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Hemophilia and its considerations in the dental practice

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Abstract
Introduction: Hemophilia is an is an X-linked recessive inherited disorder. It belongs to the group of hereditary disorders caused by the deficiency of one or more coagulation factors.
Objective: To analyze the literature on the considerations in the dental office in the management of the hemophiliac patient, particularly the etiology, clinical characteristics, diagnosis, treatment and dental management.
Methodology: In order to carry out this literature review, an electronic search was necessary using PUBMED and Google Scholar with the words "Hemophilia AND dentistry" "etiology, clinical and dental characteristics, diagnosis and treatment" and "coagulation factors".
Results: Hemophilia is due to an alteration in one of the genes that determine the way in which the organism produces coagulation factor VIII or IX. It occurs in 1 in 10,000 male births. It manifests as excessive bleeding in the joints, pain and edema, ecchymosis, urinary tract and digestive tract bleeding. It results in prolonged bleeding from wounds, dental extractions and surgery. The diagnosis of hemophilia is made by taking a blood sample and measuring the degree of factor activity. The main treatment for severe hemophilia is to receive specific clotting factor replacement. During the consultation, a detailed medical history should be taken and comprehensive clinical examinations should be ordered appropriately. The patient should provide the following information: type and severity of his hemophilia, medication ingest, whether he requires pre-treatment with factor concentrate, or an antifibrinolytic agent.
Conclusion: Hemophilia is an X-linked recessive inherited disorder. It belongs to the group of inherited disorders caused by deficiency of one or more clotting factors. Practice guidelines are needed to improve the diagnostic process, improve the quality of dental care.

Keywords: Hemophilia, coagulation factors, coagulopathies, hemophilic patient, dental management

1. Introduction
Hemophilia is an X-linked recessive inherited clotting disorder involving a lack of clotting factor VIII, FVIII (hemophilia A) or clotting factor IX, FIX (hemophilia B). In its latest annual report, the World Federation of Hemophilia (WFH) states that 196,706 patients with hemophilia are registered worldwide, and that 80 to 85% of them have hemophilia A [1]. Hemophilia A is the most common, with a frequency of 80 to 85% of cases. Coagulation factor abnormalities result in prolonged clotting time and excessive bleeding tendencies, which is a risk in the dental office. Hemophilia B, also called Christmas disease, is a congenital coagulopathy secondary to a quantitative or qualitative abnormality of coagulation factor IX [2]. Classification of hemophilia severity is based on clinical bleeding symptoms and plasma factor levels [3]. It is clinically identified by prolonged clotting time, excessive bleeding in skin, mucous membranes, secondary joint complications, among others. In hemophilia, the factors in deficit are diminished in quantity, structure and function, resulting in an altered coagulation cascade and a significant increase in bleeding time [4].
The classification of hemophilia focuses on the plasma level of FVIII/FIX. Hemophilia is classified as severe, moderate and mild. In severe hemophilia the clotting factor level is 1% (<0.01), bleeding episodes are spontaneous mainly in joints and muscles. In moderate hemophilia the frequency is 1%-5%. Bleeding may occur from insignificant trauma.

However, hemorrhages are less frequent and may present joint involvement. In mild hemophilia there is a >5% factor, may bleed from severe trauma, surgery etc. Hemorrhage is infrequent and joint involvement is rare [5].

In mild hemophilia, patients may not present signs of the disease until they face situations such as accidents, dental procedures and surgeries; the diagnosis may even be made until adulthood [6].

In moderate hemophilia, bleeding may occur after relatively minor injuries, while in severe hemophilia, major bleeding may occur as early as the first year of life [7]. Patients with severe hemophilia present spontaneous bleeding or bleeding following even minor trauma in about 1 to 6 episodes per month and may present life-threatening events [8].

There are few updated reports in the literature describing the dental management of patients with hemophilia. In addition, it has been found that knowledge of the disease among health personnel is low. The aim of this paper is to analyze the literature on the characteristics of hemophilia, particularly its etiology, clinical features, diagnosis, treatment and dental management.

2. Materials and methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using PRISMA guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews (AMSTAR-2) [9].

The search was performed using Boolean logical operators AND, OR and NOT.

It was constructed with the words “hemophilia”, “etiology”, “clinical features”, “diagnosis”, “treatment”, “dental management”. The keywords were used individually, as well as each of them related to each other. Initially, the titles of all the articles were selected, the abstract of each one was evaluated, and the articles were chosen for a complete reading review.

3. Results & Discussion

3.1 Etiology

In most cases hemophilia is inherited and manifests clinically in males. Women can carry the gene that causes hemophilia [9]. When a woman who is a carrier has children, she has a 50% chance that her sons will have hemophilia and a 50% chance that her daughters will be carriers. Although sons of men with hemophilia will not inherit the disease, all daughters born to fathers with hemophilia will be carriers. In addition, in one-third of all cases, there is no family history of the disease and hemophilia occurs as a result of a new mutation of the 10 gene [2]. This X-linked congenital bleeding disorder has a frequency of approximately 1 in 10,000 births [10]. Hemophilia A is more common than hemophilia B, accounting for 80 to 85% of all cases. The life expectancy of people born with hemophilia who have access to adequate treatment should approach normal with currently available treatment [11]. For this hematological disease there is no racial or geographic selectivity; the disorder does not usually show a family history since about one third of cases worldwide are caused by a spontaneous or sporadic genetic mutation [12]. The incidence of hemophilia A is approximately 1 in 10,000 persons. A positive family history can be traced among male relatives. However, 30% of cases are caused by new mutations and therefore may not be associated with a family history [13]. Hemophilia is due to an alteration in one of the genes that determine how the body produces clotting factor VIII or IX. It occurs in 1 in 10,000 male births [14].

3.2 Clinical Characteristics

The types of hemophilia cause phenotypes similar to each other, usually characterized by hemarthrosis, deep muscle hematomas and cerebral hemorrhages or hemorrhages affecting any part of the body [15]. Seventy percent of cases present the disease phenotype in their male ancestors, hence the importance of anamnesis in the consultation [16]. Hemorrhage in hemophilia is usually delayed, that is, it does not immediately follow the injury, trauma, or surgery, but starts a few minutes after the wound or injury. This is explained by the fact that the patient has complete primary hemostasis or presents an initial clot which can be described as normal, indicating that secondary hemostasis was not effective, which under physiological conditions should form a definitive fibrin clot from the platelet plug [3]. Nasal bleeding and mucosal hemorrhages including the mouth, are typical of hemostatic conditions such as hemophilia. The clinical manifestations depend on the level of factor deficiency, which allows their classification [17]. As mentioned, the main consequences of bleeding episodes in hemophilic patients are: hemarthrosis (70-80%) and muscle/soft tissue bleeding (10-20%). Bleeding affects joints with predominant sequence: knee (45%), elbow (30%) and ankle (15%). These hemorrhages cause joint pain, swelling and decreased range of motion. Other major hemorrhages account for 5-10%. Central nervous system (CNS) bleeding accounts for less than 5% [18]. Prolonged bleeding may occur from wounds, dental extractions and surgery. Hemophilia can be suspected in patients with spontaneous bleeding or bleeding secondary to trauma9. Regarding dental manifestations, it is common to find spontaneous mucosal bleeding, episodic, prolonged, spontaneous or traumatic gingival bleeding. There is also hemarthrosis of the temporomandibular joint and pseudotumors of hemophilia [19]. It manifests as excessive bleeding in the joints, pain and edema, ecchymosis, urinary tract and digestive tract hemorrhages.

3.3 Diagnosis

The diagnosis of hemophilia can be considered or suspected in patients with spontaneous hemorrhages or secondary to trauma, especially if they appear in the early stages of life or at birth [2]. It can be diagnosed by prolongation of the APTT that corrects with the addition of normal plasma and the determination of the FVIII/FIX level is necessary for its diagnosis. It should also be taken into account that in von Willebrand's disease, as a differential diagnosis of higher incidence, FVIII dosage may be decreased. The diagnosis of hemophilia can be considered in situations such as neonates with the presence of muscle hematomas at vitamin K or vaccine administration sites, intracranial hemorrhage, cephalohematoma or hematomas at venipuncture sites. In children, the onset of ambulation may cause subcutaneous hematomas in legs, hemarthrosis in ankles or knees in patients with severe hemophilia. Cutting of the frenulum or upper lip (traumatic) is another common site of persistent hemorrhage in these patients [23]. For early diagnosis in patients with a family history, it is advisable to obtain umbilical cord blood and determine the FVIII/FIX level in the case of male neonates born to mothers who are carriers or who are likely to be carriers [18]. The diagnosis of mild hemophilia B can be difficult due to the normally decreased levels of FIX in

neonates that normalize around the sixth month [25]. Molecular diagnosis is the method for identifying the mutation responsible for hemophilia and is the recommended method for carrier detection. On the other hand, prenatal diagnosis is possible by genetic study of a chorionic villus biopsy between 9 and 11 weeks of gestation, or by amniocentesis (around 20 weeks of gestation) [2]. The mutation in the family must be known beforehand in order to perform the study. In some cases, it is also possible to perform the genetic study on embryos [20].

A detailed evaluation of the bleeding history of the patient and his family will be an important aid in guiding the correct diagnosis of hemophilia [10]. In patients with congenital coagulopathies, alterations in the tests that globally measure coagulation are evident. Confirmation of the type of hemophilia is obtained when an absence of significant decrease in the deficient factor is detected [9]. Many blood coagulation tests are performed if the person under study is the first in the family with a bleeding disorder. Once the defect has been identified, other family members will require less testing for diagnosis [31, 32, 33]. Tests included are partial thromboplastin time, prothrombin time, Factor VIII dosage, Factor IX dosage, complete blood count and platelet count [19]. Accurate and timely diagnosis is important and essential for the effective management of patients [22]. According to the guidelines, hemophilia should be suspected in patients with easy bruising in early childhood, spontaneous bleeding and excessive bleeding after trauma or surgery. It is well known that children, even with a severe form of hemophilia, may not have bleeding episodes until they begin to explore the world on their own. The results of studies showed that up to 1/3 of all cases of hemophilia are the result of a spontaneous mutation of the factor VIII and IX genes where there was no previous family history [17]. To corroborate the diagnosis, coagulation tests are required to identify how long it takes for the blood to clot and whether there is a decrease or absence of any clotting factor [34, 35, 36]. These tests should be followed by quantification of the affected clotting factor to determine the type and level of severity, serving as a basis for monitoring.

Accurate diagnosis is important and indispensable for effective treatment. Hemophilia should be suspected in patients with a history of a propensity to bruise during early childhood; spontaneous bleeding (particularly in joints and soft tissues); and excessive bleeding following trauma or surgery [24]. While the history of bleeding usually spans a lifetime, some children with severe hemophilia may not present with symptoms of bleeding until after the first year of age or later, particularly when they begin to walk [38, 39]. Patients with mild hemophilia may not have excessive bleeding unless they suffer trauma or surgery [25].

The diagnosis of hemophilia is made by taking a blood sample and measuring the degree of factor activity. Hemophilia may be suspected in patients with spontaneous bleeding or bleeding secondary to trauma.

3.4 Treatment

Treatment for persons with hemophilia is required to be oriented towards comprehensive care. Treatment of patients with hemophilia A or B requires the replacement of deficient clotting factors by intravenous infusion, either to control or prevent bleeding [24]. This replacement protocol is the "on-demand" treatment, since it is the most common method, when it is applied once bleeding has occurred, that is, the factor is applied in response to a hemorrhagic event [17]. Treatment can be administered periodically, without waiting for a bleeding event to occur, as a preventive measure; this is known as prophylaxis [37]. According to the evidence, this scheme is considered best practice in patients with severe levels of hemophilia [26]. Likewise, it is considered that the best way to treat hemophilia is to replace the missing clotting factor so that the blood can clot normally. The two main types of clotting factor concentrates are blood plasma-derived clotting factor concentrates and recombinant clotting factor concentrates. Within the clotting factor concentrates there are several made from human blood plasma proteins [18]. All blood and its derivatives, such as plasma, are routinely tested for the virus. The clotting proteins are separated from the other parts of the plasma, purified and made into a freeze-dried product. This product is tested and treated to remove any possible virus before being packaged for use [8].

In recombinant clotting factor concentrates, until 1992, all clotting factor replacement products were manufactured from human blood plasma. In 1992, the U.S. Food and Drug Administration (FDA) approved clotting factor VIII concentrate (8), which is not made from human plasma [2]. The concentrate is manufactured with genetic information using DNA technology. All commercially prepared clotting factor concentrates are treated to eliminate or inactivate blood-borne viruses. In addition, recombinant factors VIII (8) and IX (9) are available that do not contain plasma or albumin and therefore cannot transmit blood-borne viruses [13]. The products can be used on an as-needed basis, when a person has a bleed, or on a regular basis to prevent a bleed from occurring [10]. Today, people with hemophilia and their families can learn how to apply or administer clotting factor at home [20]. Receiving clotting factor at home means that bleeds can be treated more quickly, which means less severe bleeding and side effects. Other treatment options include desmopressin acetate, epsilon aminocaproic acid, among other medications [19]. The main treatment for severe hemophilia is to receive specific clotting factor replacement. This replacement therapy may be administered to treat an ongoing bleeding episode.

3.5 Dental Management

The degree of hemophilia the patient has should be considered. Mild hemophilia may not be diagnosed until adolescence if surgery, severe trauma, or dental extractions have been avoided. Therefore, in some cases, a dentist may be the first to diagnose a patient with hemophilia. It has been found that 30% of mild cases have been initially diagnosed after an episode of severe oral bleeding [3]. The dentist should have basic knowledge to treat patients with hemostasis disorders. The main task is to take a correct clinical history and from this data to be able to make an appropriate treatment plan together with the patient's treating physician [21]. Preventive and local measures should be assessed, together with the specific treatment for each hemostasis disorder [14]. It is of utmost importance to involve the patient in their treatment, explaining that with proper dental care and prophylactic measures, the dentist's intervention will be minimal, reducing the risk of possible bleeding complications [12]. There should be close communication between the dentist and the patient's healthcare team to provide comprehensive and quality dental care [13]. When performing any intervention in the mouth, it is essential to avoid accidental damage to the oral mucosa. Injury can be avoided by careful use of saliva collectors, careful removal of impressions, careful placement of x-ray film, particularly in the sublingual region, protection of soft tissues during reconstructive treatment by use of a gum

shield or application of soft yellow kerosene such as petroleum jelly [16].

It is important to note that patients may present with episodes of spontaneous bleeding during tooth brushing, food abrasion or with periodontal disease due to the number of enlarged capillaries near the surface of the thinner regions of the gingiva [15]. Successful dental treatment of patients with hemophilia is the result of cooperation between hematologists and dentists [27]. It may be required to increase the factor level to adequate coverage before and possibly after more intensive treatments such as scaling and root planning [7]. It should be remembered that in some cases, safe dental treatment can only be performed in hospital or community dental services [28, 29].

3.6 Local Anesthesia Considerations

Local anesthesia is an important procedure during dental treatment. Lower alveolar blocks require factor replacement, as there is a risk of bleeding into the surrounding muscles due to rich vasculature and blind injection, which could potentially compromise the airway due to hematoma formation in the retromolar or pterygoid spaces [22, 30]. It is suggested that oral surgery, periodontal surgery and any dental treatment requiring anesthesia with inferior alveolar nerve block and lingual infiltration anesthesia may be the only treatments that require hospitalization [21]. There are no restrictions regarding the choice of the type of local anesthetic agent used, although those with vasoconstrictors may provide additional local hemostasis [9]. Dental pain can usually be controlled with a minor analgesic such as paracetamol [20]. Acetylsalicylic acid should not be used because of its inhibitory effect on platelet aggregation. The use of any non-steroidal anti-inflammatory drugs (NSAIDs) should be discussed beforehand with the patient's hematologist because of the effect these drugs have on platelet aggregation [40]. There are no restrictions on the type of local anesthetic agent used, although vasoconstrictors may provide additional local hemostasis [3]. It is important to inform patients and parents of children about the risks of local oral trauma before the anesthetic wears off. Buccal infiltration can be used without the need for factor replacement [19], it will anesthetize the entire upper dentition as well as the anterior lower dentition and premolars. The use of Articaine as a local anesthetic is recommended, several studies have shown that alveolar-inferior block could be avoided, and buccal infiltration of the mandible can be used as an alternative to inferior alveolar blocks [13].

During the consultation, a detailed medical history should be taken, and comprehensive clinical examinations should be ordered appropriately. The patient should provide the following information: type and severity of his hemophilia, medications he is taking, and whether he requires pre-treatment with factor concentrate, or an antifibrinolytic agent.

4. Conclusions

Hemophilia is an X-linked recessive inherited disorder. It belongs to the group of inherited disorders caused by deficiency of one or more clotting factors. There are three types of hemophilia: A, B and C, which occur due to deficiency of factor VIII, IX and XI, respectively. Accurate and timely diagnosis is important and essential for the effective treatment of patients. According to the guidelines, hemophilia should be suspected in patients with easy bruising in early childhood, spontaneous bleeding, and excessive bleeding after trauma or surgery. Practice guidelines are needed to improve the diagnostic process and quality of care.

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