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RESEARCH ARTICLE

BLEEDING DISORDER

Dr. Rohini Dua Prof. & Head, Department of Pediatric & Preventive Dentistry, National Dental College & Hospital, Derabassi, S.A.S Nagar, Punjab.

Dr. Sanjana Arora Senior Lecturer, Department of Pediatric & Preventive Dentistry, National Dental College & Hospital, Derabassi, S.A.S Nagar, Punjab.

Dr.Heena RaniPostgraduate Student, Department of Pediatric & Preventive Dentistry, National Dental College & Hospital, Derabassi, S.A.S Nagar, Punjab. *Corresponding Author

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Abstract

Blood is a form of connective tissue made up of two main components: Red blood cells, white blood cells, and platelets make up the fluid which is known as plasma and a cellular component. Disorders related to blood and bone marrow fall under hematopoietic system disorders. Bleeding disorders are conditions where blood does not clot correctly. Normally, platelets clump together to create a plug at the location of a blood vessel injury. Clotting factors, which are proteins found in the blood, collaborate to form a fibrin clot. This clot holds the platelets in place, assists with healing, and helps reduce blood loss.Hemorrhagic disorders can be either inherited or acquired and may result from issues like blood vessel abnormalities, deficiencies in clotting factors, or problems with platelets.

Introduction:-

The body has a built-in system to control bleeding when injuries occur. This hemostatic system is responsible for keeping blood flowing smoothly and preventing clots from forming unnecessarily. Substances like prostacyclin, antithrombin III, and Endothelial cells, which form the inner lining of blood vessels, produce and release nitric oxide play key role in stopping platelets from clumping together and forming clots. These natural compounds also help in breaking down clots by converting plasminogen into plasmin, a process known as fibrinolysis. However, when the endothelium is damaged, it sets off a chain reaction to help manage bleeding and ensure the blood can clot where it's needed[1].Bleeding disorders are classified into two main categories: inherited and acquired. Inherited disorders are genetic, caused by a lack of specific clotting factors. Acquired disorders, however, develop later in life due to various health conditions or factors[2]. "Hemophilia is the most common inherited condition that leads to abnormal bleeding, caused by a deficiency in clotting factors such as factor VIII, IX, XI, or V". It's an X-linked condition[3]. Von Willebrand disease is another frequently inherited bleeding condition, impacting around 1 to 2% of the population[4,5]. Acquired bleeding disorders include various conditions like acquired hemophilia, those caused by medications like heparin or coumarin, and those related to conditions like liver disease, a lack of vitamin K, or disseminated intravascular coagulation[6].

Corresponding Author:- Dr. Heena Rani
Address:- Postgraduate Student, Department of Pediatric & Preventive Dentistry, National Dental College & Hospital, Derabassi, S.A.S Nagar, Punjab.

Classification of Bleeding disorder

Congenital: (i) Hemophilia A
(ii) Hemophilia B
(iii) Hemophilia C
(iv) Parahemophilia
(v) Von willebrand's disease

Acquired:

(i) Acquired Hemophilia
(ii) Secondary to drugs: Heparin
Coumarin

(iii) Related to Disease : Liver disorders
Vitamin K deficiency
Disseminated Intravascular Coagulation(DIC)

Congenital Bleeding Disorder

Definition

Hemophilia:

The term Hemophilia is derived from the combination of "hemo" (related to blood) and "philia" (indicating a fondness or affinity), signifying an affection or predisposition toward blood[7]. Hemophilia is a rare, typically inherited disorder where blood doesn't clot properly, causing prolonged bleeding or oozing at the site of an injury[8].

Von Willebrand Disease:

This disease is a bleeding condition caused by either a qualitative or quantitative deficiency of von Willebrand factor[9].

History

In 1803, Philadelphia physician John Conrad Otto described a condition he called "a hemorrhagic tendency in certain families," referring to affected males as "bleeders[10]."John Conrad Otto identified that the disorder was inherited, primarily affecting males but transmitted by healthy females. His research was the second significant study on X-linked genetic disorders, following John Dalton's work on color blindness. In 1813, John F. Hay furthered this knowledge by noting that males with the condition could transmit the trait to their unaffected daughters[11,12].

A Finnish physician in 1924 identified a genetic bleeding disorder in the Åland region, later named 'Von Willebrand Disease'[13]. The term "haemophilia" comes from "haemorrhaphilia," a word introduced by Friedrich Hopff in 1828 while conducting research at the University of Zurich[10,14]. Important breakthroughs include Patek and Taylor's identification of anti-hemophilic globulin in 1937, and Alfredo Pavlovsky's 1947 laboratory discovery that differentiated between hemophilia A and B[15]. Hemophilia is commonly known as 'the royal disease' because it was widespread among European royal families. Queen Victoria carried hemophilia B and passed it on to her descendants[16,17] . Queen Victoria transmitted the hemophilia gene to her son, Leopold, and through her daughters, Beatrice and Alice, the disorder spread to the royal families of Germany, Spain, and Russia[18].

Hemophilia

Classification:

1. According to the plasma levels of FVIII/FIX:

(a) Severe hemophilia, with clotting factor levels below 1%, causes spontaneous bleeding, mainly in joints and muscles.
(b) Moderate hemophilia, with 1%-5% factor levels, leads to bleeding after minor injuries, though less frequently. Jointsmay be affected.
(c) Mild hemophilia, with factor levels over 5%, causes bleeding from major trauma or surgery, but hemorrhages and joint issues are rare[19].

2. According to the deficiency of factor:
(a) Hemophilia A arises from a lack of factor VIII
(b) Hemophilia B, sometimes called Christmas disease, is due to a deficiency in factor IX.
(c) Hemophilia C, or Rosenthal syndrome, is due to a lack of factor XI.
(d) Parahemophilia (Owren's disease) involves a deficiency in factor V[20].

3. According to the presence at birth:
(a) Congenital hemophilia is inherited and present from birth.
(b) Acquired hemophilia develops later in life and is not inherited or linked to abnormal genes[21].

Etiology

Hemophilia is an X-linked condition caused by low levels of Factor VIII or IX. Approximately one-third of cases occur due to spontaneous mutations[22].

Genetics:

· Females have two X chromosomes, whereas males have one X chromosome and one Y chromosome.
· Because hemophilia is an X-linked recessive condition, women who are carriers generally do not exhibit symptoms, as their other X chromosome usually compensates.
· Heterozygous females carry the gene but are usually unaffected.
· In males, with no compensating gene on the Y chromosome, a defective X gene causes hemophilia[23].
· Sons of carrier mothers have a 50% chance of inheriting hemophilia, while sons of affected mothers have a 100% chance.
· Females need two defective X chromosomes to have hemophilia, so they are usually carriers.
· Female carriers can develop mild hemophilia because of X-chromosome inactivation.
· Mothers have a 50% likelihood of passing the defective gene to their daughters, whereas fathers with the condition will always pass it on to their daughters.
· Sons cannot inherit the hemophilia gene from their fathers[24].
· Spontaneous mutations cause around 33% of hemophilia A cases and 30% of hemophilia B cases[25] .
· If a woman's son has hemophilia, it means she is either a carrier of the condition or the hemophilia resulted from a new, spontaneous mutation[26].
· Men with hemophilia cannot transmit the condition to their sons but will pass the carrier status on to all of their daughters.

· Daughters of affected males will be carriers, while sons will only have hemophilia if their mother is a carrier[27].

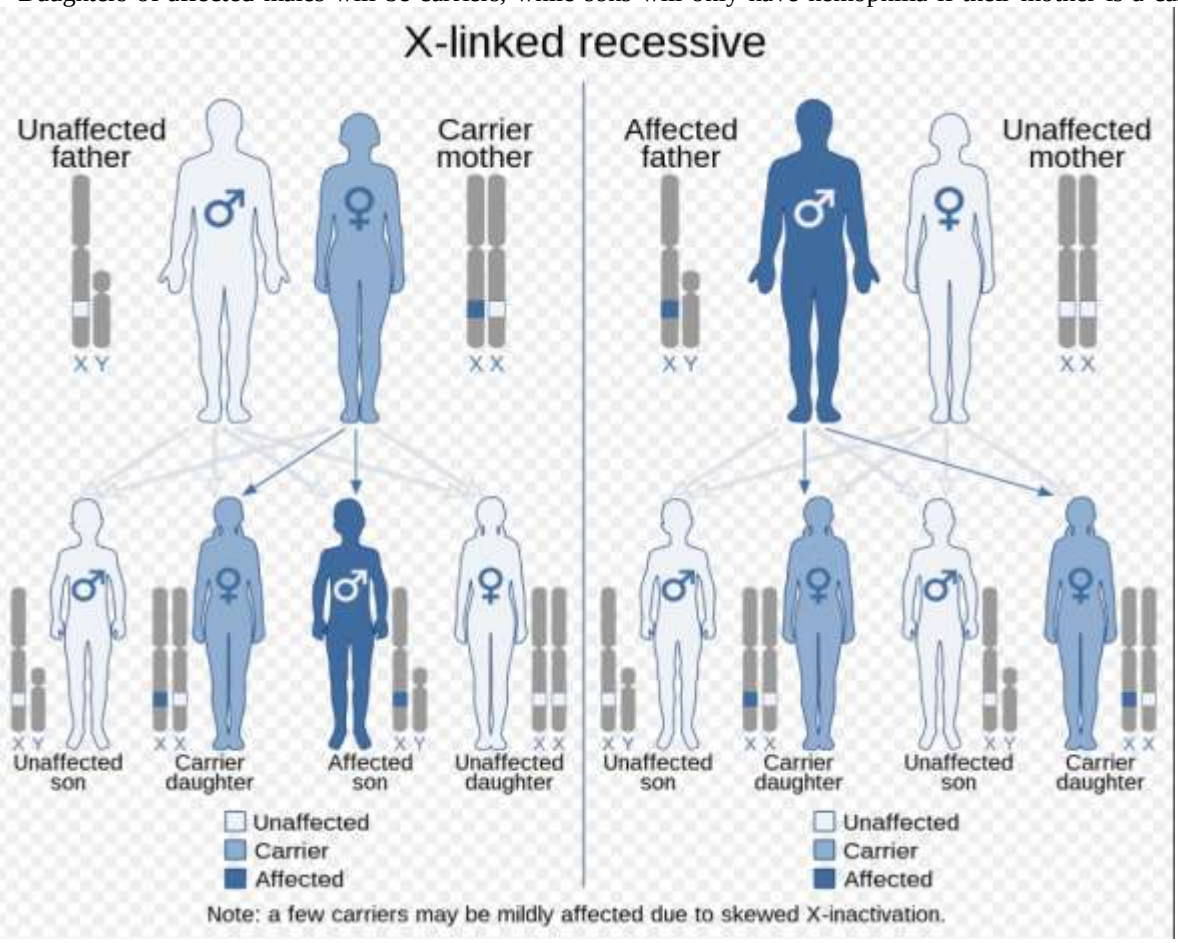

Figure 1:-

Epidemiology:

- Hemophilia affects people globally, regardless of race or socioeconomic status[28].
- Hemophilia A is the most frequent inherited bleeding disorder, affecting about 1 in 5,000 males, and follows an X-linked recessive inheritance pattern.
- Hemophilia B is known as Christmas disease, affects about 1 in 30,000 males and is named after Steven Christmas, the first patient diagnosed in 1952.
- The prevalence of hemophilia increases in populations with high levels of consanguinity.
- Females can be carriers of the hemophilia gene, often asymptomatic, or may have a partial deficiency of the involved factors[29].

Hemophilia A

Hemophilia A, the most frequent form of the condition, results from a lack of factor VIII, accounting for 80-85% of cases. This X-linked recessive disorder is due to an insufficient or defective factor VIII, also known as anti-hemophilic globulin (AHG)[30].Hemophilia A can be caused by various mutations, with around 150 different point mutations identified[31].Hemophilia A notably affected European history through Queen Victoria's family, known as the "Royal disease." It spread to other European royal families via her descendants[30].

Clinical Features

· Individuals with severe hemophilia frequently bruise easily and suffer from substantial bleeding even from minor injuries or surgeries.

· They may have spontaneous bleeding from areas like the ears and nose, and bleeding into joints, known as hemarthrosis.

· Affected weight-bearing joints may show symptoms like heat, tenderness, and pain, leading to joint damage and arthritis.
· Untreated muscle bleeding, especially in the calf, can increase pressure and cause tissue damage, leading to complications like tendon shortening.
· Tissue bleeding can form lumps that resemble tumors, called "pseudotumors of hemophilia"[32,33].

Hemophilia B
Hemophilia B, also known as Christmas disease, it is the 2nd most common form. It results from a mutation in the F9 gene, which leads to reduced levels of factor IX. This condition can be inherited or result from a new mutation. It mainly affects males, but female carriers can also have significant bleeding issues. Females with factor IX levels at or above 50% are usually asymptomatic. Named after the first patient diagnosed in 1952, Stephen Christmas, the disorder is known as "the royal disease" due to its occurrence in several European royal families. Severity varies, with severe cases causing spontaneous bleeding from birth and milder cases typically resulting in bleeding after trauma or surgery, often showing symptoms later in life[34,35,36].

Clinical Features
In clinical terms, hemophilia B generally tends to be less severe than hemophilia A[37].The severity of hemophilia B symptoms depends on factor IX levels are in the blood[38].

Mild Hemophilia
People with mild hemophilia have factor IX levels between 5% to 40%. Bleeding typically happens only following significant trauma or surgery. The condition is often diagnosed by chance[38].

Moderate Hemophilia
People with moderate hemophilia have factor levels between 1% and 5%. They often bleed after trauma, dental work, or surgery, usually showing symptoms in late childhood or adulthood. About 25% may experience recurring joint bleeding.

Severe Hemophilia
In severe hemophilia, bleeding occurs spontaneously and often starts early in life due to extremely low factor activity (less than 1%). Symptoms can appear after minor procedures or injuries during infancy and continue into later childhood, affecting areas like the central nervous system, oral cavity, and joints. Severe cases also pose risks of internal bleeding in organs such as the liver, spleen, and kidneys. Intracranial hemorrhage (ICH) is particularly dangerous and affects 3% to 4% of newborns. In infants, ICH might show as seizures or feeding difficulties, while older children might experience headaches or vomiting. Sometimes, ICH is asymptomatic and requires imaging for detection. Additionally, bleeding outside the skull, such as subgaleal bleeding or cephalohematoma, can occur right after birth[39].

Hemophilia C
FXI deficiency, also referred to as hemophilia C or Rosenthal disease, was initially identified in the 1950s by Rosenthal and his team in a family across four generations[40].In the family studied, bleeding problems were noted after surgeries and dental work. Mixing their plasma with that of hemophilia A or B patients corrected the clotting issue, indicating a different factor deficiency. FXI deficiency, unlike hemophilia A and B, is inherited autosomally and can vary in bleeding severity.

Severe FXI deficiency is rare, affecting about 1 in 1 million people but is more common in certain groups, such as Ashkenazi and Iraqi Jews. In these populations, about 8-9% are heterozygous, and around 0.2% are homozygous or compound heterozygous[41,42,43,44]. In the Jewish population, most abnormal FXI genes are caused by two specific genetic variants: Glu117Stop (type II) and Phe283Leu (type III). Severe FXI deficiency is characterized by activity levels below 20%, which is often seen in individuals with homozygous or compound heterozygous mutations. In comparison, individuals who are heterozygous usually have FXI activity levels between 20% and 60%[41,45]. The FXI gene, found on chromosome 4 and covering 23 kilobases, is mainly inherited in an autosomal recessive pattern[46].

Clinical Features
Patients with FXI deficiency usually have a prolonged activated partial thromboplastin time (aPTT) but typically experience only mild bleeding, even with severe deficiency. Common bleeding issues include problems after

surgeries, injuries, nosebleeds, and heavy periods. The highest bleeding risk, between 49% and 67%, is associated with surgeries conducted in areas with significant fibrinolytic activity, like the urogenital tract or the mouth[46]. Unlike severe FVIII or FIX deficiencies, severe FXI deficiency rarely causes spontaneous bleeding, such as joint or muscle hemorrhages. The severity of bleeding does not always match FXI activity levels. Some individuals with mild FXI deficiency (20%-60% activity), including heterozygotes, have experienced bleeding, creating a challenge in predicting bleeding risk based on FXI levels[47].

Parahemophilia

Factor V deficiency, formerly called parahemophilia, usually causes less severe bleeding than classic hemophilia, even with factor V levels below 1%. Many affected individuals might not be diagnosed until adulthood[48]. Bleeding episodes in factor V deficiency often affect mucous membranes, causing nosebleeds, heavy menstrual bleeding, and bleeding after dental work. Mutations in the ERGIC-53 gene, which is involved in intracellular transport, can result in a congenital deficiency of both factor V and factor VIII[49]. Factor V deficiency can also be caused by liver disorder or disseminated intravascular coagulation. Treatment typically includes plasma transfusions to raise factor V levels to above 20% to manage surgery or control bleeding. However, patients with congenital deficiency may develop antibodies against factor V after treatment, requiring close monitoring[50].

Oral manifestations Of Hemophilia

- Hemophilia often leads to bleeding from various areas, including the mouth such as gum bleeding and post-extraction hemorrhages.
- The frequency of oral bleeding is higher in severe cases and lower in mild cases.
- Poor oral hygiene and medical procedures can worsen oral bleeding.
- Toddlers with hemophilia frequently develop oral ulcers and bruising on the lips and tongue[51,52].

Diagnosis Of Hemophilia

Hemophilia is diagnosed based on clinical signs and lab tests. Identifying gene mutations helps advance new treatments, including gene therapy.

A. Clinical Diagnosis –

Signs like joint bleeding, brain bleeding, excessive bleeding from minor injuries, prolonged post-surgery bleeding, and heavy menstrual bleeding strongly indicate hemophilia[53].

B. Lab Diagnosis-

Hemophilia is diagnosed using tests that assess coagulation factors or activated partial thromboplastin time (aPTT). Typically, other tests like bleeding time, prothrombin time, and thrombin time will show normal results in individuals with hemophilia.

1. Activated Partial Thromboplastin Time (aPTT) assesses the function of both the intrinsic and common coagulation pathways[54].In hemophilia, aPTT is prolonged due to issues with factor VIII, which is crucial for the intrinsic pathway[55].
2. Coagulation Factor F8/F9 Assays: These tests measure the activity of factors VIII and IX to identify the type of hemophilia and assess factor levels. Normal factor VIII levels are 50-150%, which are reduced in hemophilia A[56].

C.Genetic Diagnosis –

Genetic testing confirms hemophilia diagnoses, identifies carriers, and aids in early prenatal diagnosis, which is important for managing the condition during delivery[57].

D. Prenatal Diagnosis –

Prenatal diagnosis of hemophilia is important for planning labor and delivery. This can be achieved through chorionic villous sampling (between 11 and 14 weeks), amniocentesis (after 15 weeks), or cordocentesis (after 20 weeks)[58].This diagnostic method is especially useful for foetus with a strong family history of moderate to severe hemophilia[59].

1. Amniocentesis –
Amniocentesis, performed between the 15th and 18th weeks of pregnancy, involves inserting a needle into the amniotic sac to collect amniotic fluid, which contains fetal cells. This fluid is then analyzed for mutations or through linkage analysis to identify if the foetus has hemophilia[60].

2. Cordocentesis –
Cordocentesis, or percutaneous umbilical blood sampling, is used when other tests are unclear. A needle, guided by ultrasound, is used to collect blood from the umbilical cord to measure factor VIII and IX levels in the fetal blood[61].

3. Chorionic Villous Sampling –
Chorionic villous sampling, commonly done between the 11th and 14th weeks of pregnancy, involves extracting chorionic villi via the cervix or abdomen using ultrasound. The fetal cells are then tested for mutations or through linkage analysis to diagnose hemophilia[60].

Prophylactic therapy:
Prophylactic treatment for hemophilia consists of routine infusion of clotting factors to prevent bleeding episodes from occurring spontaneously.This standard treatment for severe hemophilia in children uses factor concentrates of FVIII and FIX[62].Prophylaxis aims to prevent bleeding and joint damage, helps to maintain normal musculoskeletal function[63,64].Long-term prophylaxis effectively reduces bleeding and prevents joint damage in hemophilia. Even starting prophylaxis later can decrease bleeding frequency and minimize physical and psychological impacts[65].

Prophylaxis aims to keep factor levels above 1% of normal, which can turn severe hemophilia into a milder form[65].

Management Of Hemophilia
Managing hemophilia includes educating patients, providing clotting factor replacements. Effective bleeding control and health maintenance are supported by proper exercise and nutrition[66].The main goals are to prevent and treat bleeding, offer comprehensive care with a multidisciplinary team, support home therapy, address psychosocial health, and provide rehabilitation[67].

Acute bleeding is managed with factor replacement therapy and additional pharmaceutical treatments.
Factor replacement:
Replacement therapy for hemophilia began with fractionated human plasma (FFP) in the 1930s, greatly reducing mortality and improving patient outcomes. Although FFP requires large volumes due to its low clotting factor levels, it is still used for acute bleeding and in resource-limited areas where clotting factors are not readily available.

Cryoprecipitate:
In the 1960s, cryoprecipitate was introduced as a more concentrated source of Factor VIII, offering 100 units in a small volume. It remains widely used due to its availability and cost, though it is less ideal for specific treatments due to the need for freezing and its lack of heat treatment. The 1960s and 1970s saw the development of advanced Factor VIII and IX concentrates, enabling more targeted therapy for hemophilia.

Alternative pharmaceutical treatments for bleeding include:
Desmopressin:
Desmopressin (DDAVP) is a synthetic form of vasopressin that increases the levels of factor VIII and von Willebrand factor (VWF) in the bloodstream by stimulating their release from blood vessel cells. It is used to treat mild to moderate hemophilia A and can be administered through an IV, under the skin, or as a nasal spray. However, it may become less effective over time (tachyphylaxis) and isn't suitable for all patients. A typical IV or SC dose of 0.3 µg/kg can raise FVIII levels 2 to 10 times, with an average increase of 3 times. The intranasal spray is especially convenient for home use[67,68].

Tranexamic acid :
This antifibrinolytic medication aids in stabilizing clots by inhibiting the conversion of plasminogen into plasmin. It is especially useful in hemophilia for managing bleeding from skin and mucous membranes, such as oral bleeding and nosebleeds. It's particularly effective during dental procedures like oral bleeding from teething or tooth loss[67].

Epsilon aminocaproic acid:
This drug, though similar to tranexamic acid, is less frequently used due to its shorter duration, lower effectiveness, and higher risk of toxicity. It is taken orally every 4-6 hours. Common side effects include gastrointestinal issues, and a rare but severe side effect is myopathy, which can show up as elevated creatine kinase levels or myoglobinuria[67].

Surgical management:
Patients with hemophilia should have their surgeries managed in a specialized setting with close coordination among medical staff, surgeons, and coagulation specialists. It's crucial to know the patient's inhibitor status beforehand. Whenever possible, begin with a bolus dose of clotting factors and follow up with a continuous infusion to avoid dangerously low factor levels due to delays in additional doses[68].

Dental management
1. The main goal is to provide dental care and guidance to avoid common problems like cavities and gum disease.
2. Brushing twice daily with fluoride toothpaste and using mouthwashes with triclosan or chlorhexidine helps control plaque.
3. Reducing intake of sticky, sugary foods between meals prevents enamel demineralization by keeping mouth pH above 5.5.
4. Using pit and fissure sealants can also help prevent cavities[69].
5. People with hemophilia are at higher risk for gum disease because they may find it difficult to maintain proper oral hygiene[70].
6. The space between the gums and teeth contains various bacteria that can lead to gum disease.
7. Regular oral hygiene, along with professional dental cleanings and check-ups, is crucial to prevent inflammation and maintain oral health[71].

Von Willebrand disease
In 1926, Eric von Willebrand discovered von Willebrand disease (VWD) in a family from the Åland Islands in Finland. He characterized it as an autosomal dominant bleeding disorder[72].

Epidemiology
VWD is the most frequently occurring inherited bleeding disorder, impacting roughly 0.8% to 2% of individuals in Europe and America[73,74].

Pathophysiology
Von Willebrand disease (VWD) is caused by either insufficient levels or defects in von Willebrand factor (VWF), a large protein produced by endothelial cells and megakaryocytes, VWF helps platelets adhere to damaged blood vessels and stabilizes factor VIII. This protein ranges in size from 450 kDa to over 10,000 kDa and is situated on chromosome 12p13.2[75].

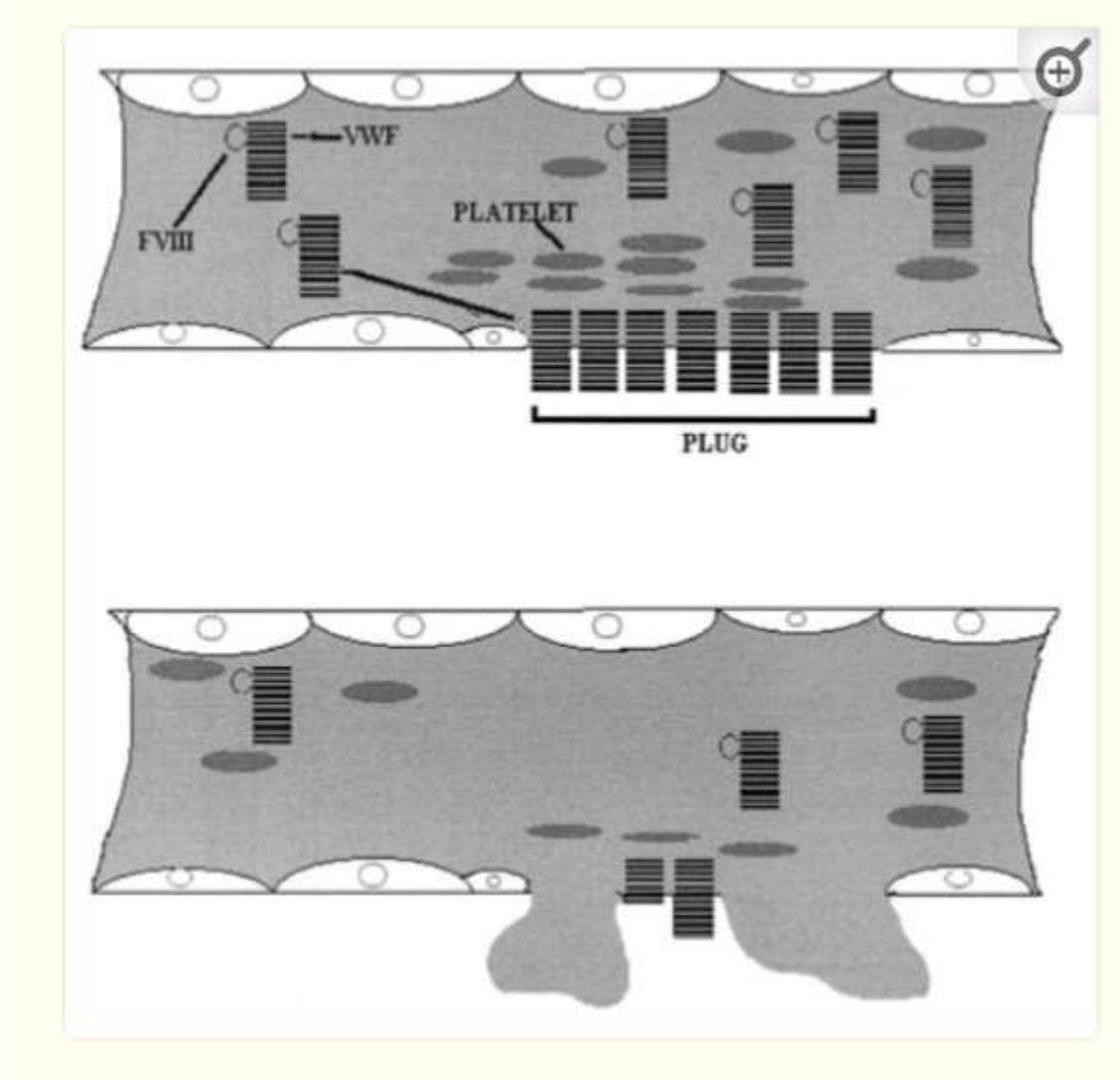

Figure 2:- Top: Normal von Willebrand factor (VWF) functions in platelet adhesion and binding of Factor VIII (FVIII). **Bottom**: Blood vessel damage caused by Von Willebrand's disease[75].

Classification Of Von Willebrand Disease

Von Willebrand disease (VWD) is classified into three main types:

Type 1:is characterized by reduced levels of normal VWF (ranging from 10% to 50% of the usual amount) and accounts for almost 80% of VWD cases.

Type 2 : Affecting 15% to 20% of VWD patients, this type is marked by functionally abnormal von Willebrand factor (VWF) at varying levels. It is further divided into subtypes: Type 2A, which is characterized by the absence of larger VWF multimers; Type 2B, where VWF has an increased tendency to bind to platelets; Type 2M, which maintains a normal pattern of VWF multimers; and Type 2N, where VWF has a notably reduced ability to bind to factor VIII.

Type 3: which represents less than 1% of cases, is marked by an almost complete absence of von Willebrand factor (VWF)[76].

Clinical Features

Von Willebrand disease (vWD) symptoms usually appear in mucous membranes, during dental work, or after surgery. Common issues include easy bruising, nosebleeds, and heavy menstrual bleeding. These symptoms can also occur in people without bleeding disorders[77].Signs that may indicate vWD include excessive bleeding from minor cuts, unexplained bruising, large bruises after blood draws, frequent nosebleeds, and regular gum bleeding[78].

Bleeding following dental work or surgery can be quite severe, so it's important to diagnose and manage von Willebrand disease (vWD) before undergoing these procedures. Women are often diagnosed more frequently due to higher bleeding risks during menstruation and pregnancy, with up to 95% experiencing heavy menstrual bleeding[79].

Diagnosis

Diagnosing von Willebrand disease (VWD) involves several tests, including activated partial thromboplastin time (aPTT), bleeding time (BT), and platelet function analyzer (PFA-100). An extended aPTT may suggest reduced levels of factor VIII and VWF, but a normal aPTT does not rule out the presence of VWD. While bleeding time can be extended in severe cases of VWD, it isn't very sensitive. On the other hand, the PFA-100 test is more accurate, with over 90% sensitivity and specificity for diagnosing VWD[80].

Treatment

Managing von Willebrand disease (VWD) involves patient education and choosing the right treatment. Patients should avoid medications with acetylsalicylic acid due to its antiplatelet effects and carefully check all medications. They need to understand how to manage bleeding episodes and use prophylaxis before surgeries. It's recommended to visit a specialized hemophilia care center for ongoing treatment. Treatment choices depend on the VWD type, severity, and bleeding risk, and include desmopressin acetate (DDAVP), plasma concentrates with VWF, and antifibrinolytic agents[81].

Acquired Bleeding Disorder

1. Acquired Hemophilia

Hemophilia, meaning "love of blood," is the most prevalent and serious bleeding disorder. It has three types: A, B, and C, each linked to deficiencies or problems with clotting factors VIII, IX, and XI[82]. Most hemophilia cases are inherited, but a rare form called acquired hemophilia A occurs when the body produces antibodies against factor VIII[83].

Etiology

Factors that may raise the risk of developing acquired hemophilia A (AHA) include:

1. **Immunological Disorders**, which make up 17 to 18% of cases[83], are linked to conditions like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)[84].
2. **Obstetrical Causes**: Acquired hemophilia A (AHA) can be triggered by the post-partum period, which accounts for about 8.4% of cases. Abnormal bleeding within up to 12 months after childbirth should prompt consideration of AHA.
3. **Hematological and Oncological Causes**: Acquired hemophilia A (AHA) can be triggered by certain cancers and related conditions, such as solid tumors (like those in the lung, prostate, pancreas, or breast), blood cancers, chronic lymphocytic leukemia, and multiple myeloma.
4. **Dermatologic Disorders:** include conditions such as psoriasis, pemphigus, and epidermolysis bullosa.
5. **Pharmacological Causes:** Various medications can contribute to acquired hemophilia A, including both beta-lactam and non-beta-lactam antibiotics, interferons, NSAIDs, clopidogrel, amiodarone, rivastigmine, sunitinib, heparin, phenytoin, methyldopa, and fludarabine.
6. **Infectious Diseases:** Acquired hemophilia A can be associated with acute infections, such as hepatitis B and C[85].

Epidemiology

Acquired hemophilia is quite rare, affecting about 1.5 people per million each year[86,87]. The incidence of acquired hemophilia varies with age, occurring at a rate of 0.045 cases per million annually in individuals under 16 and 14.7 cases per million annually in those over 85[85]. Consequently, acquired hemophilia is more frequently observed in adults compared to children. Acquired hemophilia is more frequent in women aged 20 to 40, often due to risks associated with pregnancy and the post-partum period. In contrast, it is more common in men over 85 years old[88].

Diagnosis

To diagnose acquired hemophilia, doctors conduct a complete blood count and a coagulation profile. The blood count usually shows normal platelet levels, while the coagulation profile often indicates a significantly extended activated partial thromboplastin time (aPTT), often 2 to 3 times longer than the normal range. This extension may result from deficiencies in intrinsic pathway factors such as FVIII, FIX, FXI, FXII, or from antibodies targeting these factors[89].

Management
Managing acquired hemophilia A typically involves two main strategies: controlling bleeding and eliminating the antibodies causing the condition[88].

Anticoagulation Agent
2. Warfarin
Warfarin is a drug that prevents blood clotting by interfering with vitamin K epoxide reductase. This leads to lower levels of vitamin K-dependent clotting factors (II, VII, IX, X) and proteins C, S, and Z. This increases bleeding risk, especially if the INR is too high (above 5). Risk factors include age, previous bleeding, stroke history, hypertension, use of other blood-thinning drugs (like NSAIDs), and liver or kidney problems.

Managing warfarin-related bleeding depends on severity and INR levels. For high INR without bleeding, stopping warfarin and possibly giving oral vitamin K might be enough. Significant bleeding or surgery requires more intensive reversal, such as factor replacement, to restore normal clotting[90].

3. Heparin
Heparin is an anticoagulant that works by enhancing antithrombin, which then inhibits thrombin, preventing clot formation. It's used for both treating and preventing blood clots. High doses can cause severe bleeding, but since heparin has a short half-life (about 8 hours), stopping it usually manages bleeding. For rapid reversal, protamine sulfate is effective for unfractionated heparin but only partially reverses low-molecular-weight heparin. Protamine has little effect on fondaparinux and danaparoid, which is used for treating heparin-induced thrombocytopenia[91,92].

Disesase Related
4. Liver Disease
Coagulopathy in liver disease can be tricky to differentiate from disseminated intravascular coagulation (DIC) because both can affect clotting. Key issues in liver disease include:
1. **Thrombocytopenia**: Caused by low thrombopoietin, enlarged spleen, or megakaryocyte suppression (from alcohol or infections).
2. **Coagulation Problems**: Result from the liver's reduced ability to produce clotting factors, vitamin K deficiency (often due to alcohol or jaundice), and abnormal fibrinogen.
3. **Increased Fibrin Degradation**: Due to poor liver clearance or hyperfibrinolysis, which affects clot stability.

Patients with liver dysfunction may have both procoagulant and anticoagulant factors reduced, leading to less bleeding than expected from lab results. Complications like kidney issues or infections can worsen bleeding risks. Treatment may involve factor replacement and care with FFP (fresh frozen plasma) to avoid increasing portal pressure, which could cause variceal bleeding. For bleeding due to hyperfibrinolysis, antifibrinolytic agents like tranexamic acid can be used, and viscoelastic tests like thromboelastogram (TEG) help diagnose this condition[93].

5.Vitamin K Deficiency
Vitamin K is crucial for the modification of clotting factors II, VII, IX, X, as well as proteins C, S, and Z, allowing them to bind to phospholipid membranes through calcium. Deficiency can arise from various issues like hemorrhagic disease in newborns, poor diet, prolonged antibiotic use, cholestatic liver disease, malabsorption, or medications like anticonvulsants and warfarin. Treatment typically involves administering oral or intravenous vitamin K. In more severe cases, fresh-frozen plasma (FFP) or prothrombin complex concentrate (PCC) might be necessary[6].

6.Disseminated Intravascular Coagulation (DIC)
DIC involves widespread activation of the clotting system, resulting in the formation of numerous small blood clots in the tiny blood vessels.This process can cause organ dysfunction and lead to a reduction in clotting factors and platelets. It can cause either bleeding or thromboembolism, depending on how fibrinolysis and coagulation factors balance out. Common triggers include severe infections, obstetric complications, major trauma, and certain cancers like acute promyelocytic leukemia. Diagnosis is based on:
1. Depletion of clotting factors (leading to prolonged INR/PTT and variable fibrinogen levels)
2. Reduction in anticoagulants like antithrombin
3. Increased fibrinolysis products like D-dimers
4. Falling platelet counts

Treatment targets the underlying cause and manages complications, with options including FFP and platelet transfusions for bleeding or low-molecular-weight heparin for thromboembolic issues[6].

Conclusion:-

Bleeding disorders often result from inherited deficiencies in specific clotting factors, which can greatly affect a patient's daily life and lead to severe complications. Early diagnosis and treatment are key to improving life quality and preventing complications. Factor replacement therapy is an effective short-term treatment for hemophilia.

Acquired bleeding disorders have various causes and require a detailed medical history and physical exam to interpret lab results and choose the right treatment. Treatment focuses on managing acute bleeding and addressing the underlying cause. Factor concentrates and sometimes platelet concentrates can help control bleeding. To eliminate autoantibodies, potent immunosuppressive drugs are used, which are effective for most patients.

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