Review Article

Hemophilia A: Dental considerations and management

Shilpa Padar Shastry, Rachna Kaul, Kusai Baroudi[1], Dilshad Umar[2]

Vydehi Institute of Dental Sciences and Research Center, Bangalore, Karnataka, India, [1]Departments of Restorative Dental Sciences and [2]Orthodontics Al-Farabi College of Dentistry, Riyadh, Saudi Arabia

Corresponding author (email: <dilshadu@yahoo.com>)
Dr. Dilshad Umar, Fathimas, Jain Compound, Attavar, Mangalore, Karnataka, India.

Abstract

Aim: To review hemophilia A with emphasis on its oral manifestations, investigations, and dental management. **Materials and Methods:** Search was conducted using internet-based search engines, scholarly bibliographic databases, PubMed, and Medline with key words such as "Hemophilia A," "factor VIII," "bleeding and clotting disorders," and "dental management." **Results:** 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. It is broadly divided into hemophilia A, B, and C, which occur due to deficiency of factor VIII, IX, and XI, respectively. Hemophilia A is an X-linked recessive hereditary disorder and is the most common of the three, accounting for 80–85% of the cases. **Conclusion:** Understanding this complex entity is very important for a dentist to provide appropriate dental treatment and avoid undesirable consequences.

Key words: *Bleeding disorder, bleeding time, clotting disorder, clotting time, factor VIII, hemophilia A, Royal disease*

INTRODUCTION

Dentists may encounter patients with various types of bleeding disorders in their day today practice. Initial recognition of such bleeding disorders and their possible systemic causes plays a significant role in reducing potential complications. Bleeding disorders can be classified as coagulation factor deficiencies, platelet disorders, vascular disorders, and fibrinolytic defects. Among these, hemophilia A, hemophilia B (Christmas disease), and von Willebrand's disease are the commonly encountered congenital coagulation defect disorders.[1]

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. It is broadly divided into hemophilia A (deficiency of factor VIII), hemophilia B or Christmas disease (deficiency of factor IX), and hemophilia C or Rosenthal syndrome (deficiency of factor XI). Other variants include parahemophilia (Owren's disease), which occurs due to factor V deficiency, and acquired hemophilia.[1,2] Hemophilia A is more common than hemophilia B, accounting for 80–85% of the total hemophilia. Hemophilia challenges the skills of dental specialists by inducing bleeding during treatment, which can even be life threatening in certain cases. 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. The aim of this article is to review hemophilia A with an emphasis on its oral manifestations, investigations, and dental management.

Access this article online	
Quick Response Code:	Website: www.jispcd.org
	DOI: 10.4103/2231-0762.149022

MATERIALS AND METHODS

The review protocol involved the study of all existing published literatures on hemophilia. Eligibility criterion to include the articles in the review was that the articles should describe the oral manifestations

and dental management protocols of hemophilia (case series, review, original papers). A total of 28 articles were considered to compile the present report. Search was conducted using internet-based search engines, scholarly bibliographic databases, PubMed, and Medline with key words such as "hemophilia A," "factor VIII," "bleeding and clotting disorders," and "dental management." The search included the articles published from 1965 to 2010. Studies or articles in languages other than English were excluded from the study.

RESULTS

Hemophilia A, which occurs due to deficiency of factor VIII, is the most common of the three, accounting for 80–85% of the cases. It is an X-linked recessive hereditary disorder characterized by a deficient or defective factor VIII coagulant [factor VIII C or anti-hemophilic globulin (AHG)].[3] It is ordinarily carried through females and affects males. A case of a female hemophiliac has been documented by Gilchrist in 1961.[4] The incidence of hemophilia A is approximately 1 in every 10,000 persons.[5] A positive family history may be traced among male relatives. However, 30% cases are caused by new mutations and, hence, may not be associated with a family history.[3,6]

DISCUSSION

Hemophilia A is caused due to factor VIII deficiency, the gene for which is located on the long arm of the X chromosome at Xq28 and consists of 26 exons.[7] It can arise from various mutations and approximately 150 point mutations have been characterized.[8] Hemophilia has played an important role in Europe's history because it occurred in Great Britain's Queen Victoria's family and became to be known as the "Royal disease" as it spread to the royal families of Europe through Victoria's descendants.[3]

Hemophiliacs are divided into two groups:

- Those who have non-functioning factor VIII analogues and
- Those who do not have the abnormal factor VIII at all.

The former group comprises the majority. Those in the latter group may develop antibodies to factor VIII during transfusion.

The severity of hemophilia has been classified into the following three forms by the subcommittee on factors VIII and IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis:

- Severe form where the factor level is less than 1% of normal (<0.01 IU/ml)
- Moderate form where the factor level is 1–5% of normal (0.01–0.05 IU/ml)
- Mild form with the factor level more than 5–40% of normal (>0.05–0.40 IU/ml).[9]

Clinical features

Severe cases may manifest with massive intrauterine hemorrhage leading to still birth and neonatal intracranial hemorrhage. Tendency toward easy bruising, and massive hemorrhage after trauma or minor surgical procedures are commonly encountered. Also, spontaneous hemorrhage from the middle ear, epistaxis, bleeding into the joints causing hemarthrosis, and bleeding into soft tissues may occur. Weight-bearing joints become hot, tender, and painful, leading to synovial hypertrophy, destruction of cartilage, and secondary osteoarthritis. Untreated muscle hematomas in calf muscle can cause a rise in pressure with eventual ischemia, necrosis, fibrosis, and subsequent contraction and shortening of Achilles tendon. Tissue hemorrhage forms tumor-like masses termed as "pseudotumors of hemophilia."[1,10,11] Complications in hemophiliacs include musculoskeletal complications such as chronic hemophilic arthropathy, synovitis, contractures, pseudotumor formation, development of inhibitors against factor VIII, and most importantly transfusion-related infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A viruses.[12,13]

Oral manifestations

Hemophilia is characterized by bleeding from multiple sites, frequently manifested in the mouth as gingival and post-extraction hemorrhages. Patients may also have multiple oral bleeding events over their lifetime, depending on the severity of hemophilia. Bleeding episodes are more frequently encountered in severe hemophilia, followed by moderate hemophilia, and are minimal in mild hemophilia. Poor oral hygiene and iatrogenic factors can also induce the oral bleeding. In toddlers, oral ulcerations and ecchymosis involving lips and tongue are common. Sonis and Musselman (http://www.ijdr.in/article.asp?issn=0970-9290;year=2011;volume=22;issue=3;spage=454;epage=461;aulast=Adeyemo - ref57) reported an average of 29.1 bleeding events per year in hemophilia patients, of

which 9% involved oral structures (labial frenum, 60%; tongue, 23%; buccal mucosa, 17%; gingiva and palate, 0.5%). Hemarthrosis of temporomandibular joints is unusual.[14,15]

Investigations

Positive family history or a clinical history of exaggerated bleeding response to minor trauma gives a clue regarding the presence of hemophilia A. Laboratory diagnosis demonstrates normal platelet count, normal bleeding time (BT), prolonged activated partial thromboplastin time (APTT), and normal prothrombin time (PT). Prolonged APTT in hemophilia A evaluates the intrinsic and common pathways of blood coagulation. APTT is considered normal if the control APTT and the test APTT are within 10 s of each other. Control APTT is usually 25 ± 10 s. It is determined by adding an activator to plasma (e.g. kaolin) along with an extract of phospholipid (to mimic plasma membrane). Normal BT assesses the vascular and platelet phases of blood clotting, but is of limited sensitivity. PT test evaluates the extrinsic system and measures the presence or absence of clotting factors I, II, VII, and X. In order to standardize PT, in 1983, the World Health Organization (WHO) introduced the international normalized ratio (INR). It is the ratio between the PT of a patient in seconds and a control PT standardized by means of International Sensitivity Index (ISI), which indicates the sensitivity of the thromboplastin used as reagent. In this context, human brain thromboplastin is assigned the reference standard of 1. An ISI greater than 1 indicates a less sensitive thromboplastin, whereas a value less than 1 indicates a more sensitive thromboplastin. For a PT value within the normal range, INR = 1.[1,5-7] Definitive diagnosis is established by quantification of the procoagulant activity of factor VIII, which is found to be reduced in hemophilia A.[1,6]

Dental management

Identification of the patients based on clinical and family history, disease antecedents, and laboratory testing is an important phase. Consultation with a specialist to determine the type of disorder involved is essential. Counseling can help to increase the awareness of importance of good oral hygiene in order to avoid invasive dental care and reduce the number of visits to the dentist.

The most important objective is to provide dental care and dental care instructions which help patients to prevent most prevalent dental diseases like dental caries and periodontal diseases. Teeth should be brushed at least twice daily for plaque control with toothpaste containing fluoride and mouthwashes of triclosan or chlorhexidine which also help reduce plaque.[1] Minimizing the intake of any food containing sticky carbohydrates between meals reduces the possibility of pH drop below 5.5 (normal 7.0) and demineralization of enamel and dentine. Another approach is to use pit and fissure sealants to reduce the incidence of dental caries.[16] Hemophilic patients are susceptible to periodontal diseases more than ordinary people because of their inability to perform oral hygiene procedures.[17] Moreover, gingival sulcus hosts various aerobic and anaerobic organisms leading to periodontal destruction. Regular oral hygiene instructions and practice prevents these organisms from causing gingival inflammation and also develops in the patient an awareness of the need to return regularly for professional prophylaxis, examination, and treatment.[18]

Providing dental treatment to hemophilia A patients

Patients with hemophilia A require multiple visits to achieve a definitive dental treatment, even on one tooth. The management of patients with hemophilia A depends on the severity of the condition (mild, moderate, or severe) and the invasiveness of the planned dental procedure. Avoidance of brusque maneuvers during dental treatment and local hemostatic measures are recommended. It is also essential to prevent accidental damage to the oral mucosa when carrying out any dental procedure by the cautious use of use of saliva ejectors, protection of soft tissues during restorations, and taking care in the placement of X-ray films. Aspirin and its derivatives must be avoided. Resorbable sutures are recommended if needed. Hemophiliacs treated with human plasma derivatives may be the carriers of hepatitis B or C viruses, HIV, parvovirus, or transmissible spongiform encephalopathy. Necessary tests and precautionary measures are required.[19]

Surgical treatment

Hemophilia patients are at high risk of secondary bleeding following oral surgery. International guidelines advise the use of clotting factor replacement therapy for all invasive surgical interventions in patients with hemophilia.[20]

The World Federation of Hemophilia (WFH) recommends the use of factor concentrates to cryoprecipitate or fresh frozen plasma for replacement therapy in patients with hemophilia. Surgical treatment must be planned to minimize the risk of bleeding or hematoma formation. Patient's hematologist must

be consulted before treatment initiation regarding the factor levels, factor replacements, type of surgery, and the need for systemic hemostatics. If necesary, replacement therapy comprising coagulation factor VIII or desmopressin (DDAVP) [Table 1][21] is administered. All the measures to reduce the risk of infection (administration of antibiotics, topical antiseptic mouthwashes) must be instituted. Surgery must be performed with caution to reduce trauma to soft tissues, and also measures to reduce intraoperative and postoperative hemorrhage must be undertaken. Proper suture placement may help to prevent clot formation postoperatively and surgical stent should be fabricated to protect the surgical site during healing.[22,23] Post-extraction bleeding should initially be managed with pressure and other local hemostatic measures such as fibrin glue and oxidized cellulose. Anti-fibrinolytic agents such as tranexamic acid (adult dose 1 g three times a day) and epsilon aminocaproic acid (EACA) (50 mg/kg four times a day) are used at the start of the surgery and should be continued for a total of 7 days.[24,25] Persistent oozing and bleeding following the procedure requires hematologist consultation and additional systemic hemostatic therapy.[16]

Restorative treatment and endodontic treatment

Endodontic therapy is preferred over extraction whenever possible, as endodontic treatment generally has low risk of bleeding in patients with hemophilia A. Working length of the root canal is calculated precisely to ensure that the instruments do not pass through the apex of the root canal during root canal treatment. There is a risk of bleeding with the use of matrix bands, rubber dam, or wooden wedges during restorative treatment, which can be controlled by local means or the application of topical agents. A rubber dam should be used to prevent soft tissue lacerations. High-speed suction can injure the mucosa in the floor of the mouth and cause hematoma or ecchymosis. Surgical endodontics requires factor VIII replacement up to 50–75%. The need for postoperative maintenance of factor levels should depend on the type of surgery and the severity of hemophilia.[24]

Table 1: Clotting factor administration in hemophilia a prior to surgery

Condition	Dose of factor VIII
Mild bleeding	Dose: 15 U/kg factor VIII every 8-12 h for 1-2 days Target: 30% of normal level
Major bleeding	Dose: 50 U/kg factor VIII every 8-12 h for 7-14 days Target: 80-100% of normal level
Adjuvant therapy	Desmopressin, tranexamic acid or epsilon aminocaproic acid (for mild disease)

Periodontal treatment

Maintaining healthy periodontium is important to prevent extraction, tooth loss, and bleeding. Supragingival scaling can be carried out initially along with oral hygiene instructions, followed by subgingival scaling after the inflammation has subsided. Periodontal surgery is regarded as a high-risk procedure with a significant risk of blood loss and poses greater challenge to hemostasis than a simple extraction.[25]

Dentures or orthodontic treatment

Orthodontic treatment or removable prosthesis is not contraindicated in the cases of hemophilia A. However, these appliances may encourage plaque accumulation, which necessitates vigorous oral hygiene programs. Nevertheless, care must be taken to avoid damage to gingiva.[16,25]

Pain and infection control in hemophilia A

Dental pain can usually be controlled with a minor analgesic such as acetaminophen. Aspirin is avoided as it has effect on platelet aggregation. The use of any non-steroidal anti-inflammatory drug (NSAID) must be discussed with the patient's hematologist because of its effect on platelet aggregation. Penicillin is the first line of drug used to control dental infection in conjunction with metronidazole to give good coverage of both the aerobic and anaerobic bacteria. Erythromycin and clindamycin can be prescribed to patients who are allergic to penicillin.[26] Periodontal infections are mostly due to different species of bacteria, especially anaerobic bacteria. Metronidazole is considered the drug of choice due to its action against anaerobic organisms.

Local anesthesia

Although there are no restrictions with respect to the type of local anesthesia used, those with vasoconstrictors may provide additional local hemostasis. Buccal infiltration is sufficient to anesthetize all the upper teeth and lower anterior and premolar teeth. Mandibular molar teeth are anesthetized using inferior alveolar nerve block after increasing the clotting factor levels by appropriate replacement therapy, as there is a risk of bleeding into the muscles along with potential airway compromise due to a hematoma in the retromolar or pterygoid space.[27] The intraligamental technique or interosseous technique should be considered as a potential alternative to the nerve blocks.[12]

Oral hygiene instructions

Good oral hygiene is essential to prevent periodontal disease and dental caries which predispose to gum

bleeding. Routine dental examinations should be conducted regularly, beginning from the time the baby teeth start to erupt. Teeth should be brushed twice a day with a medium texture brush and toothpaste containing fluoride to remove plaque deposits (1000 ppm fluoride toothpaste for children under 7 years of age and 1400 ppm fluoride toothpaste for children people over 7 years of age). Fluoride supplements may also be prescribed if required (not recommended if the water supply has a fluoride content of 1 ppm or more) in the form of fluoride drops, fluoride tablets, topical application of fluoride using trays, and fluoride mouth rinses.

Oral hemorrhage may be encountered in hemophiliacs. Early consultation with a dentist or oral and maxillofacial surgeon is essential to determine the source of bleeding. Dental extraction, gingival bleeding due to poor oral hygiene, and trauma are the most common causes of oral hemorrhage. Local treatments like direct pressure on the area using a damp gauze swab, maintained for at least 15 min must be considered. Suturing of the wound, application of local hemostatic agents, and use of EACA or tranexamic acid as a mouthwash can be administered.[28]

CONCLUSION

Hemophilia should be suspected in patients with a history of easy bruising in early childhood, spontaneous bleeding, particularly into the joints, muscles, and soft tissues, or prolonged bleeding following trauma or surgery. Hemophilia runs in families; therefore, a family history of bleeding disorders should be carefully elicited. Hemophilic patients form a priority group for dental and oral health care, since bleeding after dental treatment may cause severe or even fatal complications. Moreover, maintenance of oral hygiene and prevention of dental diseases is of great significance to improve the quality of life and avoid the dangers of surgery. 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. Genetic counseling is an important part of hemophilia care to help people with hemophilia, carriers, and their families make more informed choices about having children where there is a possibility of having a child with hemophilia or risk of having another affected child and the options available. Dentists can not only provide complete oral care for hemophilia A patients but also contribute in the genetic counseling through wide range of tests for diagnostic and carrier detection, as well as individual counseling.

REFERENCES

1. Patton LL. Bleeding and clotting disorders. In: Greenberg MS, Glick M, Decker BC, editors. Burket's Oral Medicine: Diagnosis and Treatment. 10th ed. Hamilton, ON: BC Decker; 2003. p. 454-77.
2. Rogaev EI, Grigorenko AP, Faskhutdinova G, Kittler EL, Moliaka YK. Genotype analysis identifies the cause of the "royal disease". Science 2009;326:817.
3. Tiuntseva YA, Herreid CF. Hemophilia: The Royal Disease. Available from: http://www.sciencecases.org/hemo/hemo.asp. [Last accessed on 2014 Jul 11].
4. Gilchrist GS, Hammond D, Melnyk J. Hemophilia A in a phenotypically normal female with XX-XO mosaicism. N Engl J Med 1965;273:1402-6.
5. Kumar JN, Kumar RA, Varadarajan R, Sharma N. Specialty dentistry for the hemophiliac: Is there a protocol in place? Indian J Dent Res 2007;18:48-54.
6. Lawn RM, Vehar GA. The molecular genetics of hemophilia. Sci Am 1986;254:48-54.
7. Dala A, Pradhan M, Agarwal S. Genetics of bleeding disorders. Int J Hum Genet 2006;6:27-32.
8. Schwaab R, Oldenburg J, Schwaab U, Johnson DJ, Schmidt W, Olek K, *et al*. Characterization of mutations within the factor VIII gene of 73 unrelated mild and moderate haemophiliacs. Br J Haematol 1995;91:458-64.
9. White GC 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J; Factor VIII and Factor IX Subcommittee. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost 2001;85:560.
10. Dumontier C, Sautet A, Man M, Bennani M, Apoil A. Entrapment and compartment syndromes of the upper limb in haemophilia. J Hand Surg Br 1994;19:427-9.
11. Cordingley FT, Crawford GP. Ulnar nerve palsy in a haemophiliac due to intraneural hemorrhage. Br Med J (Clin Res Ed) 1984;289:18-9.
12. Gupta A, Epstein JB, Cabay RJ. Bleeding disorders of importance in dental care and related patient management. J Can Dent Assoc 2007;73:77-83.
13. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. HSS J 2010;6:37-42.
14. Rakocz M, Mazar A, Varon D, Spierer S, Blinder D, Martinowitz U. Dental extractions in patients with bleeding disorders. The use of fibrin glue. Oral Surg Oral Med Oral Pathol 1993;75:280-2.
15. Sonis AL, Musselman RJ. Oral bleeding in classic hemophilia. Oral Surg Oral Med Oral Pathol 1982;53:363-6.
16. Harrington B. Primary dental care of patients with haemophilia. Haemophilia 2000;6 Suppl 1:7-12.
17. Freedman M, Dougall A, White B. An audit of a protocol for the management of patients with hereditary bleeding disorders undergoing dental treatment. J Disability Oral Health 2009;10:151-5.
18. Webster WP, Courtney RM. Diagnosis and Treatment of Periodontal Disease in the Hemophiliac. In: Proceedings Dental Hemophilia Institute. New York: National Hemophilia Foundation; 1968. p. 288.
19. Jover-Cerveró A, Poveda Roda R, Bagán JV, Jiménez

Soriano Y. Dental treatment of patients with coagulation factor alterations: An update. Med Oral Patol Oral Cir Bucal 2007;12:E380-7.
20. Stubbs M, Lloyd J. A protocol for the dental management of von Willebrand's disease, haemophilia A and haemophilia B. Aust Dent J 2001;46:37-40.
21. Blinder MA. Bleeding disorders (Web site of the Washington University School of Medicine]. Available from: http://hematology.im.wustl.edu/conferences/presentations [Last accessed on 2014 Apr 2]
22. Israels S, Schwetz N, Boyar R, McNicol A. Bleeding disorders: Characterization, dental considerations and management. J Can Dent Assoc 2006;72:827.
23. Brewer A, Correa ME. Guidelines for Dental Treatment of Patients with Inherited Bleeding Disorders. Treatment of Hemophilia monograph no. 40, World Federation of Hemophilia; 2006.
24. Australian Haemophilia Centre Directors' Organisation. A Consensus Statement on the Dental Treatment of Patients with Inherited Bleeding Disorders. Australia: Australian Haemophilia Centre Directors' Organisation (AHCDO); 2010.
25. Sciullo PA, Nacht ES, Tesone AR. Postsurgical complications in an undiagnosed hemophiliac: A case report. ASDC J Dent Child 1972;39:194-6.
26. Gill Y, Scully C. Orofacial odontogenic infections: Review of microbiology and current treatment. Oral Surg Oral Med Oral Pathol 1990;70:155-8.
27. Nazif M. Local anesthesia for patients with hemophilia. ASDC J Dent Child 1970;37:79-84.
28. Franchini M, Rossetti G, Tagliaferri A, Pattacini C, Pozzoli D, Lorenz C, *et al.* Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers. Haemophilia 2005;11:504-9.

How to cite this article: Shastry SP, Kaul R, Baroudi K, Umar D. Hemophilia A: Dental considerations and management. J Int Soc Prevent Communit Dent 2014;4:S147-52.

Source of Support: Nil, **Conflict of Interest:** None declared.