Review Article

Genetic risk factors for inhibitor development in patients with hemophilia and rare bleeding disorders

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Abstract

Inhibitor development is a lifelong challenge for patients with bleeding disorders who received replacement therapy. Most commonly, inhibitor formation was observed in hemophilia a patient, but patients with rare bleeding disorders (RBD) especially patients with deficiency of factor XIII (FXIII) and factor V (FV) can develop an inhibitor against exogenous factors. Several factors considered as risk factors for inhibitor formations in these patients. Genetic risk factors are the main accused that can cause inhibitor formation in hemophilia patients, but are less important in RBDs. In this review study, we searched Medline and Web of Science databases for English sources and the following key words: hemophilia, inhibitor, rare bleeding disorder, a rare inherited disorder, acquired hemophilia, acquired rare bleeding disorders, treatment complication, genetic in hemophilia, polymorphism in rare bleeding disorder, mutation in hemophilia and other required keywords. Hemophilia A (HA) patients who had the large deletion, nonsense mutation or intron 22 inversion are more susceptible to inhibitor development. Gene polymorphisms in the immune system are also considered as other risk factors in HA patients.

Keywords: Hemophilia, rare bleeding disorder, inhibitor

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Introduction

Inherited coagulation disorders are a variety of bleeding disorders with highly variable prevalence and different pattern of inheritance. These bleeding disorders can have a high prevalence such as hemophilia A (HA) with a prevalence of 1 in 5000 male or be as rare as factor XIII deficiency (FXIIID) with estimated incidence of 1 in 2 million in the general population.

A wide spectrum of bleeding disorders was observed in patients with inherited coagulation disorders that are more severe in patients with HA and hemophilia B (HB) in comparison with rare bleeding disorders (RBD) that including inherited deficiency of factors I (FI), II (FII), V (FV), combined V and VIII (FV-VIII), VII (FVII), X (FX) and as well as XI (FXI) and XIII (FXIII) (1, 2). Based on severity

Table 1: Incidence of inhibitor development in rare and common bleeding disorders and related risk factors.

Factor deficiency	Pattern of inheritance	Incidence	Rate of inhibitor development	Risk factors
I	recessive	1: 1 milion	Extremely rare	Replacement therapy
II	recessive	1: 2000000	Extremely rare	Replacement therapy
V	recessive	1: 1 million	Rare	Infections, surgical procedures, transfusion and antibiotics administration malignancy, pregnancy and autoimmune diseases, exposure to topical bovin preparation.
V-VIII	recessive	1: 2 million	Rare	Replacement therapy
VII	recessive	1: 500000	Extremely rare	Replacement therapy
VIII	Sex-linked	1: 10000	Up to 30%	ethnicity, Family history of inhibitors, the HLA complex genotype, interleukin 10 and tumor necrosis factor α (TNF- α) polymorphisms, factor VIII mutation type, age at first treatment, intensity of treatment, continuous infusions.
IX	Sex-linked	1 :30000	Up to 10%	Replacement therapy
X	recessive	1 : 500000	Extremely rare	Replacement therapy
XI	recessive	1 : 1000000	Rare	Replacement therapy, using Fresh Frozen Plasma as a substitution, type II Jewish mutation (Glu117 stop), antifibrinolytic agent.
XIII	recessive	1 : 1000000	Rare	Using durgs, cohns disease, liver disease, leukemia, disseminated intravascular coagulation, ulcerative colitis, Henoch Schonlein Purpura, inflammatory bowel disease, sepsis, stroke, pulmonary embolism, systematic lupus erythromatosis, autoimmune diseases

of coagulation factor deficiency, patients with inherited deficiency of coagulation factors need regular or on demand exogenous factor replacement therapy.

Exposure to exogenous factors in these patients is a risk factor for inhibitor development. This inhibitor Interferes with transfused factor and rendering them ineffective. Rate of inhibitor development is vary in patients with inherited factor deficiencies and depend on type of deficiency (common or RBD) and severity of deficiency (mild, moderate and severe deficiency) as well as type and frequency of replacement therapy (3). Although inhibitor development is rarely observed in patients with deficiency of FVII and FX but is more common in patients with FV and FXIII deficiencies and consider as the most significant complication of treatment in hemophilia patient (4).

Inhibitor development in patients with hemophilia causes high rate of morbidity such as high rate of bleeding diathesis, increased disability and decreased quality of life. Rate of inhibitor development is more common in patients with severe HA than mild and moderate deficiency and was observed up to 30% of severe deficient patients (5). In other word, overall inhibitor prevalence of 5–7% and when limited to patients with severe disease the prevalence is much higher at 12–13%. The incidence of new FVIII inhibitors in patients with severe FVIII deficiency is approximately 30%. Inhibitors are less common in patients with mild or moderate hemophilia occurring in approximately 3–13% of patients.

Most of these inhibitors are high titer (>5 BU)

Fig. 1. Coagulation factor VIII structure. Factor VIII consists of a heavy chain with A1 and A2 domains, a connecting region with a B1 domain that is not required for clotting, and a light chain with A3, C1, and C2 domains. Most of inhibitor against factor VIII, bind to the C2 or, less often, the A2 domain on factor VIII (1)

and were developed shortly after exposure to exogenous FVIII. Factor VIII consists of two chains including a heavy chain with A1 and A2 domains, a connecting region with a B1 domain that is not required for clotting, and a light chain with A3, C1, and C2 domains (Figure 1). Most of the inhibitors are directed against C2 domain and less often A2 domain. C2 doamin binds to von Willebrand factor, phosphatidylserine on activated platelets and and inhibitor against this domain causes decrease procoagulant activity of FVIII. Specific mutation such as Trp2229Cys in C2 domain and Arg593Cys in A2 domain may predispose to inhibitor formation (3-5).

Rate of inhibitor development is less in patients with HB and can be observed in about 3-5% of these patients. As previously mentionedoOne of the most important risk factor, is underlying gene defects and since missemse mutations as the main cause of HB are consider as low risk factor for inhibitor development, inhibitor is less common in HB. The rate of inhibitor development affected by different factors and genetic risk factors consider as an important factor in this issue (6). Genotype of patients with HA is an important factor in formation of inhibitor. It was demonstrated that patients with large deletion, nonsense mutation and intron 22 inversion has a higher risk of inhibitor formation. Some missense mutation even in patients with mild and moderate deficiency increased the risk of inhibitor formation.

Gene polymorphisms are other genetic risk factor for inhibitor development in patients with hemophilia and a consider number of studies were conducted on role of interleukins and tumor necrosis factor α (TNF-α) on inhibitor development in different populations. A number of these studies were demonstrated a role for genetic polymorphisms in IL-10 and TNF-α in inhibitor development in patients with HA (7-9). Gene polymorphisms in coagulation FII and FV leiden also were performed and some important result were obtained and polymorphisms of these factors consider as another culprit but more studies with large population and prospective nature should performed to demonstrated this issue. In contrast to haemophilia A, in others inherited coagulation factor deficiencies due to the rarity of disorders and absent of common mutations and polymorphisms in some of them, there is no clear relation found between genetic risk factors and development of an inhibitors.

Developing inhibitors against factor V is rarely occur but it's a challenging condition that can be potentially lifethreatening. Factor V inhibitors can develop without any clear causes but most of cases associated with clinical events including infections, surgical procedures, transfusion and antibiotics administration. In addition, malignancy, pregnancy and autoimmune diseases can also lead to developing inhibitors (10).

In the past, coagulation factor V inhibitors more frequently resulted from patient's exposure to topical bovine preparations but today due to the availability of recombinant bovine and also recombinant human thrombin, surgical use of thrombin is restricted (11, 12). Therefore most cases associated with non bovine thrombin preparations. Bovine thrombin is mixed with fibrinogen to form sealant that used in surgical procedures (cardiac surgery and neurosurgery) to aid homeostasis. Because the thrombin contains bovine factor V its act as a potent stimulus for development of antibodies. Clinical manifestations of patients affected by factor V inhibitors vary from asymptomatic to lifethreatening episodes. Some studies showed the relation between plasma residual factor activity and bleeding tendencies among patients with acquire factor V deficiency (13). In patients with severe factor XI deficiency as other rare bleeding disorders, developing inhibitors against factor XI had been described. Almost in all cases that develop inhibitors , patients had received replacement therapy (14) .in the

study that conducted on 118 patients with factor XI deficiency, seven patient that received fresh frozen plasma as a substitution therapy developed an inhibitors that titers from 3 to 25 BU/ml. Molecular analysis was demonstrated that all of these patients were homozygote for so-called type II Jewish mutation (Glu117stop).

This study suggested only patients with homozygote or compound heterozygote develop inhibitors. In some situations, using antifibrinolytic agents lead to reasonable response. In addition based on different studies in cases those are not responsive to antifibrinolytic agents, use of rVIIa is recommended (15).

Although factor XIII inhibitors are also arise very rarely but same as acquired factor V deficiency and contrary to other rare bleeding disorders have more frequency. Factor XIII inhibitors arise from underlying disorders and in some cases result from using drugs (16). In acquired factor XIII deficiency with inhibitors bleeding episodes are lifethreatening and based on some studies several subjects died due to cerebral hemorrhage. Autoantibodies that form against factor XIII lead to decrease production or increased consumption of coagulation factor XIII (17). Disease that associated with developing inhibitors against factor XIII including Crohn s disease, liver disease, leukemia, disseminated intravascular coagulation, ulcerative colitis, Henoch Schonlein Purpura, inflammatory bowel disease, sepsis, stroke, pulmonary embolism and systematic lupus erythromatosis. In addition, factor XIII inhibitors are associated with autoimmune diseases as neutralizing or non-neutralizing types. Neutralizing types have effect on activation of factor XIII while non-neutralizing form an immune complex that later cleared by reticuendothelial system.

Immunosupression therapy, plasmapheresis and intravenous gamma globulins can be used for elimination of inhibitors (18).

Conclusion

Rate of inhibitor formation is affected by several factors but genetic risk factors seem to be the most crutial. These facrors can be used for identification of higher risk patients and further for management of them.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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