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REVIEW

Hemophilia A in the third millennium

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ABSTRACT

Hemophilia A is an X-linked hereditary bleeding disorder due to the deficiency of coagulation factor VIII (FVIII). According to the degree of FVIII deficiency, mild, moderate or severe forms are recognized. Although patients with mild hemophilia A usually bleed excessively only after trauma or surgery, those with severe hemophilia experience frequent episodes of spontaneous or excessive bleeding after minor trauma, particularly into joints and muscles. The modern management of hemophilia began in the 1970s and is actually based upon several plasma-derived or recombinant FVIII products. In addition, the synthetic drug desmopressin can be used to prevent or treat bleeding episodes in patients with mild hemophilia A. Long-term and continuous substitution therapy (prophylaxis), the recommended treatment in severe hemophilia, prevents bleeding and the resultant joint damage. In the last twenty years the high standard of hemophilia care has greatly improved the quality of life of patients and their life expectancy has reached that of the non-hemophilic male population, at least in high-income countries. The most serious and challenging complication of treatment of hemophilia A is the development of inhibitors, which renders FVIII concentrate infusion ineffective and exposes patients to an increased risk of morbidity and mortality. In this narrative review, the actual knowledge on the clinical features and management of patients with hemophilia A is summarized.

1. Introduction

Hemophilia A is a hereditary X-chromosomal recessive disorder caused by mutations in the factor VIII (FVIII) gene, leading to the deficiency or absence of this protein as an essential component of the intrinsic pathway of blood coagulation [1–4]. The prevalence of hemophilia A is commonly reported as 1 in 5000 male live births. Depending on the FVIII activity in patient plasma, hemophilia A is classified as severe (<1%), moderate (1–5%) or mild (>5% to <40%) [5]. The bleeding phenotype generally corresponds to the degree of severity of FVIII deficiency.

FVIII is a plasma glycoprotein consisting of six domains A1–A2–B–A3–C1–C2. The encoding gene is located on the long arm of the X chromosome (Xq28). The mature protein is a heterodimer with a light chain consisting of domains A3–C1–C2 and a heavy chain of domains A1–A2–B. The majority of FVIII is thought to be synthesized in liver sinusoidal cells [6]. Multiple mutations leading to hemophilia A have been identified in the FVIII gene: the most common, affecting approximately half of the patients with severe disease, is a large inversion and translocation of exons 1–22, which completely disrupts the gene. Patients with gene mutations that severely truncate or prevent the production of FVIII (intron 1 and 22 inversions, large deletions, non-sense mutations) are more susceptible to the development of FVIII alloantibodies than those carrying point mutations, small deletions or insertions [7–9]. The diagnosis of hemophilia A, that should be suspected whenever unusual bleeding occurs in a male, is confirmed by the results of laboratory screening tests, including a prolonged partial thromboplastin time contrasting with a normal platelet count, prothrombin time and bleeding time. The definitive diagnosis relies on the specific assay of FVIII coagulant activity in plasma.

In this narrative review, we present the actual knowledge on the most important clinical and therapeutic aspects of hemophilia A. A search was performed on PubMed using the following terms without time limits: “hemophilia A”, “factor VIII”, “prophylaxis”, “inhibitors”, “recombinant factor VIII concentrates”, “plasma-derived factor VIII concentrates” and “hemophilia gene therapy”. The date of the last search was April 20, 2013. The bibliographic references of all retrieved original articles and reviews were assessed for additional relevant articles.

2. Clinical manifestations of hemophilia A

The clinical hallmarks of hemophilia A are muscle and joint hemorrhages, particularly in knees, elbows and ankles [4]. Acute hemarthroses usually begin with mild discomfort and a slight limitation of joint motion, followed by pain, joint swelling and cutaneous warmth. If untreated, joint hemorrhage usually leads to severe limitation of motion. Unfortunately, the pathologic processes continue even after bleeding stops, because inflammation causes damage of the blood-filled joints leading to synovitis, which in turn increases the likelihood of frequently recurring hemarthroses in the same joints (the so called target joints). The final

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step of this vicious circle that causes hemophilic arthropathy is the narrowing of the joint space due to loss of the cartilage, development of bone cysts and limitation of motion resulting in permanent disability [10]. Intramuscular hematomas account for 10 to 25% of all bleeds in hemophilia and can cause severe problems by compressing vital structures [3]. Inadequate treatment of hematomas can lead to pain, anemia, compartment syndrome with nerve damage, reduced range of motion, loss of function, wasting and pseudotumor formation. Bleeding into the iliopsoas muscle, a typical clinical manifestation of hemophilia characterized by flexion contraction of the hip joint, can be limb-threatening and should be treated aggressively. Bleeding from the gastrointestinal and urinary tracts, as well as intracranial hemorrhage may also occur, but less frequently than muscolo-skeletal bleeding. However, cerebral bleeding is the most dangerous and life-threatening hemorrhagic event in hemophilic patients and requires urgent management. Symptoms often occur soon after trauma, but sometimes bleeding is delayed, as for example in the presence of subdural hematomas. Thus, hemophilic patients with unexplained and persistent headaches should always be suspected of having hemorrhage in the brain parenchyma, subdural or epidural hematomas [11]. Intracranial hemorrhage may also occur spontaneously at any age, but especially in newborns and elderly patients [11]. Zanon and colleagues recently collected 112 cases of intracranial hemorrhage in 88 hemophilia patients and found that the severity of hemophilia and the presence of an inhibitor were strongly associated with the risk of developing this dramatic bleeding complication (hazard ratios 3.96 [2.39–6.57] and 2.52 [1.46–4.35], respectively) [12].

3. Treatment of hemophilia A

The modern management of hemophilia A started in the 1970s with the industrial development of plasma-derived FVIII concentrates [13,14]. The widespread availability of such products radically improved hemophilia care, because it made possible for patients to treat themselves at home, with the resulting early control of hemorrhages and the reduction of the musculoskeletal damage typical until then of untreated or poorly treated patients. However, the improved quality of life (QoL) and life expectancy characteristic of that decade were dramatically interrupted in the 1980s, when many patients died of blood-borne infections by the human immunodeficiency virus (HIV) and the hepatitis viruses transmitted by factor concentrates manufactured from human plasma pooled from thousands of donors [15]. As a consequence of these devastating epidemics, the need for a safe treatment became crucial for the hemophilia community [16]. The implementation of purification methods (cryoprecipitation, ion exchange, gel permeation or monoclonal antibody immunoaffinity chromatography), and of viral inactivation (solvent detergent, heat treatment/pasteurization) or removal (ultrafiltration) techniques for the production of plasma-derived factor concentrates, as well as the adoption of new methods to screen viruses in blood donations (i.e., nucleic acid testing [NAT]), greatly improved the safety of plasma-derived products, as shown by the fact that blood-borne transmissions of hepatitis viruses or HIV have no longer occurred in the last 25 years [16]. However, the most important advance in this pharmacological field was represented by the rapid progress in DNA technology (following the cloning in 1984 of the FVIII gene), which allowed the industrial production of recombinant FVIII, culminating with the publication in 1989 of the first report on the clinical efficacy of this product in two patients with severe hemophilia [17]. Three different generations of recombinant FVIII are commercially available: first generation products use animal-derived proteins in the cell culture medium and human serum albumin to stabilize FVIII in the final formulation; second-generation products use human-derived proteins in the culture medium but no albumin is added to the final formulation; and third-generation products are manufactured with no protein other than FVIII in the culture medium or final formulation. Second and third generation recombinant FVIII may be full-length or lack the B-domain, which is disposable for the coagulant activity [18]. Table 1 reports the characteristics of the main plasma-derived and recombinant FVIII products. However, for a comprehensive list and more details on the characteristics of these products, the readers are referred to a recent publication of the World Federation of Hemophilia (WFH) [19]. Table 2 summarizes the recommended dosages of FVIII for the treatment/prevention of bleeding episodes in hemophilia A.

An exception to the use of FVIII products is represented by mild hemophilia A, for which the administration of the synthetic vasopressin analog desmopressin acetate, injected intravenously or subcutaneously at a dosage of 0.3 μg/kg, does transiently increase two- to four-fold the plasma levels of FVIII and von Willebrand factor (VWF) [20,21]. Since its first clinical use in 1977, desmopressin has spared several patients with mild hemophilia A from the risk of acquiring blood-borne viral infections due to the infusion of non-virally inactivated plasma-derived FVIII concentrates [20]. Its clinical use depends on the target for post-treatment plasma FVIII levels, which in turn depends on the patient's baseline FVIII activity. To assess the degree of response to desmopressin, hemophilia A patients should undergo a test infusion prior to the therapeutic use of this drug. It is generally agreed that a FVIII post-infusion level of at least 30% is sufficient for the treatment of minor bleedings or minor surgery, such as dental extractions. On the other hand, levels higher than 50% post-administration are required for major surgery [22]. Repeated infusions of desmopressin over a short time period (2–3 doses given at 12–24 h) almost always induce tachyphylaxis with a decreased plasmatic response, probably because FVIII and VWF stores are exhausted [23]. Hence, instead of desmopressin, FVIII concentrates should be chosen for the management of severe bleeding or when prolonged treatments are predicted (i.e., prophylaxis of bleeding during major surgery). Desmopressin usage has a few, self-limited and minor side-effects including facial

Table 1
Main characteristics of licensed plasma-derived and recombinant FVIII products.

Plasma-derived FVIII			
Product	Manufacturer	Albumin content	Purification/viral inactivation
Alphanate	Alpha Therapeutics	Yes	HLC/SD/DH
Beriate	CSL Behring	No	IEC, pasteurization
Biostate	CSL Bioplasma	Yes	HGP/GF/SD/DH
Emoclot DI	Kedrion	No	IEC/SD/DH
Fanhdi	Grifols	Yes	HLC/SD/DH
Haemate P	CSL Behring	Yes	MP/pasteurization
Haemoctin SDH	Biotest	No	IEC/SD/DH
Hemofil M	Baxter	Yes	IAC/SD
Immunate	Baxter	Yes	IEC/SD/VH
Koate-DVI	Talecris	Yes	MP/SE/SD/DH
Wilate	Octapharma	No	IEC/SE/SD/DH
Recombinant FVIII			
Product	Manufacturer	FVIII stabilizer	Purification/viral inactivation
Recombinate[a]	Baxter Healthcare	Human albumin	IAC/IEC
Kogenate FS[b]	Bayer Healthcare	Sucrose	IAC/IEC/SD/UF
Helixate FS[b]	CSL Behring	Sucrose	IAC/IEC/SD/UF
Refacto[c]	Pfizer	Sucrose	IAC/IEC/SD
Advate[d]	Baxter Healthcare	Trehalose	IAC/IEC/SD
Xyntha/Refacto AF[e]	Pfizer	Sucrose	IAC/IEC/SD/NF

Abbreviations: rFVIII, recombinant factor VIII; HLC, heparin ligand chromatography; DH, dry heating; IAC, immunoaffinity chromatography; IEC, ion exchange chromatography; HGP, heparin/glycine precipitation; GF, gel filtration; SD, solvent/detergent treatment; HLC, heparin ligand chromatography; MP, multiple precipitation; VH, vapor heat; SE, size exclusion; UF, ultrafiltration; NF, nanofiltration.

[a] First-generation full-length.
[b] Second-generation full-length.
[c] Second-generation B-domain deleted.
[d] Third-generation full-length.
[e] Third-generation B-domain deleted.