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HAEMOPHILIA: A ROYAL DISEASE

Dr. Mandeep Kaur*

Assistant Professor, Dept of Oral Pathology & Microbiology, Indira Gandhi Govt Dental College, Jammu. *Corresponding Author

ABSTRACT Haemophilia is a bleeding disorder that slows the blood clotting process. It is characterized by a prolonged bleeding after any injury, surgery and extraction of tooth. In severe cases, spontaneous and continuous bleeding occurs even after minor trauma or even when there is no obvious injury. Milder forms of hemophilia do not necessarily involve spontaneous bleeding. It is inherited in X-Linked recessive pattern and the gene associated with it is located on the X chromosomes. The median life expectancy was ~30 years until the 1960s, but improved understanding of the disorder and development of efficacious therapy based on prophylactic replacement of the missing factor has caused a paradigm shift, and today individuals with haemophilia can look forward to a virtually normal life expectancy and quality of life. The aim of this review is to improve the understanding of hemophilia which is considered a genetic disease with a high impact on the quality of life of people who suffer from it.

KEYWORDS : Haemophilia, factor VIII, bleeding disorder, X-linked recessive.

INTRODUCTION

Classic haemophilia; factor 8 deficiency; haemophilia A.

INCIDENCE

The incidence of this well-known inherited condition is one in every 10 000 live male births (only boys are affected, due to the mode of inheritance). All races can be affected. Haemophilia is a descriptive name used to describe a number of blood disorders which all have clotting problems as the basic defect. There are a number of 'factors' associated with the clotting mechanism of the blood. Haemophilia A is specifically deficient in factor VIII. Other factors are involved in the clotting disorders of other similar diseases, such as Christmas disease and Von Willebrand's disease.

HISTORY

Haemophilia has been known for many years. Early references to a bleeding condition highly suggestive of haemophilia date back to the 2nd century AD. The Babylonian Talmud indicates that if a woman has lost her first two sons after circumcision she is exempt from the obligation to have the third son circumcise. Rabbi Simon ben Gamaliel forbade a boy to be circumcised because the sons of his mother's three older sisters had died after circumcision. Potential haemophilia cases were subsequently described in the 10th century.[1,2]

In 1803, John Conrad Otto, a Philadelphia physician, was the first to publish an article recognizing that a hemorrhagic bleeding disorder primarily affected men, and ran in certain families. He traced the disease back to a female ancestor living in Plymouth, New Hampshire, in 1720. Otto called the males "bleeders." In 1813, John Hay published a paper in the *New England Journal of Medicine* proposing that affected men could pass the trait for a bleeding disorder to their unaffected daughters. Then in 1828, Friedrich Hopff, a student at the University of Zurich, and his professor Dr. Schonlein, are credited with coining the term "haemorrhaphilia" for the condition, later shorted to "haemophilia."

In 1926 Finnish physician Erik von Willebrand published a paper describing what he called "pseudohemophilia," a bleeding disorder affecting men and women equally. It was later named von Willebrand disease. In 1957 Inga Marie Nilsson and researchers at the Malmo University Hospital in Sweden determined that VWD was caused by low levels or deficient von Willebrand factor.

In 1947, Dr. Alfredo Pavlovsky, a doctor in Buenos Aires, Argentina, distinguished two types of hemophilia in his lab—A and B.

Factor I deficiency was first described in 1920. Factors II and V deficiency were identified in the 1940s. The 1950s saw an explosion of work on rare factor deficiencies, as deficiencies of FVII, X, XI and XII were first recognized. In 1960, FXIII deficiency was described.[3]

TIME LINE

1828 - Term "haemorrhaphilia" first used. Later shortened to "haemophilia."
1926 - Erik von Willebrand identifies a bleeding disorder, later called von Willebrand disease (VWD)
1940s - whole blood transfusions given at hospital
1948 - National Hemophilia Foundation (NHF) opens as The Hemophilia Foundation, Inc.
1952 - Researchers describe what is now called factor IX clotting protein
1954 - NHF establishes a Medical Advisory Council, later called Medical and Scientific Advisory Council (MASAC)
1955 - First infusions of factor VIII in plasma form
1957 - Researchers in Sweden identify von Willebrand factor as the cause of VWD
1958 - First use of prophylaxis for hemophilia A
1964 - Dr. Judith Graham Pool discovers cryoprecipitate
1968 - First FVIII concentrate available
1970s - Primary prophylaxis therapy experiments begin
1970s - Freeze-dried plasma-derived factor concentrates available
1977 - Desmopressin identified to treat mild hemophilia and von Willebrand disease
1980s - Factor VIII, FIX and von Willebrand factor genes cloned
1982 - CDC reports first AIDS cases among people with hemophilia
1985 - First inactivated factor concentrates available
1992 - FDA approves first recombinant FVIII products
1995 - Prophylaxis becomes standard of treatment in US
1997 - FDA approves first recombinant FIX products
1998 - First human gene therapy trials begin
2000s - FDA approves first recombinant factor products made without human or animal plasma derivatives
2009 - FDA approves RiaSTAP to treat factor I deficiency
2011 - FDA approves Corifact to treat factor XIII deficiency
2013 - Gene therapy trials underway at three sites in the US

A Royal Disease

Hemophilia is sometimes referred to as "the royal disease," because it affected the royal families of England, Germany, Russia and Spain in the 19th and 20th centuries. Queen Victoria of England, who ruled from 1837-1901, is believed to have been the carrier of hemophilia B, or factor IX deficiency. She passed the trait on to three of her nine children. Her son Leopold died of a hemorrhage after a fall when he was 30. Her daughters Alice and Beatrice passed it on to several of their children. Alice's daughter Alix married Tsar Nicholas of Russia, whose son Alexei had hemophilia. Their family's entanglement with Rasputin, the Russian mystic, and their deaths during the Bolshevik Revolution have been chronicled in several books and films. Hemophilia was carried through various royal family members for three generations after Victoria, then disappeared.

Pathogenesis

Haemophilia A has an X-linked recessive inheritance. There is an abnormal factor VIII molecule in sufferers from this condition, leading to the abnormal clotting mechanism. Between one-fifth and one-third of all cases are thought to arise sporadically as new mutations. The disease can be mild, moderate or severe. It is thought that there may be a different type of genetic inheritance in these three manifestations of

the disease. About half of all known cases of classic haemophilia have the severe form of the disease. About 80% of sufferers have positive family history of haemphilia. Haemophilia B results from deficiency of factor IX. There is hemophilia C as well, which occurs due to deficiency of clotting factor XI but is rare. Sometimes acquired hemophilia can present related to age or childbirth and usually resolves with appropriate treatment. The condition can be diagnosed antenatally by fetoscopy[4,5].

Clinical Features

All the features of haemophilia are entirely due to the defective clotting mechanism. The condition can be diagnosed at birth. Excessive bleeding from the umbilical cord can be the first clue of a possible bleeding disorder. In severely affected boys, haemorrhages into joints are common. This occurs following only minimal trauma, or may be nothing more than the usual vigorous movements of joints common to all active children. Hips, knees and ankles in the lower limbs can all be affected as can wrists and elbows in particular in the upper limbs. This leads to painful, swollen joints, the excess blood inside the capsules of the joints causing the pain. Mild deficiency is seen in 5-40% of cases, moderate deficiency in 1-5% and severe deficiency in less than 1% cases. Hemathroses incidence is 70-80% cases, involvement of muscles is seen in 70-80% and that of CNS is less than 5% cases.

Appropriate treatment must be given early to avoid damage and eventual destruction of the affected joints. Before the advent of specific treatment, deformed joints due to degenerative arthritis were the inevitable result of frequent haemorrhagic incidents. This was especially evident in the weight-bearing joints such as hips and knees. Bruising in soft tissues all over the body is commonly seen in haemophiliac boys. In young children, bleeding from minor injuries to the tongue and lips is common. During the early days of learning to walk, falls are common and are often associated with damage to the mouth region. Inadvertent biting of the tongue is also common when learning to cope with solid food. Both these everyday events can lead to severe haemorrhage in the boy with haemophilia. Bumps on the head are again very common during the growing years. This can result in disastrous bleeding into the brain unless rapid treatment is given. This is one of the major causes of death in the young child with haemophilia. Less severely affected children will not be so vulnerable to minor injury. It is only when surgery (for tonsillectomy and other relatively minor procedures) is undertaken that the clotting defect is a problem. The more serious injuries, such as those caused in road accidents, will also result in severe bleeding. In cases of suspected child abuse, the possibility of haemophilia should also be ruled out[6,7].

Haemophiliac boys are especially susceptible to infection with hepatitis B. This can lead to progressive liver disease with a potentially fatal out come. As soon as the diagnosis of haemophilia is made, immunization against hepatitis B should be given. Treatment is by the administering factor VIII. Prompt infusion of this compound will limit the damage done by bleeding into joints. The treatment must be given as soon as the bleeding occurs. Some boys with haemophilia will develop a specific 'inhibitor', or immunity, to routine treatment. Subsequent haemorrhagic events will then need to be treated at a specialized haemophiliac centre. Some years ago, blood products used to treat haemophiliac patients were, regrettably, contaminated with HIV and a number of sufferers have succumbed to AIDS as a result. Heat treated products, which render HIV non-infectious, are now used for treatment[8].

Treatment

It can be difficult to strike the correct balance in a boy with haemophilia between over-protection and lack of restraint. Parents will feel they must avoid even the slightest injury to their son with the resultant probability of severe haemorrhage. On the other hand, the child must be allowed to explore and investigate his environment as part of the growing process. It is all too easy for the boy with haemophilia to develop emotional problems as a result of his genetic inheritance. Support and advice from doctors, nurses and other professionals experienced in the handling of children with haemophilia is important. Parents become very experienced during the early years in assessing the significance of any injury, and will also become adept at giving the appropriate treatment. Schooling will obviously present greater risks to the haemophiliac child. Teachers must be fully conversant with the action to be taken if a knock or other injury results in a bleed into a joint or other tissues.

VON Willebrand's Disease (or Pseudo-haemopidlia)

This is a condition which also has a relative deficiency in factor VIII. Unlike haemophilia A, Von Willebrand's disease can affect both boys and girls, as the inheritance pattern is either an autosomal dominant or an autosomal recessive. Symptoms of bleeding are much less pronounced than in haemophilia A. Nevertheless, epistaxis (nosebleed) is common and bruising on minimal injury can result. In girls excessive menstrual flow can be a problem resulting in much discomfort and possibly in anaemia. Excessive bleeding following surgery can also be a problem. Treatment is by administering cryoprecipitate factor 8. Immunization against hepatitis B is also a wise precaution. Later in life care must be taken in women to control bleeding following childbirth[10].

CONCLUSION

With adequate quick treatment of bleeding episodes, the outlook is good nowadays for haemophiliac boys. Careers which include physical activities must be avoided, and contact sports must not be indulged. The telephone number of the haemophiliac centre responsible for the treatment of the child should be available in school. If in any doubt as to the action to be taken following an injury, advice can be obtained from this source. Contact sports and other violent physical activities must not be part of the curriculum for the haemophiliac boy. Education has an important part to play in the future career of a boy with this condition. Manual work cannot be contemplated. so intellectual pursuits and careers are of vital importance. Care should also be taken in the use of aspirin in haemophiliac boys due to the possibility of Reye's syndrome occurring in a small number of children.

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