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A Case of Congenital Mild Hemophilia Diagnosed After Wisdom Teeth Extraction

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ABSTRACT

Hemophilia A is a recessive congenital deficiency of factor VIII that is characterized by normal bleeding time, normal prothrombin time, and prolonged activated partial thromboplastin time. In moderate and severe cases, abnormal bleeding is observed even after minor trauma, and the diagnosis is usually made by the age of 5–6 years, whereas in mild cases, abnormal bleeding is detected after major trauma or surgery. Herein, we present a case of hemophilia A that was discovered due to difficulties with hemostasis after tooth extraction.

Key words activated partial thromboplastin time; mild hemophilia A; persistent bleeding; tooth extraction

Hemophilia, an X-linked inherited congenital hemorrhagic disease caused by a deficiency of factor VIII (FVIII) or factor IX (FIX), has an incidence of 1 in 10,000 live births.[1] Hemophilia A, an X-linked recessive bleeding disorder caused by a deficiency of FVIII, is usually characterized by occasional spontaneous or prolonged bleeding, following minor trauma or abnormal coagulation test results. In general, most hemophiliacs are diagnosed preoperatively, and extractions are performed according to an individualized hemostatic management plan. In a previous report, two cases of mild hemophilia were reported that were discovered after tooth extraction[2] and gingival valve removal[3]; however, in these reports, preoperative activated partial thromboplastin time (APTT) testing was not performed. One of the patients with normal preoperative APTT results had uncontrollable bleeding after thyroidectomy,[4] which led to the diagnosis of mild hemophilia A. In this paper, we report a case of persistent bleeding after tooth extraction in which the bleeding could not be completely stopped by conventional treatment. The patient had no history of bleeding. Because of the ineffectiveness of various hemostatic measures, we suspected a coagulopathy and performed coagulation factor testing. Ultimately, he was diagnosed with mild hemophilia A. Mild hemophilia is relatively rare compared to moderate-to-severe hemophilia characterized by spontaneous bleeding. It is generally believed that the APTT test can detect this coagulopathy before surgery. However, we did not perform preoperative APTT testing because there was no history of bleeding. This case report aimed to increase oral surgeons' understanding of preoperative coagulation screening tests and to provide a rational evaluation and treatment procedure for bleeding patients with possible mild hemophilia after tooth extraction.

PATIENT REPORT

A 22-year-old male patient was aware of discomfort in his bilateral posterior molars and visited a local dentist a few days before his first visit to our department. He was referred to our department for the bilateral extraction of wisdom teeth in his mandible.

His medical and family history was unremarkable.

The general examination revealed that the patient was well nourished, and there was no evidence of a hemorrhagic disease such as purpura on the extremities or trunk.

An intraoral examination revealed wisdom teeth on the right and left sides of the maxilla and mandible. The maxillary wisdom teeth had erupted, while the mandibular ones were almost completely buried (although their crowns were partially visible).

Panoramic radiographs showed bilateral maxillary and mandibular horizontally erupted wisdom teeth.

The first treatment plan was to extract the right lower wisdom tooth under local anesthesia in an outpatient clinic. Infiltration anesthesia and transfer anesthesia with 3.6 mL of 2% xylocaine were administered to the gingiva of the right-side mandibular wisdom tooth, and the tooth was extracted. A longitudinal incision was made on the buccal side of the right lower seventh, a centrifugal incision was made from the center of the right lower seventh centrum, the mucoperiosteal valve was shifted, the alveolar bone was shaved, the crown and root were divided, and the tooth was extracted.

Oxidized cellulose was inserted into the extraction socket, and the extraction site was sutured as closely as

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Abbreviations: APTT, Activated partial thromboplastin time; FFP, Fresh-frozen plasma; FIX, Factor IX; FVIII, Factor VIII; PT, Prothrombin time

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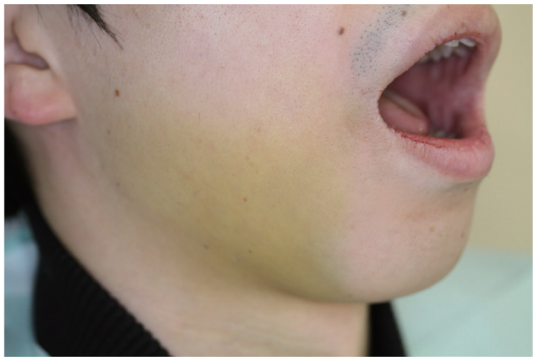

Fig. 1. Internal bleeding in the right cheek.

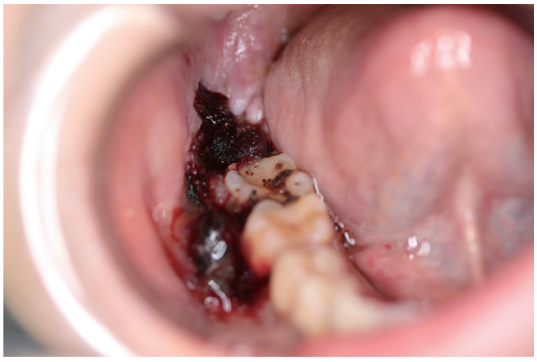

Fig. 2. Intraoral photograph. A weak blood clot is seen in the wound.

Table 1. The coagulation test results at different time points

	During the first visit to the Department of Hematology and Oncology		During re-examination		FVIII One hour after administration		
PT	13	H	12.8	H	12.7	H	Sec
PT-INR	1.1		1.1		1.09		
APTT	47.3	H	45.3	H	42.5	H	Sec
FIB	289		199.7	L	406.2	H	mg/dL
D dimer	0		0		0		μg/mL
FVIII	20	L	22	L	61		%
FXII	36	L	37	L			%
vWF	106		101				%
Anti-FVIII inhibitor							BU/

APTT, Activated partial thromboplastin time; FIB, Fibrinogen quantity; FVIII, factor VIII; FXII, factor XII; PT, Prothrombin time; PT-INR, Prothrombin time international normalized ratio; vWF, von Willebrand factor.

possible with 3-0 silk thread. The patient was placed under pressure with gauze for five minutes, and the procedure was terminated after confirming local hemostasis. The next day, there was no bleeding from the wound. However, five days after the surgical procedure, the patient came to our emergency department because of bleeding from the wound. Purpura was observed on the right side from the buccal area to the lower part of the jaw. The extraction socket, which was covered with a weak blood clot easily bled upon irritation (Figs. 1 and 2). The patient was anesthetized with 1.8 mL of 2% xylocaine, and pressure hemostasis was performed with gauze. After that, bleeding was observed again on the 7th postoperative, infiltration anesthesia was performed with 1.8 mL of 2% Xylocaine, and after the removal of the blood clots, oxidized cellulose was additionally inserted and sutured, and blood tests were performed to investigate the bleeding tendency. The patient's platelet count and bleeding time were within the standard values (Table1); however, a mild prolongation of PT and APTT was observed, and the patient was referred to the Department of Hematology and Oncology of our hospital. Since the PT and APTT were mildly prolonged, he was prescribed carbazochrome sodium sulfonate hydrate and tranexamic acid, to which he responded accordingly. The patient was again seen by a hematologist on postoperative days 9 and 13, and he was referred back to the hematology/oncology clinic. After close examination, including the possibility of abnormalities in coagulation factors, the levels of FVIII and factor XII (FXII) were found to be low (20% and 36%, respectively), and the level of FVIII was also low (22%) on repeat examination, with no evidence of an FVIII inhibitor. Based on the above, we diagnosed the patient with mild hemophilia A. A second anamnesis revealed no family history of hemophilia A. The posterior hemorrhage

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from the wound was caused by postoperative bleeding. Posterior bleeding from the wound was not observed after 17 days postoperatively and had stopped when the diagnosis was made. When a left-side mandibular horizontal impacted wisdom tooth was extracted, the patient was hospitalized and administered with a recombinant FVIII, rurioctocog alfa before extraction. One hour after the administration of rurioctocog alfa, the FVIII level increased to 61%. Carbazochrome sodium sulfonate hydrate and tranexamic acid were administered postoperatively, and a hemostatic bed sheet was placed. The stitches were removed on the seventh postoperative day, and the patient was informed there was a slight bleeding event on the night of the sixth day, which was stopped by gauze compression for about thirty minutes. Considering the possibility of further bleeding, the hematology/oncology department performed FVIII supplementation, and there was no posterior bleeding until epithelialization was confirmed.

DISCUSSION

Hemophilia A, an X-linked recessive bleeding disorder characterized FVIII deficiency, accounts for 80%–85% of all hemophilia cases.[1] Hemophilia usually occurs only in males who inherit the X chromosome of the affected mother, and female patients are rare. The estimated prevalence of hemophilia A at birth is 24.6 per 100,000 males for all severities of hemophilia A. The definitive diagnosis of hemophilia is made by performing tests such as coagulation factor analyses or genetic testing.[1] Hemophilia A is considered severe when coagulation factor activity is less than 1%, moderate when coagulation factor activity lies between 1% and 5%, and mild when coagulation factor activity lies between 5% and 40%.[5] Severe hemophilia A is diagnosed by the age of one year due to abnormal bleeding, while moderate hemophilia A is diagnosed by the age of 5–6 years due to subcutaneous or intramuscular bleeding at the time of bruising. However, mild cases are often detected due to trauma or difficult postoperative hemostasis, and they may not be diagnosed until a certain age. Von Willebrand factor, bleeding time, and PT are often normal, FVIII coagulation activity is low, and the APTT is prolonged. Clinically, APTT is generally considered to be an appropriate test to predict the risk of intraoperative bleeding.[6] However, the WFH guidelines state that the results of the APTT test alone cannot be used to exclude mild hemophilia A or B because the APTT may be within the normal range in some cases of mild hemophilia.[1] APTT results can be influenced by many factors, resulting in false-negative and false-positive results, which may lead to a false diagnosis.[7] In the present case, there was no history of hemostasis, no evidence of hemophilia in the family history, and only a mild prolongation of the APTT, which did not raise any active suspicion of hemophilia A. In this case, the level of FXII was also low. Factor XII is not considered to be involved in coagulation, since John Hageman, who was first identified as a patient with factor XII deficiency, did not show any bleeding tendency and died of pulmonary embolism.[8] In this, as well, the possibility of posterior hemorrhage due to FXII was considered low, and only FVIII was supplemented and the tooth was extracted.

Hemostasis management in hemophilia includes treatment with clotting factor replacement. There are three types of replacement therapy. Replacement of clotting factors when bleeding occurs, pre-replenishment therapy in which clotting factors are replenished before an event with a high probability of bleeding, and periodic replacement therapy in which coagulation factors are periodically replenished to maintain a constant level of clotting factors. Because the frequency of bleeding in patients with mild-to-moderate hemophilia is lower than that in patients with severe hemophilia, the periodic replacement of coagulation factors is used to attenuate severe disease to mild-to-moderate disease and to prevent the development of hemophilic arthropathy. The two types of replacement therapy are classified according to the timing of initiation: primary periodic replacement and secondary periodic replacement. Primary periodic replacement therapy is a method of preventing hemophilic arthropathy in patients with severe hemophilia by starting regular injections of coagulation factor products before the age of two years or after the first joint bleed and administering these injections over a prolonged period. Secondary periodic replacement does not meet the definition of primary periodic replacement therapy; however, it involves the initiation and prolonged administration of periodic injections of coagulation factor products.

In pediatric patients with severe hemophilia, the early initiation of periodic replacement therapy is recommended to decrease the frequency of bleeding and to prevent the development of hemophilic arthropathy.[8]

For tooth extractions, local hemostasis alone is considered sufficient for normal extractions in patients with mild hemophilia. In the case of moderate or severe hemophilia, hemostasis should be ensured with the use of a hemostatic splint and, in some cases, with the use of replacement therapy. In the case of the extraction of an impacted tooth, FVIII replacement should be performed immediately before extraction with a target peak factor level of 50%–80%. In the present case, since hemophilia was not diagnosed before the extraction procedure, no

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replacement therapy was performed for the extraction of a right-sided impacted wisdom tooth. Tranexamic acid was also administered for post-extraction bleeding; however, it did not provide adequate hemostasis.

Guo et al. described the causes of post-extraction bleeding as follows[9]:

1) Failure to follow postoperative instructions: Insufficient gauze compression or eating food that is too hot can cause blood to ooze out from the incision site. It is recommended to continue gauze compression until bleeding is eliminated.
2) Loose sutures: Slow bleeding is observed from the wound. The suture should be reinforced under local anesthesia until the bleeding stops, and the patient should be discharged after one hour of observation under gauze pressure.
3) Alveolar fracture: small fragments should be removed but large fragments with adequate blood supply should be repaired and fixed.
4) Bony hemorrhage: small fractures of the alveolar bone due to the use of excessive force during tooth extraction may cause rupture of the nutrient vessels in the alveolar bone. Aspirate to locate the bleeding site and curettage the local cancellous bone using an elevator or periosteal debridement to help stop the bleeding in that area.[10]
5) Infection: If the infection is extensive, granulation tissue may form in the extraction fossa, impairing coagulation and causing massive bleeding.[10] The management of postoperative infection involves thorough cleaning of the wound site, curettage of infected granulation tissue, and appropriate antibiotics.[11, 12] If an abscess is formed, it must be incised and drained.

In addition to the above considerations regarding bleeding, the WFH recommends that patients with hemophilia undergo tooth extraction and other intraoral invasive procedures such as periodontal surgery and dental implants only after consultation with a hematologist and with an individualized hemostatic management plan.[1]

In this case, a left lateral wisdom tooth was extracted at 61% FVIII with replacement therapy, and the patient did not have frequent posterior bleeding as in the contralateral case, and generally had a good outcome. It is difficult to predict abnormal blood coagulation when there is no abnormality in the patient's medical or family history as in the present case. When hemostasis is difficult to achieve after tooth extraction or other potentially hemorrhagic procedures, it is necessary to consider the possibility of abnormal blood coagulation factor levels as an option.

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