ORAL MANIFESTATIONS OF HEMOPHILIA-A -A SCOPING REVIEW

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ABSTRACT:

Hemophilia comprises a group of hereditary disorders caused due to the deficiency of one or more clotting factors leading to prolonged clotting time and excessive bleeding tendencies that may be fatal. The three main types are haemophilia A (factor VIII deficit), haemophilia B or Christmas disease (factor IX deficiency), and haemophilia C or Rosenthal syndrome (factor XI deficiency). Other variations include acquired haemophilia and parahemophilia, which are both caused by factor V deficiency and manifest as Owen's illness.[1,2] With 80–85% of all

haemophilia cases being haemophilia A, it is more prevalent than haemophilia B. Haemophilia tests the dental professionals' abilities by causing bleeding during procedures, which in some circumstances can be fatal. The significant prevalence of oral issues among these people makes it challenging to dental treatments. The high incidence of dental problems in these individuals poses difficulty in their dental management,emotionally as well as psychologically. But with proper care and precautions, treatment for these individuals can be made possible

Keywords : Hemophilia A, bleeding, caries, women, hemorrhage.

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INTRODUCTION

Haemophilia is a genetic bleeding illness which is most frequently brought on by defects in the coagulation factors VIII and IX[1]. Over the decades, it has been difficult to acknowledge that women and girls with haemophilia may bleed as substantially as affected males due to the assumption that haemophilia only affects males and is transmitted through unaffected females. It's possible that the group of women who have been labelled "haemophilic females" have complicated genetic underpinnings for their phenotype. Additionally, women and girls who are heterozygous for either haemophilia A (HA), a fault or deficiency of factor VIII (FVIII), or haemophilia B (HB), a defect or deficiency of factor IX (FIX), may experience severe bleeding that need therapy. Both the FVIII gene (F8) and the FIX gene (F9) are found towards the end of the long X chromosome arm. The pattern of X-linked inheritance, which has been known for the haemophilias from antiquity, results from the function of the X chromosome in determining sex.[2]

There are two prevalent subtypes of haemophilia: haemophilia A (blood coagulation factor VIII deficiency, HA), and haemophilia B (blood coagulation factor IX deficiency, HB). Surveys of the prevalence of these illnesses occasionally include Haemophilia C (blood coagulation factor XI deficit, HC) and Von Willibrand disease (Von Willibrand factor deficiency, VWD).[3] Women are more frequently heterozygote carriers with no or minimal symptoms of bleeding. Rarely,

women can develop haemophilia due to X-chromosome inactivation (lyonization phenomenon), Turner's disease, partial or whole X chromosome deletion, or if both parents have the defective gene.[1]

With 80–85% of all haemophilia cases being haemophilia A, it is more prevalent than haemophilia B. The oral cavity is a common and problematic source of bleeding in the haemophiliac patient. Haemophilia tests the dental professionals' abilities by causing bleeding during procedures, which in some circumstances can be fatal. These people have a high incidence of dental issues, which makes it challenging for them to maintain their dental health on an emotional and psychological level. But treatment for these people is achievable with the right care and precautions.[4] According to the severity of the haemophilia and the form of the damage, the use of numerous units of plasma, cryoprecipitates, or other concentrates are assessed, the treatment of severe bleeding episodes has typically needed hospitalisation and continuous replacement therapy for 7 to 10 days.[5]

METHODOLOGY

Extensive literature survey was conducted to identify the published case study, reviews, original research and bibliography on haemophilia. Search was conducted using internet based data bases such as Pubmed and cochrane library. Key words such as Hemophilia A, Bleeding and clotting disorders and oral manifestations of haemophilia were used in the broad screening. Inclusion criteria included open access, original papers, reviews that describe the oral manifestations and dental management of haemophilia. Articles in languages other than English are excluded. Articles were filtered by title screening, followed by abstract screening to exclude the irrelevant articles. A total of 30 articles were considered for this review.

PATHO-PHYSIOLOGY

The pathophysiology comprises of two pathways—the intrinsic or contact pathway and the extrinsic or tissue factor (TF) pathway—are both activated during the formation of blood clots. Both processes involve a series of cascade enzyme activation events that result in the crosslinking of fibrin monomers and the activation of platelets, which result in the development and stabilisation of a blood clot. Disruption of the endothelium and exposure of tissue factor (TF) in the sub-endothelium initiate the extrinsic pathway. To activate factors IX and X into IXa and Xa, respectively, tissue factor attaches to active factor VIIa to create a complex. Factor XII, Prekallikrein, and high-molecular-weight Kininogen in the blood are exposed to an artificial surface, activating the intrinsic pathway. A conformational shift in factor XII causes a little amount of factor XIIa to be produced, which then activates PK to kallikrein with reciprocal activation of factor XII to XIIa. Factor XI generates factor XIIa as a result, which then activates factor XI to factor XIa, converting factor IX to factor IXa. At the point where factor Xa is produced, both paths meet. Prothrombin (factor II) is changed into thrombin (factor IIa) by factor Xa. In turn, thrombin assists in the release of factor VIII from the von Willebrand factor and activates it into factor VIIa, activates platelets by disabling phospholipids that bind factor IXa, and activates factor XIII into factor XIIIa, which aids in clot stabilisation by cross-linking fibrin monomers. A tenase complex made up of factor IXa, factor VIIa, calcium, and phospholipids attracts a lot of factor X to activate it. In turn, prothrombin is transformed into thrombin with the aid of factor Xa, calcium, and phospholipids in the prothrombinase complex. Then, fibrinogen is divided into monomers by the assistance of thrombin. Because the intrinsic pathway of the coagulation cascade cannot be properly triggered when factor VIII and factor IX are insufficient or dysfunctional, the process of clot formation is inadequate.[6]

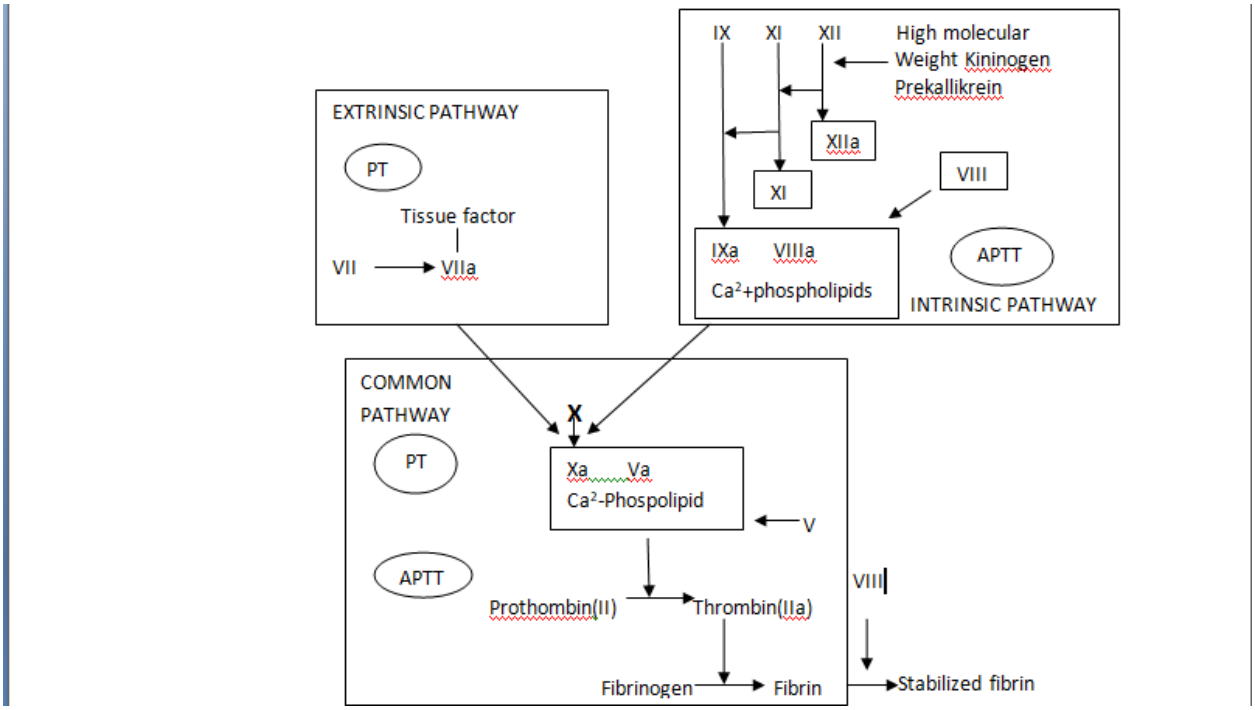

Fig.1: Patho-physiology of Hemophilia [12]

CLINICAL FEATURES:

The presence of spontaneous bleeding, which varies in frequency and severity depending on the level of factor present at the plasma level, is a symptom of haemophilia, which is characterised by a lack of coagulation factors that causes a decrease in haemostasis.

■ Mild deficiency (5–40% FVIII activity): It usually only presents with bleeding after surgical procedures.

■ Moderate deficiency (1 to 5% FVIII activity).

■ Severe deficiency(<1%FVIII activity): More frequently occurring spontaneous bleeding, which primarily affects the joints, is one of its defining characteristics. It can manifest as early as conception and displays a severe bleeding characteristic.[7]

Muscle and joint haemorrhages, notably in the knees, elbows, and ankles, are the clinical hallmarks of haemophilia A. The typical initial symptoms of acute hemarthroses are mild discomfort and a minor restriction in joint motion, which are thereafter followed by pain, joint swelling, and cutaneous warmth. Joint haemorrhage typically results in a severe limitation of motion if left untreated. Sadly, the pathologic processes go on even after the bleeding stops because inflammation damages the blood-filled joints, causing synovitis, which raises the risk of recurrent hemarthroses in the same joints (the so-called target joints). The narrowing of the joint space as a result of cartilage loss, the growth of bone cysts, and motion restriction that results in lifelong impairment is the last stage of this vicious cycle that causes hemophilic arthropathy.[8]

Joints that bear weight develop warmth, tender, and pain, which trigger synovial hypertrophy, cartilage degradation, and secondary osteoarthritis. Calf muscle hematomas that are left untreated can increase pressure and eventually lead to ischemia, necrosis, fibrosis, and later Achilles tendon contraction and shortening. Massive intrauterine bleeding leading to stillbirth and newborn cerebral bleeding are possible symptoms of severe cases. After trauma or minor surgical operations, there is a propensity for quick bruising and severe haemorrhage. Additionally, spontaneous middle ear bleeding, epistaxis, bleeding into joints that results in hemarthrosis, and bleeding into soft tissues are all possible. Haemophilia pseudotumors are tumor-like structures caused by tissue bleeding.[4]

ORAL MANIFESTATIONS:

Multiple sites of bleeding are a hallmark of haemophilia, which usually takes the form of gingival and post-extraction haemorrhages in the mouth. Depending on the degree of severity of their haemophilia, patients may also experience several oral bleeding incidents throughout their lifetime. Bleeding episodes are less common in mild haemophilia and more common in severe haemophilia, followed by moderate haemophilia. Oral bleeding can also be brought on by iatrogenic causes and poor oral hygiene. Oral ulcerations and ecchymosis affecting the lips and tongue are frequent in toddlers.[4]

Dental caries and gingivitis/periodontitis are the two main oral conditions that haemophiliac individuals have, just like the general population. It is probable that congenital coagulation problems are risk factors for dental caries, gingivitis, periodontitis, and ensuing alveolar bone loss since these patients are reluctant to take necessary precautions against common bleeds.[9]

TABLE

AUTHOR	KEY FOCUS AREA	FINDINGS	CONCLUSION
Shilpa Padar Shastry et al [4], 2014	Review hemophilia A with emphasis on its oral manifestations, investigations, and dental management	Hemophilia A, which occurs due to deficiency of factor VIII, is the most common of the three, accounting for 80–85% of the cases	The close cooperation between hematologists, general physicians, oral physicians and surgeons, and general dentists will help to provide utmost care and appropriate

			treatment for patients with hemophilia A, avoiding all unfavorable consequences.
Ruta Zaliuniene et al [9], 2014	Overview the oral health aspects in hemophilia patients	Main consequences of bleeding episodes in hemophilic patients are: hemarthrosis 70-80%, muscle/soft tissue bleeding 10-20%. Bleeding affects joints with predominant sequence: knee (45%), elbow (30%) and ankle (15%).	The population's share of people with congenital hemorrhagic diatheses is quite minimal. Due to the fact that the majority of dentists lack the necessary experience to manage oral issues in such patients, treating these patients presents a challenge.
Katayoun Salem et al [13], 2018	Assessment of the oral and dental health status in children and adolescents with hemophilia in Rasht, Iran.	The mean age of the subjects was 10.49±4.21 years in the case group and 10.5±4.07 years in the control group. 92.5%	92.5% of the patients with hemophilia had factor VIII deficiency and the rest had deficiencies of factors VII and IX. Prevention

		of the patients exhibited factor VIII deficiency and the most frequent blood group was A (34%)	of dental problems is the main principle in oral care and might result in the avoidance of emergency events.
Ricardo Martínez-Rider et al [14], 2017	Clinical case report on dental management of child with incidently detected hemophilia.	An 8.10-year-old boy without history of significant bleeding events. Clinic complaining of lack of eruption of both permanent upper central incisors, vestibular squared incision over the gingiva with flap apical reposition, to expose the incisal third of both incisor crowns	The patient underwent an 8-hour intravenous infusion of tranexamic acid (250 mg), vitamin K (5 mg), and normal saline to control the bleeding; at the end of this period, the haemorrhage was eventually stopped, and the patient was released.
Yanji Qu et al [3], 2014	Review on studies providing data of the prevalence of hemophilia	The overall weighted prevalence of hemophilia was 3.6	Based on the prevalence of haemophilia in mainland China

	or its subtypes	per 100,000 and the prevalence among males was 5.5 per 100,000.	identified by our study, 49,339 haemophiliacs are thought to reside there.
Connie H. Miller et al [2], 2021	Application of tools in understanding the genetic causes of haemophilia in women and girls.	Coagulation parameters, F8 or F9 sequencing, F8 inversion testing, multiplex ligation-dependent probe amplification, karyotyping and X chromosome inactivation studies performed on the patient and parents	Homozygous females with two abnormal alleles will have the same phenotype as hemizygous males, while heterozygous females are usually protected by the presence of a normal allele on their second X chromosome
Xavier Frachon et al [15], 2005	To evaluate the effectiveness of a protocol combining general management through the injection of factor concentrates or	4 of the 6 incidences of postoperative haemorrhage took place following the compression period. In 2 cases, injecting	A combination of an injection of coagulation factor concentrate or DDAVP, and use of an effective local hemostasic technique

	DDAVP and local hemostasis using biological glue and gelatin packing, a retrospective study of 55 dental extractions performed during 19 interventions in 16 patients with haemophilia A or B was conducted.	an antihemophilic factor concentrate was necessary in addition to repeating the local hemostasic procedures. Following the injection of the factor concentrate and the reapplication of the compression in the remaining 4 cases, the patients' conditions returned to normal.	can, in most cases, prevent the onset of excessive, postsurgical bleeding.
M. FRANCHINI et al [8],2005	In a retrospective study conducted at three Italian haemophilia centres over a ten-year period, data on the oral health of patients with congenital hemorrhagic diseases was assessed.	. Between 1993 and 2003, 247 patients with inherited bleeding disorders underwent 534 dental procedures including 133 periodontal treatments, 41 conservative dentistry procedures, 72	A total of 10 bleeding issues (1.9%) were noted, the majority of which included individuals with severe or moderate haemophilia A who required multiple teeth extractions. Therefore, it has been demonstrated that their

		endodontic treatments and 288 oral surgery procedures.	protocol of management for patients with genetic bleeding predisposition having oral therapy or surgery is successful
Gary Benson et al [1], 2018	Reviews on creating treatment regimens for people with haemophilia, covering the complete spectrum from clinical care for a newborn who has just been diagnosed to that for an elderly patient with several concomitant conditions.	Treatment options for managing bleeds in patients with mild/moderate haemophilia who have developed inhibitors are recombinant activated factor VII (FVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) or, if antibodies are directed against exogenous FVIII only, DDAVP.	Management strategies consider not only the vast differences in hemophiliac patients' needs, but also risks of inhibitor development and approaches to optimally engage patients.
Martha Cecilia Elizondo Rojas et al [10], 2022	Reviewing considerations in the dental office in the	In order to control or avoid bleeding, haemophilia A or B	The recommendations state that patients with early childhood easy

	management of the hemophiliac patient.	patients must receive intravenous infusions of replacement clotting factors. Since it is used most frequently after bleeding has started—in other words, in reaction to a hemorrhagic event—this replacement strategy is known as the "on demand" treatment.	bruising, spontaneous bleeding, and severe bleeding after trauma or surgery should have haemophilia suspected. Practise recommendations are required to enhance the diagnosis procedure and level of care.
Sara Israels et al [16], 2006	Reviews on preoperative systemic precautions and intraoperative hemostatic measures.	Techniques for managing postoperative bleeding episodes such as Reapplication of pressure packs, Packing or repacking sockets with Gelfoam, Reinjection of local	Studies conducted in the last ten years have revealed a surprising level of intricacy related to the hemostatic process. Blood loss at the site of damage is immediately stopped by a finely orchestrated

		anesthetic with epinephrine, use of astringents are recommended.	action of cellular and soluble components.
Waldemar Reich et al [17], 2009	Prospective assessement to determine the incidence of postoperative bleeding after oral surgery under local anaesthesia performed in outpatients with haemostatic disorders within a 5-year period.	One hundred twenty one (70 males, 51 females) out of 2,056 outpatients with different haemostatic disorders (acquired or hereditary) were included. Postoperative bleeding was observed in 12 patients (9.9%). In three cases, inpatient treatment became necessary.	Treatment modalities such as Collagen vlies, primary suture, fibrin glue with with appropriate operative technique enabled an effective wound management.
Naveen Kumar J et al [18], 2007	Prescription a simple protocol to diagnose bleeding disorders and a	A prolonged activated partial thromboplastin time (APTT), normal	Endodontic therapy may typically be performed under antifibrinolytic

	modified scheme for endodontic and periodontal therapy in a hemophiliac patient.	prothrombin time (PT), normal bleeding time (BT), and low Factor VIIIC are the main diagnostic laboratory findings in haemophilia. Because even the APTT may be normal in mild cases, factor VIII assays are typically necessary.	cover in all patients other than severe haemophiliacs. Avoiding instrumentation via the periapex is crucial in endodontic therapy. Replacement of LA and Factor VIII to a level of between 50 and 75% is necessary for periodontal surgery. Postoperative factor level maintenance is case-dependent, as expected.

DENTAL MANAGEMENT

The initial step is to identify the patients based on their clinical and family histories, risk factors for the disease, and laboratory results. The main goal is to give patients dental treatment and care recommendations that will help them avoid the most common dental illnesses, like dental caries and periodontal disorders. Due to their incapacity to practise proper oral hygiene, hemophilic patients are more prone to periodontal disorders than the general population. Additionally, the gingival sulcus is home to a variety of aerobic and anaerobic microbes that cause periodontal

degeneration. The patient becomes aware of the necessity of routine visits for professional prophylaxis, examinations, and treatment as well as the prevention of these organisms from producing gingival irritation.[4]

Spontaneous mucosal bleeding, episodic, protracted, spontaneous, or traumatic gingival bleeding are all very common. Additionally, there are hemophilia-related pseudotumors and hemarthrosis of the temporomandibular joint. Haemophilia patients must receive care that is focused on comprehensive care. In order to control or avoid bleeding, haemophilia A or B patients must receive intravenous infusions of replacement clotting factors. This replacement approach is known as the "ondemand" treatment because it is used the most frequently when bleeding has already started, i.e., when the factor is used in reaction to a hemorrhagic episode. As a preventative step, treatment can be given on a regular basis without having to wait for a bleeding event to happen; this is known as prophylaxis. This plan is regarded as best practise in individuals with severe haemophilia, according to certain scientific research. Similarly, it is believed that replacing the deficient clotting factor is the best strategy to treat haemophilia so that the blood can coagulate normally. Blood plasma-derived clotting factor concentrates and recombinant clotting factor concentrates are the two primary varieties.[10]

It is important to take into account the patient's level of haemophilia. If surgery, serious injury, or teeth extractions are avoided, mild haemophilia may not be discovered until adolescence. As a result, a dentist might occasionally be the one to identify a patient's haemophilia. According to research, 30% of mild instances were only discovered after a major oral bleeding episode. To treat patients with hemostasis issues, the dentist needs to have a foundational understanding. The essential aim is to gather accurate clinical history so that you can use this information to create a proper treatment plan with the patient's treating physician. It is crucial to involve the patient in

their care and emphasise the fact that with good oral hygiene and preventative measures, the dentist's involvement will be minimal, lowering the likelihood of any potential bleeding issues. To deliver thorough and high-quality dental care, there should be close communication between the dentist and the patient's medical team. Avoiding unintentional harm to the oral mucosa is crucial when performing any procedure in the mouth. Usage of Saliva collector, impression removal, placement of x-ray film, especially in the sublingual region, use of a gum shield to protect soft tissues during reconstructive treatment, and application of soft yellow kerosene like petroleum jelly can all help prevent injury. Due to the abundance of expanded capillaries on the surface of the thinner regions of the gingiva, patients may present with bouts of spontaneous bleeding during teeth brushing, food abrasion, or periodontal disease. Haematologists and dentists working together results in successful dental care for haemophiliac patients. Before and potentially after more extensive treatments like scaling and root planning, it could be necessary to raise the factor level to ensure proper coverage.

Using local anaesthesia for dental treatment is crucial. Factor replacement is necessary for lower alveolar blocks because they run the risk of hematoma formation in the retromolar or pterygoid spaces, which could limit the airway and cause bleeding into the muscles that surround them due to rich vasculature and blind injection. The only procedures that can necessitate hospitalisation are oral surgery, periodontal surgery, and any dental procedure requiring anaesthesia with inferior alveolar nerve block and lingual infiltration anaesthesia. There are no limitations on the kind of local anaesthetic agent that can be employed, albeit those that contain vasoconstrictors may offer more local hemostasis. Most dental discomfort can be managed with a mild painkiller like paracetamol. Since acetylsalicylic acid prevents platelet aggregation, it shouldn't be utilised. Non steroidal anti-inflammatory medicines (NSAIDs) have an impact on platelet aggregation,

hence the patient's haematologist should be consulted before using any NSAIDs. Without the necessity for factor replacement, buccal infiltration can be used to anaesthetize the entire upper teeth as well as the anterior lower dentition and premolars. It is advised to use Articaine as a local anaesthetic, and various studies have demonstrated that inferior alveolar blocks can be avoided in favour of buccal infiltration of the jaw.[10]

CONCLUSION:

Hemophilia is an X-linked recessive inherited disorder. It is a member of the class of hereditary diseases brought on by a shortage of one or more coagulation factors.[10] Patients with a history of spontaneous bleeding, especially into the joints, muscles, and soft tissues, or prolonged bleeding after trauma or surgery should be suspected of having haemophilia. A family history of bleeding disorders should be carefully elicited because haemophilia runs in families.[4] Any patient with a bleeding disease requires dental management in collaboration with a haematologist.[11]

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