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AN UPDATE ON HAEMOPHILIA A

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Abstract

Hemophilia A is an X-linked recessive disease caused by a defect in functional coagulation of plasma VIII (FVIII), which can be inherited or caused by spontaneous mutations. The development of inhibitory alloantibodies against FVII can seriously complicate the management of genetic cases. In rare cases, the development of autoantibodies against FVII can lead to acquired hemophilia A. The diagnosis of hemophilia A can be suspected because the coagulation test shows an increase in partial

thromboplastin time (PTT) when the prothrombin time (PT) and bleeding time are normal.

Keywords*: Haemophlia A, FVIII, PTT, PT*

INTRODUCTION

Hemophilia A is an X-linked recessive disease caused by a defect in functional coagulation of plasma VIII (FVIII), which can be inherited or caused by spontaneous mutations. The development of inhibitory alloantibodies against FVII can seriously complicate the management of genetic cases. In rare cases, the development of autoantibodies against FVII can lead to acquired hemophilia A (Konkle et al., 2014). Morbidity and death are primarily the result of bleeding, although infectious diseases (such as HIV infection, hepatitis) have become prominent, especially in patients before 1985 (Konkle et al., 2014). Laboratory studies for suspected hemophilia include complete blood counts, coagulation studies, and tests for FVIII. For patients diagnosed with hemophilia, regular laboratory evaluations include screening for the presence of FVIII inhibitors and screening for infectious or blood transfusion-related diseases, such as hepatitis and HIV infection. The management of FVIII levels is important for monitoring FVIII replacement therapy (Konkle et al., 2014). The treatment of hemophilia may involve prevention, management of bleeding events, immune induction for patients with factor inhibitors, and treatment and rehabilitation of patients with hemophilia synovitis. Ideally, treatment of patients with hemophilia should be provided through comprehensive hemophilia care centers (Konkle et al., 2014).

Historical background

Hemophilia is one of the oldest genetic diseases. Talmudic records from the second century confirmed male inherited bleeding disorders. The modern history of hemophilia began with John Otto's description of family members with hemophilia in 1803, followed by Nasse's first review of hemophilia in 1820. Wright showed evidence of laboratory coagulation defects in 1893: however It wasn't until 1937 that FVIII was discovered, when Patek and Taylor isolated a clotting factor from the blood, which they called

antihemophilic factor (AHF) (Nair, Shetty, and Ghosh 2012). The FVIII bioassay was introduced in 1950. Although the close relationship between FVIII and Von Willebrand (vWF) is now known, it was not taken seriously at the time. In 1953, the decrease in FVIII levels was described for the first time in patients with vWF deficiency. Subsequent research by Nilson and colleagues showed that there is an interaction between these clotting factors (Ma Alice and Carrizosa 2006). In 1952, hemophilia B was described and named Christmas disease after the last name of the first patient who underwent a detailed examination. After distinguishing hemophilia B from hemophilia A, mixing plasma from "true hemophilia" patients with that of Christmas disease patients has been shown to correct clotting time. Hemophilia A accounts for approximately 80% of hemophilia cases (Sonu et al., 2018). In the early 1960s, cryoprecipitate (thawed and centrifuged sediment from fresh frozen plasma) became the first concentrate that could be used to treat patients with hemophilia. In the 1970s, freeze-dried (ie, freeze-dried) medium-purity concentrates were obtained from a large number of blood donors. The introduction of concentrated freeze-dried products that are easy to store and transport has greatly improved the quality of life of patients with hemophilia and facilitated their preparation for surgery and home care (Sonu et al., 2018). Unfortunately, large-scale donors of up to 20,000 donors can contribute a single batch of plasma-derived FVIII concentrate, increasing the risk of viral contamination from commercial FVIII concentrate. By the mid-1980s, most patients with severe hemophilia had been exposed to hepatitis A, hepatitis B, and C viruses, as well as the human immunodeficiency virus (HIV) (Plug et al., 2006). Plasma-derived FVIII concentrate viral treatment is effective in eliminating new HIV transmission and nearly eliminating hepatitis and hepatitis C exposure. The introduction of recombinant FVIII concentrates and the phasing out of albumin used in the production of these products actually eliminates the risk of virus exposure (Naomi et al., 2016).

Pathophysiology

Factor VIII production, processing and structure

It is believed that the main site of factor VIII (FVIII) is the vascular endothelium of the liver and the cross-linked film system. The liver transplant corrects the deficiency of the FVIII of people with hemophilia (Naomi et al., 2016). FVIII Messenger RNA has been detected in liver, spleen and other tissues. The production studies of FVIII in transfected

cell lines are synthesized, the FVIII move in the lumen of the endoplasmic reticulum, where it joins several proteins that regulate the immunoglobulin binding proteins dissociates in the energy-dependent process (Naomi et al., 2016). The cutting of the signal peptide of FVIII and the addition of oligosaccharides occur in the endoplasmic reticulum. The Chaperone protein, carnexin and cardboard increase both the secretion and degradation of FVIII (Andrew and Maria, 2006). A part of the FVIII protein factor in the Endoplasmic Reticle is decomposed intracellularly. Other parts enter the Golgi device where some changes occur to produce heavy threads and light chains and modify carbohydrate. The addition of sulfates to tirosine residues of heavy and light chains is required for a complete coagulation promotion activity with the role of the sulfated region plays a role in thrombin interactions. This translated sulfation of tyrosine residues affects the coagulation promotion activity of factor VIII and its factor von Willebrand (VWF) (Andrew and Maria 2006).

Signs and symptoms of haemophilia A

- Regarding the symptoms of hemophilia A, there are internal or external bleeding events. People with more severe hemophilia bleed more severely and more frequently, while those with mild hemophilia tend to have milder symptoms, except after surgery or severe trauma. Patients with moderate hemophilia have different symptoms, which range from severe to mild (Konkle et al., 2014).
- Long-term bleeding caused by venipuncture or heel sticks is another common early sign of hemophilia; these signs may cause blood tests to indicate hemophilia (Lissauer et al., 2015). For others, especially those with moderate or mild hemophilia, any trauma will cause the first major bleeding. Hemophilia greatly increases the risk of long-term bleeding due to common injuries, or in severe cases, bleeding may be spontaneous with no obvious cause. Bleeding can occur anywhere on the body, superficial bleeding, such as superficial abrasions or lacerations, can be prolonged, and due to a lack of fibrin, the scab can also rupture, which can lead to rebleeding (Konkle et al., 2014). Although superficial bleeding is problematic, some of the more serious bleeding sites are: (Ma Alice and Carrizosa, 2006).

- Joints
- Muscles
- Digestive tract
- Brain

Muscle and joint bleeding or hemorrhage indicates hemophilia, and gastrointestinal and cerebral hemorrhage is also related to other bleeding disorders. Although joint bleeding is not usually life-threatening, it is one of the most serious symptoms of hemophilia. Repeated bleeding from the joint capsule can cause permanent joint damage and disfigurement, leading to chronic arthritis and disability. Joint damage is not the result of blood in the capsule, but the healing process. When the blood in the joints is broken down by enzymes in the body, the bones in the area are also broken down; this causes great pain for people affected by the disease (Ma Alice and Carrizosa, 2006).

Complications of haemophilia A

The treatment decision that must be made is the production of inhibitory antibodies against factor VIII due to frequent infusions. These problems arise when the body recognizes the injected factor VIII as a foreign object, because the body does not replicate itself. In these individuals, activated factor VIII (the precursor of factor VIII in the coagulation cascade) can be used to treat bleeding in patients with hemophilia and replacement factor VIII antibodies (Ma Alice and Carrizosa, 2006).

Oral manifestation of haemophilia A

Oral symptoms are characterized by a frequent bleeding of multiple sites. It is often seen as a gingival and deactivation output. Symptoms depend on the severity of hemophilia. In the case of severe hemophilia, the patient can not share multiple episodes of oral hemorrhage throughout life. Hemophilic patients are considered special groups, as they can be fatal in their daily producers. If hemophilia is diagnosed early in the episode of episodes of severe hemorrhage, 30% of

patients with hemophiliacs and 30% of cases are the most common part of the penis and language, it was observed that there was (Sonu et al., 2018).

Genetics of haemophilia A

Hemophilia A is inherited as an X-linked recessive trait. It occurs in homozygous men and women (this can only occur in men with hemophilia and carriers or daughters of women with hemophilia (Nair, Shetty, & Ghosh, 2012). However, Mild hemophilia A is known Occurs in heterozygous women, due to new activation, it is recommended to measure factor VIII and IX levels in all known or potential carriers before surgery and during clinically significant bleeding episodes (Kliegman and Robert,
2011).

Approximately 510% of patients with hemophilia A are affected because they produce dysfunctional factor VIII protein, while the rest are affected because they produce insufficient amounts of factor VIII (insufficient amounts). Severe deficiency (defined as <1 active factor VIII) of people, 4550% have the same mutation, and inversion within the factor VIII gene leads to deletion of co complete protein production (Sonu et al., 2018).

Since both forms of hemophilia may be caused by various mutations, the initial diagnosis and classification is done by measuring protein activity rather than genetic testing, although once a case of hemophilia is found, it is recommended that the family be Limb testing for genetic testing (Konkle et al., 2014). About 30% of patients have no family history; it is speculated that their disease is caused by a new mutation (Bowen, 2002).

Diagnosis of haemophilia A

The diagnosis of hemophilia A can be suspected because the coagulation test shows an increase in partial thromboplastin time (PTT) when the prothrombin time (PT) and bleeding time are normal. The TTP test is the first blood test performed when there are signs of hemophilia (Bowen, 2002). However, the diagnosis is made when factor VIII levels are very low. There is usually a family history, although this is not required. Recently, genetic testing has been used to determine a person’s risk of developing or spreading hemophilia. The diagnosis of hemophilia A also includes severity, which can range from mild to severe based on the amount of activity and functional factor VIII detected in the blood. Factor VIII levels usually do not change during a person's life. Severe hemophilia A is the most common severity and occurs in most affected people.

With the exception of severe trauma (ie, tooth extraction or surgery), patients with mild hemophilia usually have few or no bleeding episodes (Konkle et al., 2014).

Severity of haemophilia A

Due to differences in changes in the factor VIII gene (and the resulting protein), there are many different mutations that can cause hemophilia A. Patients with hemophilia usually have a certain level of active clotting factors. Individuals with less than 1 tive are classified as severe hemophilia, individuals with 15 active factors have moderate hemophilia, and patients with mild hemophilia have active clotting factor levels within 540% of the normal level (Konkle et al., 2014).

Differential diagnosis of haemophilia A

The two most common differential diagnoses are hemophilia B, which is a deficiency of factor IX, and von Willebrand disease, which is a deficiency of von Willebrand factor (necessary for normal function of factor VIII; hemophilia) C is also considered (Franchini and Lippi, 2011)).

Treatment of haemophilia A

- For the treatment of this genetic disease, most patients with severe hemophilia require regular supplementation of intravenous recombinant or concentrated plasma factor VIII. Preventive treatment regimens are highly variable and individually determined (Franchini and Lippi, 2011). In children, it may be necessary to insert an easy-to-use IV port (Ma Alice, Roberts, and Escober, 2012) to minimize frequent traumatic IV intubation. These devices eliminate the trouble of finding intravenous fluids multiple times a week, making it easier for families to prevent hemophilia. However, its use has risks. The most worrying thing is infection. Studies are different, but some show high infection rates (Francini Lippi, 2011). These infections are usually treated with intravenous antibiotics, but sometimes the device must be removed (Naomi et al., 2016). In addition, other studies have shown that there is a risk of clot formation at the tip of the catheter, rendering it useless. Some people with severe hemophilia, and most people with

moderate and mild hemophilia, receive treatment only as needed without a regular prevention plan. Patients with mild hemophilia usually use desmopressin to control their condition. Desmopressin is a drug that releases factor VIII stored in the walls of blood vessels. The treatment of hemophilia may involve the following:

- Management of haemostasis
- Management of bleeding episodes
- Use of factor replacement products and adjuvant medication
- Treatment of patients with factor inhibitors
- Treatment and rehabilitation of patients with haemophilia synovitis (Franchini and Lippi, 2011).

Deposition of treatment is as follows:

- Management ideally should be provided through a comprehensive haemophilia care center
- Home administration of treatment and infusions by the family or patient is customary
- FVIII treatment may be given prophylactically or on demand
- Hospitalization is reserved for severe or life-threatening bleeds or for patients for whom home is unavailable or impractical

For treatment of acute bleeding, target levels by haemorrhage severity are as follows:

- Mild haemorrhages (e.g., early haemarthrosis, epistaxis, gingival bleeding): maintain an FVIII level of 30%
- Major haemorrhages (e.g., late haemarthrosis, muscle bleeds): maintain an FVIII of at least 50%
- Life-or limb-threatening bleeding episodes (e.g., major trauma or surgery, advanced or recurrent haemarthrosis, major GI bleeding, any head trauma, signs

of distal neurovascular compromise of limb or compartment syndrome): maintain an FVIII level of 80%-100%

The following types of FVIII concentrates are available:

- Plasma-based products: purified to inactivate viruses
- First-generation recombinant products: produced in mammalian cell lines, contain animal and/or human plasma-derived proteins in cell culture media and in final product
- Second-generation recombinant products: produced in mammalian cell lines, contain animal and/or human plasma-derived proteins in cell culture media but none in final product
- Third generation recombinant products: produced in mammalian cell lines, contain no animal and/or human plasma-derived proteins in cell culture media or in final product.
- Extended half-life recombinant FVIII products.

Dental consideration of haemophilia A

Inferior alveolar nerve block can only be performed with appropriate replacement therapy to increase the level of clotting factors because of the risk of muscle bleeding and the risk of airway damage due to hematomas in the space after the molars or in the wing bones. Intra-ligament or interosseous techniques should be considered instead of mandibular block. Articaine has been used as an oral infiltration agent to anesthetize the molars. Tongue infiltration also requires appropriate factor replacement because the injection is performed in an area rich in the vascular plexus and the needle is not close to the bone (Andrew and Maria, 2006).

Gene therapy

In December 2017, it was reported that doctors had used a new form of gene therapy to treat haemophilia A (Rangarajan *et al*., 2017).

Prognosis

Two studies in the Netherlands followed hemophilia patients for many years (Plug et al., 2006).

Both studies found that viral infections are common among hemophilia patients, because in the last study that followed patients from 1992 to 2001, frequent blood transfusions exposed them to HIV, hepatitis B, and C infections Waiting for the risk of blood-borne infections, the life expectancy of men is 59 years. If known viral infection cases are excluded, life expectancy is 72 years, which is close to the life expectancy of the general population. 26% of the cases died of AIDS and 22% died of hepatitis C (Plug et al. 2006). However, these prognostic statistics are unreliable because infection control and the efficacy of antiretroviral drugs have improved significantly since these studies (Plug et al., 2006).

Epidemiology of haaemophilia

Hemophilia A occurs in 5,000 men approximately every 1 minute (Kliegman, 2011), while the incidence of hemophilia B is one in 30,000 men. Among them, 85% have hemophilia A and 15% have hemophilia B (Kliengman, 2011).

Conclusion

Hemophilia A is an X-linked recessive disease caused by a defect in functional coagulation of plasma VIII (FVIII), which can be inherited or caused by spontaneous mutations. The development of inhibitory alloantibodies against FVII can seriously complicate the management of genetic cases. Haemophilia A a serious bleeding disorder that can result to death if not diagnosed and any cause of bleeding prevented on time especially to haemophilia A patients going through surgery and childbirth.

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