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Hemophilia Inhibitors Prevalence, Causes and Diagnosis

Tarek M. Owaidah
King Faisal Specialist Hospital and RC
Saudi Arabia

1. Introduction

Hemophilia is a bleeding disorder that results from genetic alteration in production of coagulation factors that are important to maintain hemostasis. The commonest type is hemophilia A due to deficiency of factor VIII (FVIII), which is important zymogen co factor for clot formation. Hemophilia A is an X-linked disease that affects males at prevalence of 1:5000-10000. Hemophilia B is due to deficiency in factor (FIX) but less common with prevalence of 1:34,500 males. It is inherited also as X- linked. Although both disorders are rarely observed; they can be very serious (life threatening) and costly for families and countries. Treatment of hemophilia is based on replacement of the deficient factor. Two types of factor concentrates are available, plasma derived (pdFVIII/IX) and recombinant (rFVIII/IX) which are associated with variable incidence of inhibitor formation rates.The development of inhibitor is the most serious and challenging complication of hemophilia treatment with the enormous economic burden (1). FVIII inhibitors are immunoglobulin IgG (IgG1 and IgG4) antibodies that neutralize FVIII procoagulant activity in plasma. Inhibitors are usually classified according to their levels in plasma as a "high-titer" inhibitors, those with the highest activity >5 Bethesda Units (BU)/ml or a low-titer inhibitor type. In hemophilia A aproximately 60-70% of inhibitors are high titer inhibitors, and the remainder are low titer. Some patients develop transient inhibitors (usually low titer inhibitors that never exceed a titer of 5 BU/ml and disappear spontaneously with time (2). The development of inhibitors is associated with changes in the clinical picture with major effect on bleeding control, arthropathy status and overall quality of life. Patients with mild or moderate hemophilia may change to severe clinical behavior because of increase in factor clearance. Patients with inhibitors are resistant to the replacement therapy and thereby their bleeding symptoms become difficult to control and require either large doses of FVIII/IX or alternative hemostatic therapy with bypassing agents.
During almost 50 years many studies have addressed different aspects of inhibitors issue from risk factors to diagnosis and management of patients who developed these antibodies.

2. Type of factor inhibitors

Coagulation factor inhibitors can be 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. The non-neutralizing antibodies become clinically relevant if they result in accelerated clearance of the transfused clotting factor (3) . Both types can by classified as:

a. alloantibodies, those that develop in hemophiliacs exposed to exogenous FVIII or FIX. Most FVIII alloantibodies are directed against epitopes in the A2 and A3-C1 domains of FVIII. This binding interferes with the assembly of the FVIII-FIX complex. Antibodies directed against C2 domain affect the binding of FVIII to phospholipid and von Willebrand factor (vWF) and interfere with cleavage of FVIII by thrombin and FXa. In vitro the inactivation of factor VIII is time, temperature and pH dependent (4). Alloantibodies have type 1 reaction kinetics, which means that all FVIII added to haemophilia plasma is inhibited lineary.

b. autoantibodies, those that suddenly appear in persons with normal F8 gene and previously normal plasma levels of FVIII, causing so called "acquired hemophilia". These inhibitors occur predominantly in the elderly patients, patients with autoimmune, inflammatory process and lymphoprolipherative disorders, and rarely in association with pregnancy (5,6) and result in serious bleeding manifestation with a high morbidity and mortality of 6%-20%. Currently 70%-80% of cases of acquired hemophilia are successfully treated with immunosuppressive therapy (7,8). In vitro FVIII autoantibodies present type 2 reactive kinetics with exponential decrease of FVIII, while even at a high titre of inhibitor some residual activity of factor may be detectable. (4)

Occasionally, alloantibodies may be mistaken for autoantibodies. This occurs when an individual with a clinically silent mutation in FVIII (for example, a B-domain mutation) is exposed to wild-type FVIII. (4)

3. Prevalence of inhibitor formation

The overall prevalence of inhibitors is up to 30% in patients with hemophilia A and up to 5% in those with hemophilia B (9). Inhibitors are reported rarely in other coagulation factor deficiencies. Data on 294 individuals with deficiencies of FII, FV, FVII, FX, FXIII from North American Rare Bleeding Disorder Registry reported only 3% of patients with FV and FXIII deficiency who developed inhibitors following infusion of FFP and FXIII concentrate (10).

Risk factors for inhibitor development can be patient related (genetic, ethnicity or immune system), treatment related (type of product, exposure to FVIII/IX in terms of the age at the first treatment, treatment duration and intensity) or diagnostics related (type and sensitivity of test detecting the inhibitor, frequency of inhibitor testing). There are differences between the prevalence and incidence of factor VIII/IX inhibitors. Earlier studies reported consistently the incidence of inhibitor in the range of 25%–32%, although the prevalence eventually fell to approximately 12% as some antibodies disappeared over time (3). Some reports used both terminologies interchangeably which could be explained by difficulty to investigate inhibitor incidence due to the need for high patient number in a relatively uncommon disease. However, early studies were often undertaken on selected patients populations, using different assays for inhibitor detection and being mostly one-off studies on the proportion of inhibitors in particular patient population at a given time (11).

In several cohort studies an incidence rate of new inhibitors (number of new cases/ population at risk x the time at which new cases were ascertained) was determined in the absence of new product exposure with different incidence results. As an example, Kempton et al (2006) reported incidence rate of factor VIII inhibitors of 2.14 per 1000 person-years (12).

4. Factors affecting development of inhibitors

Several risk factors for inhibitor formation have been hypothesized. Identification of these factors may help to predict inhibitor develoment and to choose the treatment approach minimising the potential risk in particular patient. The risk of developing inhibitors varies throughout the lifetime of a patient with haemophilia, with historical evidence suggesting that most of inhibitors develop during childhood before reaching the age of 12 years (13). The risk factors interact with each other and can be classified as "non-modifiable" and environmental, or so called "modifiable" risk factors.(14)

a) Non modifiable risk factors.

These patient related factors that may enhance the risk of inhibitor development include a high-risk hemophilia genotype, co-stimulatory genotype–immunogenotype interactions, ethnicity and positive family history [15,16,17].

Mutations in FVIII are major risk factors of inhibitor development predominantly in patients with severe form of disease (18). Several gene defects that increase the risk of factor VIII/IX inhibitors have been identified. Some mutations (so called null mutations) result in severe molecular defects with complete failure of FVIII or FIX proteins synthesis. High risk mutations include multi-domain mutations, large deletions/insertions and nonsense mutations which represent approximately 8% of all mutations in severe haemophilia A, as well as the intron-22 inversion with a prevalence of around 50%. The inhibitor formation in patients with high risk mutations ranges between 25% (intron 22 inv) and 60%-80% (multidomain mutations and large deletions) (17,18,).

Small deletions, missense and splice site mutations result in partial absence of FVIII protein and their prevalence in severe hemophilia is approximately 35% (19). Also in haemophilia B the genotype is a strong determinant of inhibitor risk; patients with gene deletions or rearrangements are at high risk of inhibitor formation. These mutations are present in approximately 50% of inhibitor patients, while the frameshift, premature stop, or splice-site mutations are present in approximately 20% of patients with inhibitor of FIX. The missense mutations, which constitute the majority of genotypes in haemophilia B are at very low risk of inhibitor formation (3,20). The prevalence of inhibitors in patients with haemophilia B and null mutations ranges from 6–60% (17).

The discordance of inhibitor development and the type of mutation has been observed in patients with the same mutation of the F8 or F9 gene, including the siblings, suggesting the involvement of other genetic and environmental risk factors that may prevent or facilitate inhibitor formation (21).

Polymorphisms of the immune response genes, including the genes encoding the major histocompatibility complex (MHC) class II system, tumor necrosis factor-α(TNF-α), interleukin-10 (IL-10) and cytotoxic T-lymphocyte antigen-4 (CTLA-4), have been suggested to be the factors contributing to the risk of inhibitor (22,23,24,25). Some specific types of (HLA) genes may also be implicated in increasing the risk of inhibitor development (26).

Ethnicity was also shown to play a role in development of inhibitors. African-Americans and Latinos with haemophilia A have higher inhibitor risk than Caucasians with prevalence of inhibitors in Black patients with hemophilia A twice of white patients (27,28). The estimated incidence of new inhibitors in Finnish patients was 10.3 per thousand patient years (29). In another study on inhibitors in Japanese populations the prevalence was as high as 29.7% (30). In a close population the prevalence of inhibitors in Chinese was as low

as 3.9% in hemophilia A and 4.3% in severe cases (31). It was interesting to find a high frequency (39.2%) of very low titer of inhibitors (<1 BU mL 1) in Chinese population which was seen also in a cohort of Saudi patients (32). There are few reports about the prevalence of these inhibitors in other ethnicity like Arabs. Recent epidemiological survey of the presence of inhibitors in known cases of Saudi hemophilia A and B showed a prevalence of inhibitors of 22% and 0%, respectively (32).

b) Modifiable risk factors

These include environmental influences that are implicated in increasing the risk of inhibitor formation. Identifying the environmental risk factors implicated in increasing the probability of inhibitor development permit anticipation of disease progression and allow the potential to intervene, and thereby modify patient treatment and improve the outcomes.

Environmental factors include, age at start of prophylaxis, type of replacement therapy product and intensity of treatment (28,33). Data from several studies have supported the idea that first replacement therapy at an early age may increase the risk of inhibitor formation (34, 35, 36). These studies showed that most inhibitors develop in children with severe hemophilia at the age of 1–2 years after 9–12 treatments. More recent large studies like the CANAL study (37) and Chalmers study (38) investigated the relationship between inhibitor development and treatment characteristics in previously untreated patients (PUPs) with severe haemophilia A and confirmed that an early age of first exposure to FVIII was associated with an increased risk of inhibitor development, however, further analysis showed that after adjustment for intensity of treatment and genetic factors, this association disappeared (37,38).

Gouw et al (2007) reported a cumulative incidence of clinically relevant inhibitor of 41% in patients starting therapy before the age of 1 month, 30% in patients starting therapy between 1 and 6 months of age, 23% in patients starting therapy between 6 and 12 months of age, 20% in patients starting therapy between 12 and 18 months, and 18% in those starting therapy beyond 18 months of age, respectively. However, the same findings of disappearance of the association between inhibiors and the age of the first treatment were observed after the adjustment for other confounding factors (39).

5. The effect of type of factor concentrates on inhibitor formation

The influence of the type of FVIII concentrate in PUPs with severe hemophilia A is highly controversial due to presence of different types of these products and methodological differences between studies which rendered comparisons inconclusive (14,28 40, 41). Purified factor VIII products were developed in the 1960s and become available as concentrates for reconstitution in the 1970's. Most of the early studies addressed the role of pd-FVIII in the development of inhibitor with a cumulative incidence of inhibitors ranging from 20.3% to 33.0% in PUPs exposed to different brands of low or intermediate purity pdFVIII concentrates (31 42, 43, 44). Further studies evaluating the inhibitor formation after pdFVIII products focused on the purity of factor VIII products as a potential risk factor. Purity of FVIII concentrates is defined as the biologic activity of FVIII:C (IU) per mg of total protein. The studies of patients treated with a single plasma-derived high purity antihemophilic factor concentrate containing vWF (Alphanate®, Humate-P®, Koate®-HP) showed the incidence of inhibitors in the range from 0% to 12.4% (45,46 47, 48 ,49). Most of

the current high purity pd-FVIII products carry almost 0% risk of inhibitor formation (50, 51). There is data supporting the protective effect of vWF, a carrier protein of FVIII which is present in a large amount in most pd-FVIII products but not in rFVIII, on inhibitor formation by reducing the immunogenicity of FVIII through preventing its entry into professional antigen presenting cells (52).

Recombinant factor VIII products became available in the early 1990's after the discovery of F8 gene in 1984. The cumulative risk of inhibitors in patients treated with first generation, single rFVIII product was reported to range from 32.0% to 38.7% (53,54,55). More recent studies have shown that in patients treated with the second generation rFVIII products the incidence of inhibitors ranged from 16.7 to 32% (28,56). Choosing a product for factor replacement is crucial, which sometimes creates pressure on the treating physician. The safety of the blood product is weighted against other factors like availability and cost of products and the risk of inhibitor formation. Goudemand et al (2006) demonstrated that high-purity pdFVIII concentrates containing von Willebrand factor have lower risk of inhibitor development compared with rFVIII. Adjusted relative risk for inhibitor with rFVIII was 2.4 for all inhibitors and 2.6 for high titre inhibitors when compared with pdFVIII (28). In a systematic review of 24 international studies published between 1970-2009, Iorio et al (2010) reported a pooled inhibitor incidence rate of 14.3% for pdFVIII and 27.4% for rFVIII, with the high titre inhibitor incidence of 9.3% for pdFVIII and 17.4% for rFVIII (57). In a more recent meta-analysis by Franchini et al (2011) evaluating the data from a total of 800 patients enrolled in 25 prospective studies published between 1990 and 2007, the incidence of inhibitors did not differ significantly in recipients of plasma derived and recombinant FVIII concentrates (58) . The authors concluded that type of product does not seem to influence the inhibitor development in PUPs with severe hemophilia A (58). Poon MC et al (2002) showed the same incidence of inhibitor formation in hemophilia B patients treated with rFIX and pdFIX concentrates (59).

The major limitation of all these reviews is that they compare different plasma derived and recombinant products used in different time periods with different approaches to treatment but also to the monitoring of inhibitors.

The lack of unbiased information on this issue was the driving force behind the SIPPET study (Study on Inhibitors in Plasma-Product Exposed Toddlers). This ongoing international, prospective, controlled (open-label) and randomized clinical trial is aimed to compare the immunogenicity of plasma-derived vWF/FVIII products with recombinant FVIII concentrates, by determining the frequency of inhibitor development in PUPs and minimally treated patients (MTPs) (60,61).

Intensity of treatment has been implicated as a factor responsible for increasing the risk for inhibitor development (62). In CANAL study it was shown that adjustment for intensity of treatment overcomes the effect of age on the development of inhibitor (39). Gouw et al (2007) showed in a multicentre cohort study that intensive treatment periods (peak treatment moments and surgical procedures) increase the risk of inhibitor formation (63). Furthermore, reduced interval between exposure days (EDs) was significantly associated with increased risk of inhibitor development with adjusted relative risk of 1.0 for >100 days between EDs vs. 2.5 and 2.7 for 10–100 days and <10 days respectively (63). The highest risk of developing inhibitors is observed within the first 50 exposures to FVIII, while the risk is substantially reduced after 200 treatment days (14).

Lack of standardization of the category "previously treated patients" (PTP) has led to many different reports on the inhibitors formation in this patients population (64). Nevertheless,, current FDA approach recommends to use the incidence of inhibitor formation in PTPs as the main criteria in the safety analysis of new FVIII products.

The International Society of Thrombosis and Haemostasis Scientific Subcommittee (ISTH) defines PTPs as patients with >150 lifetime exposure days (65), but this definition has not been used strictly in the studies evaluating the incidence of inhibitor formation after exposure to factor concentrates in previously treated patients. In these studies different definitions of PTPs were used with a number of ED ranging from a single exposure to >250 ED (66,67).

Some virus inactivation steps introduced in the early 1990´s with the aim to improve the safety of FVIII concentrates increased the immunogenicity of products and resulted in inhibitor formation in PTPs. Peerlinck et al (1993) and Rosendaal et al (1997) reported sudden increase of inhibitor formation in PTPs after the treatment with pasteurized intermediate purity FVIII concentrate. Incidence of inhibitors was 31 and 20.1 per 1000 person years in Belgium and the Netherlands, respectively (68,69).

Changes in the use of products created a new research area focused on inhibitors in patients who have switched one product for another FVIII concentrate. In two Canadian surveillance studies that evaluated inhibitor formation in PTPs following the switch of pdFVIII for rFVIII, the inhibitor incidence was similar to that seen in Canada prior to the introduction of recombinant products (70,71). This was also confirmed by more recent studies. Gouw et al (2007) in the CANAL study showed that switching between factor VIII products did not increase the risk for inhibitors (39). Some of postmarketing studies evaluated the switch for the newer generation concentrates of the same class products. Vidovic et al (2009) evaluated patients switching from Kogenate® (Bayer) for Kogenate FS® (Bayer) and did not find any inhibitors in the 185 subjects monitored for 2 years (72).

6. Diagnosis of inhibitors

The tests for detection of FVIII antibodies, based on mixing the patient´s and normal plasma underwent several modifications to improve their sensitivity. The first assay to determine the potency of inhibitor was described in 1959. This assay was quite accurate but required considerable technical skill and was beyond the capability of most clinical laboratories. Later investigators with an interest in haemophilia met in Bethesda and established a method for measurement of FVIII inhibitors (73). The assay was named Bethesda assay and was based on the ability of antibody-containing plasma to inactivate the FVIII of pooled normal plasma. This assay has become a standard test to measure clinically significant FVIII inhibitors. However, it has some limitations. The assay may not detect weak and non-neutralizing antibodies. Verbruggen B et al (1995) descried a modified Bethesda assay, the Nijmegen low titre inhibitor assay (74). Two modifications of the original method were adopted to overcome the poor specificity and imperfection of Bethesda assay, especially at the low levels of inhibitor: 1) buffering of normal plasma used in the assay and control mixture, with 0.1 M imidazole to pH 7.4 prevents the pH change occurring during the 2 hours incubation, and 2) replacing the imidazole buffer in the control mixture by immunodepleted FVIII deficient plasma increases the precision of the method . The Factor VIII/IX Subcommittee of the ISTH has endorsed the recommendation that the Nijmegen-modified Bethesda assay should be adopted to quantify FVIII inhibitors (75). Several

problems with FVIII inhibitor assay have not yet been resolved including: 1) the high interlaboratory variability in the quantification of FVIII inhibitors when the reference antibody standard is unavailable; 2) inability to identify the proportion of 'non-inhibitory' FVIII inhibitors leading to accelerated clearance of FVIII in vivo; and 3) the effect of the type of FVIII-deficient plasma on FVIII inhibitor detection. Verbruggen B et al (2001) showed that chemically depleted factor VIII deficient plasma can give falsely elevated titres when used in combination with other types of deficient plasmas as a substrate plasma in the factor VIII:C assay due to the presence of activated factor V in the preparation (76).

Several new tests have been developed recently to overcome the limitations of the Bethesda assay. ELISA-based assay for detection of FVIII-specific IgG was validated and found to have a strong correlation with Bethesda method in detecting immune response to FVIII. The ELISA provides rapid screening that could be available well in advance of inhibitor confirmation by the Bethesda assay (77,78). Recently developed a new fluorescence-based immunoassay (FLI) was found to be much more sensitive for detecting especially low titre inhibitors (79).

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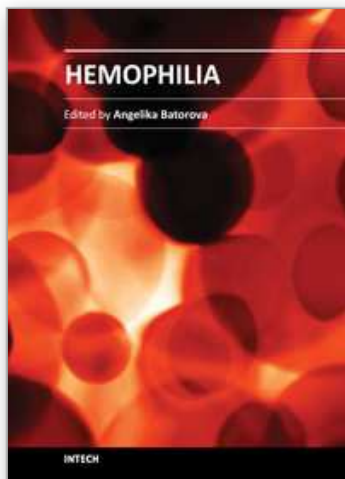
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This book demonstrates the great efforts aimed at further improving the care of the hemophilia, which may bring further improvement in the quality of life of hemophilia persons and their families.

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