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Review Article

HAEMOPHILIA: AN OVERVIEW

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ABSTRACT

Haemophilia also called hemophilia, is a mostly inherited, genetic disorder that impairs the body's ability to make blood clots, a process needed to stop bleeding. This results in people bleeding longer after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain. Those with mild disease may only have symptoms after an accident or during surgery. Bleeding into a joint can result in permanent damage while bleeding in the brain can result in long term headaches, seizures, or a decreased level of consciousness.There are two main types of haemophilia, haemophilia A due to not enough clotting factor VIII and haemophilia B due to not enough clotting factor IX. They are typically due to inheriting from one's parents an X chromosome with a non functional gene.

Keywords: *Haemophillia, , Human body fluids, Requirments*

INTRODUCTION:-

Haemophilia also called hemophilia, is a mostly inherited, genetic disorder that impairs the body's ability to make blood clots, a process needed to stop bleeding. This results in people bleeding longer after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain. Those with mild disease may only have symptoms after an accident or during surgery. Bleeding into a joint can result in permanent damage while bleeding in the brain can result in long term headaches, seizures, or a decreased level of consciousness. There are two main types of haemophilia, haemophilia A due to not enough clotting factor VIII and haemophilia B due to not enough clotting factor IX. . The clotting factors are made either from human blood or by recombinant methods .Haemophilia A affects about 1 in 5,000-10,000, while haemophilia B affects about 1 in 40,000, males at birth.

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In the 1800s haemophilia was common within the royal families of Europe. The difference between haemophilia A and B was determined in 1952. .

In fact, more than 80% of patients with FVIII autoantibodies hemorrhage into the skin, muscles, or soft tissues and mucous membranes (e.g., epistaxis, gastrointestinal and urological bleeds, retroperitoneal hematomas), whereas hemarthroses, typical of congenital factor VIII deficiency, are unusual. The hemorrhages in AHA are often serious or life threatening, such as in the case of rapidly progressive retroperitoneal hematomas or the

A person with less than 1% of normal clotting activity is described as having severe haemophilia. A person with between 1% and 5% of normal clotting activity is described as having moderate haemophilia and a person with over 5% but less than 50% of normal activity is described as having mild haemophilia.

Signs and Symptoms:-

The signs and symptoms of hemophilia will vary depending on a person's lack of clotting factors due to the condition.

- Many large or deep bruises
- Joint pain and swelling (caused by bleeding)
- Unexplained bruises or bleeding
- Blood in urine or stool
- Bleeding for longer than normal from a cut or injury, or after a lost tooth or surgery
- Nosebleeds for no apparent reason
- A painful, lasting headache
- Repeated vomiting
- Extreme tiredness or a change in normal behaviour

Inheritance Pattern:-

Haemophilia is an inherited condition. However, it is possible for the condition to appear in any family – it is thought that at least 30% of people with haemophilia have no family history of haemophilia. It is difficult to be exact about this because of the way in which haemophilia is inherited. Technically, it is a sex-linked recessive inheritance condition. The sex of a newly conceived baby is determined by the type of chromosomes it receives – one from each parent. A boy inherits his mother's X chromosome and his father's Y chromosome, and a girl has two X chromosomes, one from each parent. The defect that causes haemophilia resides in the X chromosome. A carrier female has one normal and one defective X chromosome. If she has a son, the son has a 50:50 chance of receiving his mothers defective X chromosome and therefore has a 50:50 chance of having haemophilia. The daughter of a carrier also has a 50:50 chance of being a carrier herself.

Table: 1 Classification of haemophilia. Adapted from

Factor level (IU/mL)	Classification	Predisposition to bleeding	Haemarthrosis
>0.05 to 0.40 (>5 to 40% of normal)	Mild	With severe injury, surgery	Rarely
0.01 to 0.05 (1–5% of normal)	Moderate	With slight injury	Sometimes
<0.01 (<1% of normal)	Severe	Spontaneous, with little or no trauma	Very frequently

compartment syndrome due to intramuscular bleed.

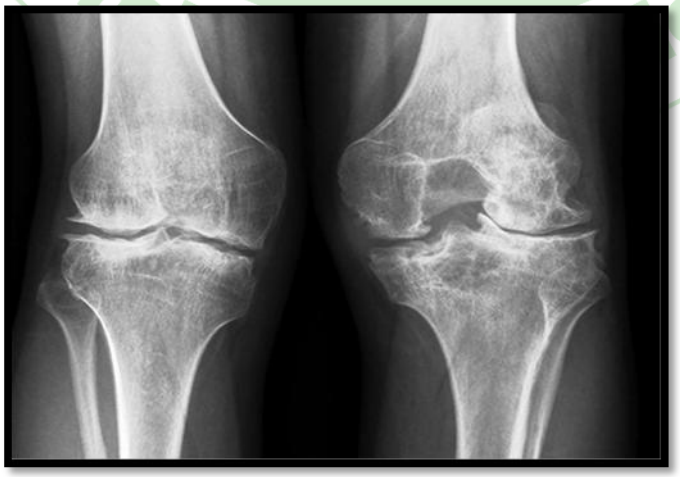

Figure- 1.1: Severe bilateral hemophilic arthropathy of the knee in a 37-yearold male.

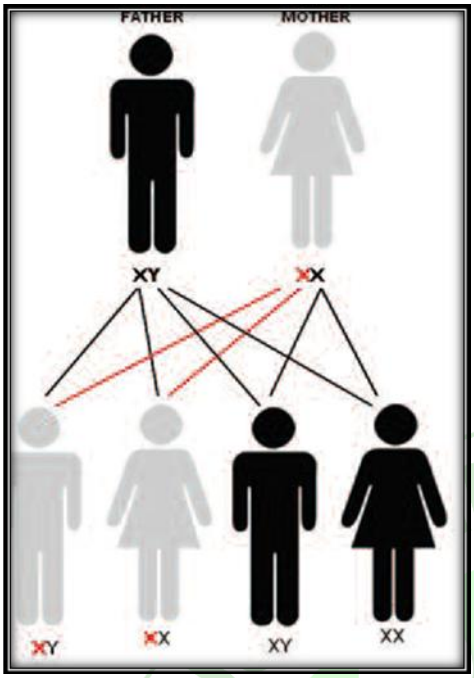

Figure-1.2: Inheritance pattern when the mother is a carrier of Haemophilia

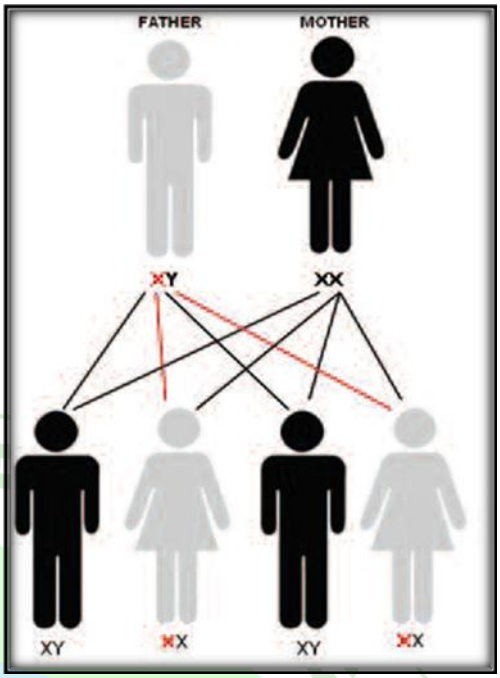

Figure-1.3: Inheritance pattern when the father has Haemophilia.

TYPES OF HAEMOPHILIA

The main types of hemophillia consist-

- Haemophilia A
- Haemophilia B
- Haemophilia C

Haemophilia A:-

Haemophilia A is a genetic deficiency in clotting factor VIII, which causes increased bleeding and usually affects males.In severe cases, heavy bleeding occurs after minor injury or even when there is no injury (spontaneous bleeding). Serious complications can result from bleeding into the joints, muscles, brain, or other internal organs. In milder forms there is no spontaneous bleeding, and the disorder may not become apparent until after a surgery or serious injury. The main treatment is called replacement therapy, during which clotting factor VIII is dripped or injected into a vein.

- **Signs and symptoms :-**

In terms of the symptoms of Haemophilia A there are internal or external bleeding episodes. Prolonged bleeding from a vene puncture or heel prick is another common early sign of haemophilia; these signs may lead to blood tests which indicates haemophilia.

While superficial bleeding is troublesome, some of the more serious sites of bleeding are:-

- Joints
- Muscles
- Digestive tract
- Brain

- **Genetics :-**

Haemophilia A is inherited as an X-linked recessive trait, and occurs in males and in homozygous females (only possible in the offspring of a carrier female and a haemophilic male. However, mild haemophili a A is known to occur in heterozygous female s due to X-inactivation, so it is recommended that levels of factor VIII and IX be measured in all known/potential carriers prior to surgery and in the event of clinically significant bleeding.

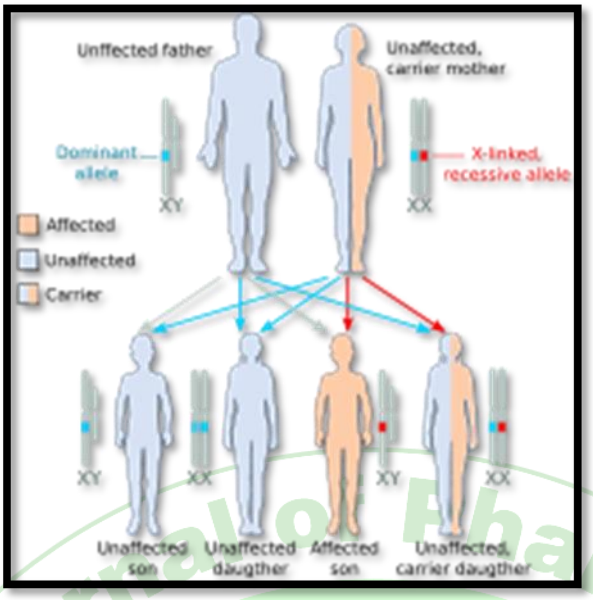

Figure-2.1. X linked recessive inheritance

Diagnosis:-

Two of the most common differential diagnoses are haemophilia B which is a deficiency in Factor IX and von Willebrand Disease which is a deficiency in von Willebrand factor (needed for the proper functioning of Factor VIII), haemophilia C is also a possible, differential diagnosis). Desmopressin raises the levels of factor VIII in the blood and may be taken intravenously or through a nasal spray. Drugs known as antifibrinolytics, which slow the breakdown of clotting factors in the blood, can also be used to treat those with a mild form of the disorder.

Treatment:-

In regards to the treatment of this genetic disorder, most individuals with severe haemophilia require regular supplementation with intravenous recombinant or plasma conc entraFactor VIII. Treatment primarily consists of replacing the missing clotting factor VIII (replacement therapy) and preventing complications that are associated with the disorder.

Complications:-

- Antibody inhibitor formation affects about 25–30%, reducing efficacy of therapy.
- Life-threatening haemorrhage.

Epidemiology:-

- Haemophilia A occurs in approximately 1 in 5,000 males, while the incidence of haemophilia B is 1 in 30,000 in male population, of these, 85% have haemophilia A and 15% have hemophilia B. It affects 1:4,000 to 1:5,000 live male births worldwide.
- It is five times as common as haemophilia B (factor IX deficiency).
- Acquired haemophilia affects around 1 to 3 people per million of the population.

Heamophillia B:-

Hemophilia B is the second most common type of hemophilia and is estimated to occur in about 1 in 25,000 male births. It affects all races equally. Hemophilia B is also known as factor IX deficiency or Christmas disease. Although the focus of this report is the genetic, or inherited, form of hemophilia B, it should be noted that another form called acquired hemophilia B can develop later in life (see "Related Disorders" section below). This is thought to be due to the effects of testosterone at maturity.

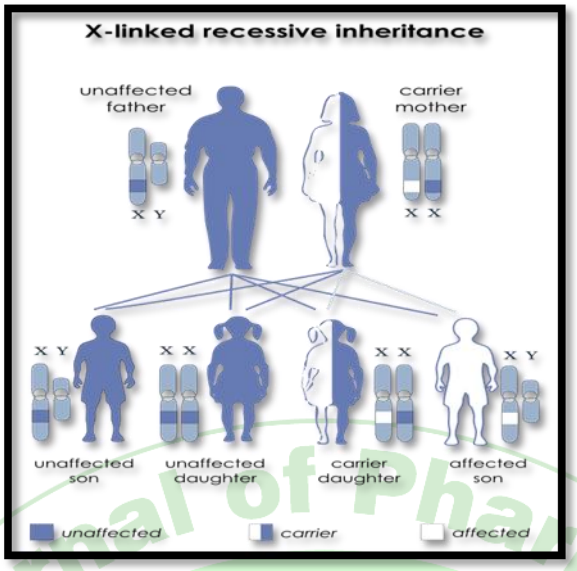

Figure-2.2: X-Linked Recessive Inheritance

Signs And Symptoms:-

Bleeding into joints with associated pain and swelling
Blood in the urine or stool
Bruising
Gastrointestinal tract and urinary tract hemorrhage
Nosebleeds
Prolonged bleeding from cuts, tooth extraction, and surgery
Spontaneous bleeding
Hemorrhage
Prolonged bleeding
Spontaneous bleeding
Easy bruising
Joint pain
Bone deformities

Genetics:-

The gene for factor IX—like the gene for factor VIII—is located on the long arm of chromosome X, within the Xq27 region. The X and Y chromosomes are called sex chromosomes. The gene for hemophilia is carried on the X chromosome. Hemophilia is inherited in an X-linked recessive manner. Females inherit two X chromosomes, one from their mother and one from their father (XX). Males inherit an X chromosome from their mother and a Y chromosome from their father (XY).

For a female carrier, there are four possible outcomes for each pregnancy:

- A girl who is not a carrier
- A girl who is a carrier
- A boy without hemophilia
- A boy with haemophilia

Causes :-

Hemophilia B is caused by an inherited X-linked recessive trait, with the defective gene located on the X chromosome. Females have two copies of the X chromosome. If the factor IX gene on one chromosome does not work, the gene on the other chromosome can do the job of making enough factor IX. Males have only one X chromosome. If the factor IX gene is missing on a boy's X chromosome, he will have Hemophilia B.

Diagnosis:-

The best place for patients with hemophilia to be diagnosed and treated is at one of the federally.A medical health history is important to help determine if other relatives have been diagnosed with a bleeding disorder or have experienced symptoms. Tests that evaluate clotting time and a patient's ability to form a clot may be ordered. A clotting factor test, called an assay, will determine the type of hemophilia and its severity

Treatment:-

Treatment includes replacing the missing clotting factor. You will receive factor IX concentrates. How much you get depends on:

- Severity of bleeding
- Site of bleeding
- Your weight and height

You should get the hepatitis B vaccine. People with hemophilia are more likely to get hepatitis because they may receive blood products. The main medication to treat hemophilia B is concentrated FIX product, called clotting factor or simply factor. Recombinant factor products, which are developed in a lab through the use of DNA technology, preclude the use of human-derived pools of donor-sourced plasma. Amino caproic acid is an anti fibrinolytic, preventing the breakdown of blood clots.

Complication:-

The bleeding can cause many problems, including neurological deficits; however, a very common finding is that recurrent bleeding into joints leads to destruction of the joint. Before the advent of recombinant factor IX, patients used to receive factor IX concentrate that was derived from the plasma of many donors.

Prognosis:-

The life expectancy and quality of life of patients with haemophilia have dramatically improved over a number of years, mainly due to new therapeutic options and the awareness to the risk of HCV and HIV infections. Prophylaxis and early treatment with factor concentrate that is safe from viral contamination have dramatically improved the prognosis of patients regarding morbidity and mortality due to severe hemophilia.

Management:-

The major concerns, even with recombinant products, are the possibility of transmission of infections and inhibitor formation. If patients have never been exposed to plasma products then recombinant factor IX is first-line. If this is unavailable then plasma-derived factor IX or prothrombin complex concentrates are available. The latter should be avoided if at all possible, as it has been associated with an increased risk of thrombosis.

In the acute situation

- Attention must be paid to trying to secure haemostasis. In the established patient, he or she may be able to self-administer factor concentrate. Get as much history as possible from the patient, who probably knows his or her disease well.
- Minor haemorrhage requires between one and three doses of factor IX. Major haemorrhage needs many doses and continued factor IX activity monitoring, with the goal of keeping the trough activity level of at least 50%. Continuous infusions of factor IX may be required.

In the chronic state

- Patient/carer information and consent, with advice regarding advantages and disadvantages of factor concentrates.
- All patients should be offered vaccination against hepatitis A and hepatitis B - give SC, not IM (may also need to be offered to carers who might inject blood products).
- Patients should wear a medical emergency identification bracelet or similar stating the disease, the normal level of factor IX and any other important information.

Haemophilia C:-

While factor VIII and factor IX deficiencies are the best known and most common types of hemophilia, other clotting factor deficiencies also exist. Low levels of factor XI (FXI) cause hemophilia C. FXI plays an important role in tissue factor-dependent thrombin generation on the surface of activated platelets. The formation of the initiating complex, TF-FVIIa-FXa, results in the generation of a small amount of thrombin. This is insufficient to produce a stable fibrin clot but stimulates a number of reactions in

the amplification loop, including the activation of FXI. Subsequent formation of the tenase complex (FIXa-FVIIIa), followed by the prothrombinase complex (FXa-FVa), leads to a large burst of thrombin.For a schematic of these processes, Haemophilia C is also known as plasma thromboplastin antecedent (PTA) deficiency or Rosenthal syndrome. Like the other hemophilias, hemophilia C is associated with bleeding, but it differs from hemophilia A and B in several ways.

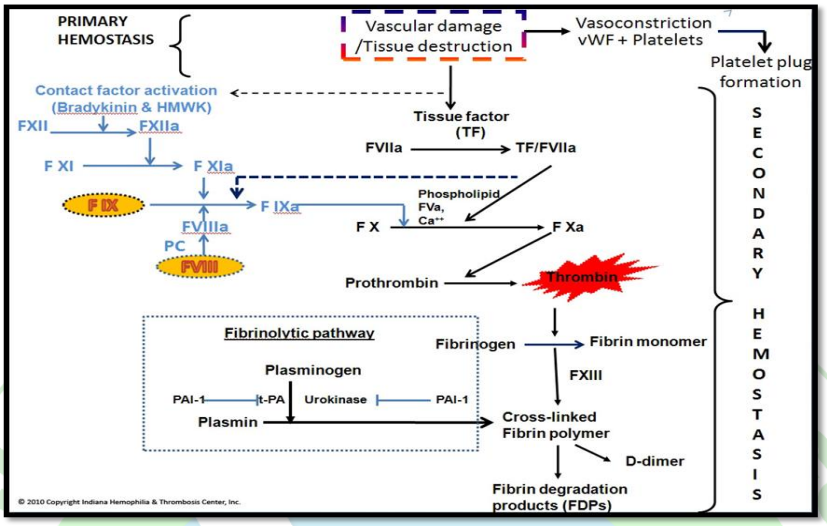

Figure-2.3: Haemophillia c

The clotting mechanism:-

Blood is carried throughout the body in a system of blood vessels. When we are injured, one or more blood vessels may be punctured, resulting in loss of blood. Or the blood vessel can be damaged deep inside the body, causing a bruise or internal hemorrhage. As soon as a vessel wall breaks, the components responsible for coagulation come together to form a plug at the break. Several steps are involved in forming a plug. The platelets, very small cells, are the first to arrive at the site where the vessel is ruptured. They stick to one another and attach themselves to the damaged vessel wall.

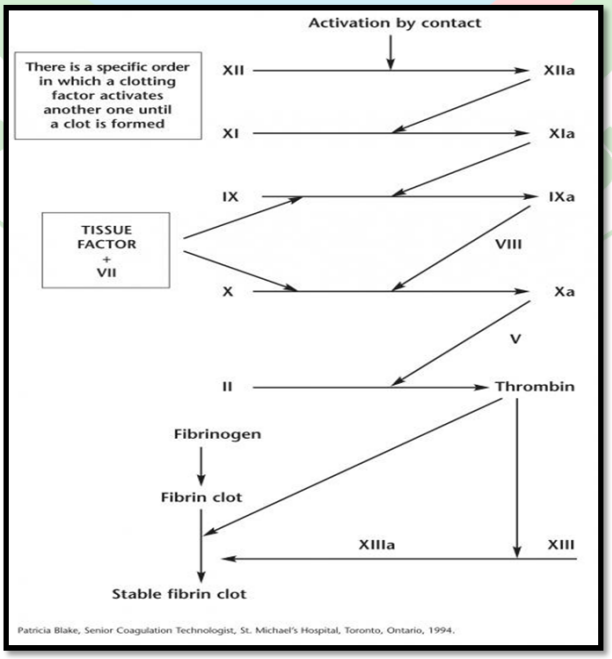

Figure-2.4: The following diagram shows schematically the order of the cascade activation of different coagulation factors to form a clot.

Sign & symptoms:-

In terms of the signs/symptoms of hemophilia C, unlike individuals with Haemophilia A and B, people affected by it are not ones to bleed spontaneously. However, people affected with haemophilia C might experience symptoms closely related to those of other forms of haemophilia such as the following:

- Oral bleeding.
- Nosebleeds.
- Blood in the urine.
- Post-partum hemorrhage (20% of cases)

Gene mutations:-

Mutations in the factor XI gene cause the congenital deficiency of factor XI clotting activity. The inheritance pattern of factor XI is autosomal but not completely recessive, because heterozygotes may have bleeding. The gene for factor XI is near the gene for prekallikrein on the distal arm of chromosome 4 (4q35). It is 23 kb, with 15 exons and 14 introns. Factor XI is synthesized in the liver and circulates in the plasma as a complex with high-molecular-weight kininogen. Factor XI has a half-life of about 52 hours. More than 200 other mutations that cause factor XI deficiency have been described and are listed in online databases.

Causes of Haemophilia C :-

Hemophilia C is primarily an inherited disorder, but unlike hemophilia A and B, the inheritance of hemophilia C follows an autosomal recessive pattern. The gene that causes FXI deficiency is not present on a sex chromosome and the condition, therefore, affects both genders equally. The FXI gene is 23kb in length, has 15 exons, and is found on chromosome 4q32-35. Factor XI is produced by the liver and circulates in the blood in an inactive form. The plasma half-life of FXI is approximately 52 hours. However, hemophilia C may be diagnosed in many other ethnic groups. In the United States, the estimated prevalence of severe hemophilia C is 1 case per 100,000 persons. In Israel, hemophilia C has been estimated to be approximately 8% among Ashkenazi Jews, making it one of the most common genetic disorders in this group. In hemophilia C.

Diagnosis of Hemophilia C

Obtaining a detailed personal and family bleeding history of a patient is very important in the diagnosis of hemophilia C. Although this condition is found in all racial and ethnic groups, it is helpful to establish the patient's background, as this may give an indication of the likely disorder.

Treatment of Hemophilia C

Patients with severe hemophilia C do not require treatment or prophylactic (preventive) therapy for daily activities. However, replacement therapy is required for dental extractions and surgery, and treatment options depend on the type of procedure. However, since FXI is not concentrated in fresh frozen plasma, a large volume of this product may be required to raise the FXI activity to a hemostatic level. Two such products are available in Europe, but their use in patients has been limited because of reports of thrombotic complications after the use of both available concentrates.

Fresh frozen plasma

The first patients who were diagnosed with this disease were treated effectively with fresh frozen plasma. Plasma is a blood derivative, a yellowish liquid that is rich in coagulation factors. There is a potential danger of transmission of viruses such as HIV and hepatitis A, B and C via plasma, since it is provided by donors and is not subjected to any virus inactivation procedure.

Factor XI Concentrate

Factor XI concentrate is delivered in lyophilized (powder) form in glass containers. It is distributed to hospitals by Héma-Québec or Canadian Blood Services. These factor concentrates are fully treated to inactivate blood-borne viruses such as HIV and the viruses responsible for hepatitis A, B and C.

Hormone Therapy

Hormone therapy is administered in the form of birth control pills, injections and, in the past few years, intra-uterine devices (IUDs). Hormone therapy is an excellent way for women with factor XI deficiency to protect themselves against abundant menstrual bleeding, since it acts by adjusting hormone levels to imitate pregnancy

DDAVP

DDAVP taken intravenously is used especially for rapid control of occasional bleeding or to prevent excessive bleeding during surgery. DDAVP acts for 8 to 12 hours, with maximum effectiveness about thirty minutes to one hour after injection. It should therefore ideally be administered within an hour before surgery

Cyklokapron

Cyklokapron (the commercial name of tranexamic acid) acts by helping hold the clot in place after it has formed. It has proven very useful in controlling mucosal bleeding (bleeding of the soft tissues, such as the mouth, nose, vagina, etc.).

Complications of Hemophilia C

The complications of hemophilia C are those primarily associated with the use of fresh frozen plasma. While today's blood products are much safer than those of the past, transmission of hepatitis A, hepatitis C, and newly discovered blood-borne diseases remain a risk for people treated with plasma-derived products.

Epidemiology:-

Hemophilia C (severe form) occurs with an estimated prevalence of 1 case per 100,000 population in the United States, a rate that makes hemophilia A 10 times more common than hemophilia C. Internationally, deficiency of factor XI is reported in most racial groups, with the highest frequency in persons of Ashkenazi or Iraqi Jewish descent ; in Israel, the estimated rate for heterozygosity is 8%. In the United Kingdom national database. Hemophilia C equally affects males and females.

Complications of Hemophilia C

The complications of hemophilia C are those primarily associated with the use of fresh frozen plasma. While today's blood products are much safer than those of the past, transmission of hepatitis A, hepatitis C, and newly discovered blood-borne diseases remain a risk for people treated with plasma-derived products. Immunization against hepatitis A and B is recommended for all individuals with hemophilia. No vaccination currently exists for hepatitis C.

Epidemiology:-

Internationally, deficiency of factor XI is reported in most racial groups, with the highest frequency in persons of Ashkenazi or Iraqi Jewish descent ; in Israel, the estimated rate for heterozygosity is 8%. In the United Kingdom national database, 1696 patients (many of whom were non-Jewish) with factor XI deficiency were registered in a population of about 60 million (data for 2006), but most of these have partial deficiency. Hemophilia C equally affects males and females.

Etiology

The severity of the deficiency is based on plasma factor XIC (clotting) activity. Severe factor XI deficiency is present when the activity of factor XI in plasma is less than 1-15 IU/dL.

Also, thrombin directly activates factor XI, and this direct activation may be more important than the activation due to factor XII. Recently, it has been shown that thrombin activation of factor XI is triggered by polyphosphate release from activated platelets. These molecules provide a template for assembly of factor XI and factor IX.

REFERENCES

1. *Cohen AJ, Kessler CM. Acquired inhibitors. Bailleres Clin Haematol 1996;9:331– 354.*
2. *Bouvry P, Recloux P. Acquired hemophilia. Haematologica 1994; 79:550–556.*
3. *Lafeber FP, Miossec P, Valentino LA. Physiopathology of haemophilic arthropathy. Haemophilia 2008; 14 Suppl 4: 3-9 PMID: 18494686 DOI: 10.1111/j.1365-2516.2008.01732.x*
4. *Robert A Zaiden. Hemophilia A. Medscap e. November 7,2014; http://emedicine.m e dscape.com/article/779322-overview.*
5. *Hemophilia. Genetics Home Reference. A ugust,2012; http://ghr.nlm.nih.gov/condit i on=hemophilia. Accessed 3/18/2015.*
6. *Hemophilia A. NORD. August 9, 2012; http://www.rarediseases.org/rare-disease-information/rare-diseases/byID/39/viewAbstract.*
7. *What is hemophilia?. NHLBI. July 13, 201 3; http://www.nhlbi.nih.gov/health/healt h -topics/topics/hemophilia.*
8. *Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia; British Committee for Standards in Haematology Jan 2013*
9. *Scott JP, Montgomer RR. Hereditary clotting factor deficiencies (bleeding disorders). In: Kliegman RM, Stanton BF, St. Geme JW III, et al., eds. Nelson Textbook of Pediatrics . 19th ed. Philadelphia, Pa: Elsevier Saunders; 2011:chap 470.*
10. *Antonarakis SE, Youssaufian H, Kajazian HK. Molecular genetics of haemophilia A & B in man. Am J molecular biology and medicine 2001; 4: 81-94.*
11. *Mannucci PM, Tuddenham EGD. The Hemophilias-from royal gene to gene therapy.N Eng J Med 2001; 344:1773-79.*
12. *Kulkarni R, Soucie JM.Pediatric Hemophilia: A Review. Semin Throm Hemost2011;37:737-44*
13. *Manony BO and Black C. Expanding hemophilia care in developing countries. Semin Throm Hemost 2005;31:561-68*
14. *Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. Lancet 2003; 361:1801–1809*
15. *Michael Price (8 October 2009). "Case Closed: Famous Royals Suffered From Hemophilia". Science Now Daily News. AAAS. Retrieved 9 October 2009.*
16. *Evgeny I. Rogaev; et al. (8 October 2009). "Genotype Analysis Identifies the Cause of the "Royal Disease"". Science. Retrieved 9 October 2009.subscription required*
17. *Gomez K, Bolton-Maggs P. Factor XI deficiency. Haemophilia. 2008;14(6):1183-1189.*
18. *Mathew P, Bolton-Maggs P. Hemophilia C. Accessed March 23, 2010*
19. *eMedicine - Hemophilia C : Article by Prasad Mathew, MBBS, DCH*
20. *"Factor XI Deficiency: Background, Pathophysiology, Epidemiology".*