhibitors in the early stages of FVIII exposure. [24]

- (d) Age of first exposure

Age at initial exposure and subsequent inhibitor development are correlated, with younger treatment recipients having a higher rate of inhibitor development. Nevertheless, in contrast to earlier findings, stepwise decline in inhibitor development with advancing age or, in fact, any discernible variation in inhibitor development amongst children who were initially exposed to FVIII at various times throughout their first year of life is not seen. Specifically, in patients treated for the first time in their first month of life, there was no excess inhibitor formation. These results have implications for the development of high titre inhibitors as well as for inhibitor development generally.[25]

CONCLUSIONS

Hemophilia A is an inherited disease due to defect in FVIII so normal homeostasis is affected leading to bleeding according to level of factor and site of bleeding, treatment of hemophilia by replacement factor may lead to inhibitor formation which is a major complication.

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