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CLINICAL reports

Medical/dental management of a patient with congenital Factor XIII

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Abstract

This clinical report presents the medical and dental management of a 7-year-old male with congenital deficiency of clotting Factor XIII who required the premature extraction of 2 primary molar teeth. Factor XIII catalyzes the cross linking of fibrin monomer into fibrin polymer inducing resistance to fibrinolysis. This clotting factor is unusual in having a long half-life (8.4 days) and requires low concentrations (0.5-2.0%) in order to control superficial bleeding. Epsilon aminocaproic acid (EACA), an antifibrinolytic agent was ineffective in the hematologic management of this patient since EACA inhibits the lysis of fibrin polymers and the genetic deficiency in this patient causes diminished fibrin substrate. The child's surgical management was successfully achieved with a single infusion of fresh frozen plasma.

The management of a patient with a bleeding diathesis is of concern for physicians and dentists alike. The purpose of this article is to report the successful management of a pedodontic patient who had congenital Factor XIII (FXIII) deficiency, a rare bleeding disorder previously unreported in the pedodontic literature.

Activated FXIII is responsible for the formation of a proper clot by the cross linking of fibrin monomers into polymers. This produces increased clot strength and resistance to fibrinolysis.[1] FXIII is composed of 2 subunits: subunit A has enzymatic activity; whereas, subunit B is the support unit. Congenital deficiency of FXIII activity is an uncommon disease, usually with an autosomal recessive pattern of inheritance and is caused by the lack of the enzymatic subunit A.[2-5] Heterozygotes with variable penetrance may be identified by measuring less than normal quantities of subunits A and B and are usually not bleeders.[6]

Homozygotes effectively lack any subunit A of FXIII and have reduced amounts of subunit B. Clinically, they may be characterized as having umbilical stump bleeding, a high incidence of spontaneous abortion, delayed wound bleeding, and frequently fatal intracranial hemorrhages.[1] The routine laboratory tests of prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), bleeding time (BT), platelet count, and platelet function tests are all within normal limits. Confirmation of the suggested clinical diagnosis may be obtained by the dissolution of a recalcified plasma clot with either 5 M urea or 1% monochloroacetic acid.[7]

Replacement therapy is simple since FXIII has a half-life of approximately 8.4 days[8] and only very small plasma concentrations (approximately 0.5-2.0% of normal) are required for normal clot cross linking which will prevent bleeding from minor injuries.[1,9] Fresh frozen plasma (FFP) infusions are efficacious for prophylaxis in patients with FXIII deficiency.[10,11] Adjunctive therapy with epsilon aminocaproic acid (EACA) to inhibit fibrinolysis also may be beneficial.[12]

Clinical Report

D.D., a 7-year, 5-month-old male, was referred to the Dental Department of The Children's Hospital of Boston for treatment of a "deep cavity" on his maxillary left second primary molar.

The past medical history was significant for a neonatal cephalohematoma and prolonged bleeding at circumcision. At age 3 he had a right inguinal herniorrhaphy which caused intractable oozing and delayed healing until a diagnosis of FXIII deficiency was made. At that time an infusion of FFP was effective in stopping the bleeding. There also was a history of

prolonged bleeding following a minor laceration of the tongue at age 5, an elbow and left knee hemarthrosis. Each hemorrhagic episode was resolved after FFP infusion.

The child's history was otherwise negative for bleeding from nasopharynx, oropharynx, urinary tract, or rectum nor was there reported hemoptysis or hematemesis. There was no history of cardiac, pulmonary, hepatic, splenic, or adrenal disease. The patient's laboratory values: CBC, PT, PTT, TT, BT, and platelet count had always been normal. Subsequent screening of all his living relatives (Fig 1) revealed that there were multiple familial heterozygotes for FXIII deficiency.

An initial oral examination revealed that a large mesiocclusal cavitation was present on the maxillary left second primary molar (tooth #J). The tooth was asymptomatic and had +3 mobility. The remainder of the examination was within normal limits, except for the presence of an ectopically erupting maxillary right first permanent molar (tooth #3). Panoramic (Fig 2) and periapical radiographs revealed prematurely

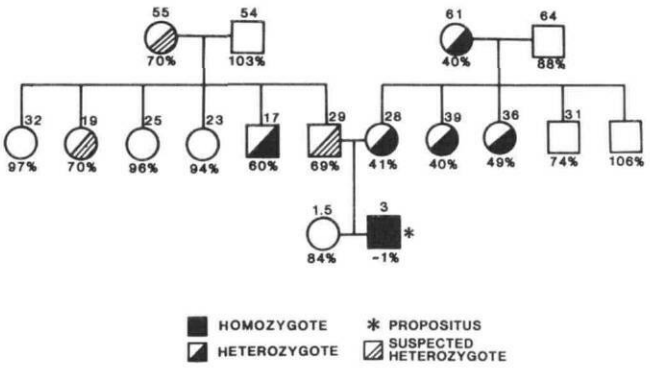

Fig 1. Family pedigree of D.D.; upper figures are individual's age and lower figures are the percentage of Factor XIII activity (courtesy of Jan McDonagh, MD).

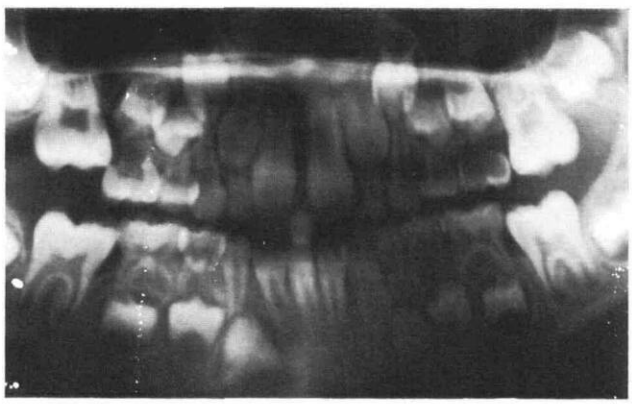

Fig 2. Panoramic radiograph showing premature resorption of maxillary right and left second primary molars.

resorbed roots of both maxillary right (tooth #A) and left (tooth #J) second primary molars and the ectopically erupting tooth #3. The etiology of the prematurely resorbed tooth #A was the ectopic eruption of tooth #3, and the resorption of tooth #J was probably a result of tooth #14 which erupted into normal position after spontaneous resolution of a mesioangular eruption path.

The goal of the treatment plan was to guide the eruption of the maxillary right first permanent molar and to regain the lost space. After tooth #3 was in the appropriate position, teeth #A and #J were extracted due to their excessive mobility and to prevent the development of periapical pathology. A brass wire was inserted between teeth #3 and #A utilizing 0.1 cc 2% xylocaine with epinephrine 1:100,000 as a local infiltrate. Placement of the brass wire was successful. However, some palatal gingival oozing was present after its placement. The oozing persisted for 4 days so the wire was removed. The patient was placed on EACA 1250 mg q6h in an attempt to control bleeding. The oozing persisted and 6 days later the patient was infused with 200 cc of fresh frozen plasma. At that time, under local anesthesia (3.6 cc 2% xylocaine with epinephrine 1:100,000) and nitrous oxide/oxygen sedation, teeth #A and #J were extracted. There was good hemostasis even without application of any packing material into the socket. The patient was given routine home care instructions and advised to continue his EACA regime for the following 9 days. The remainder of his postoperative course was uneventful. One week later the sockets had healed normally and alginate impressions were taken for diagnostic casts and for fabrication of a maxillary sagittal appliance to move tooth #3 distally (Fig 3). Rotation and 2 mm of posterior movement of #3 was completed and a fixed bilateral maxillary space maintainer was placed (Fig 4).

Discussion

The treatment of bleeding episodes in patients with coagulation deficiency requires the infusion of material containing the deficient clotting factors. For example, patients with classical hemophilia or Christmas disease, respectively, are infused with plasma fractions enriched in FVIII or FIX and subsequently supplemented with an antifibrolytic agent such as EACA. Treatment of patients with these common clotting deficiencies has been effective as documented in numerous reports.[13-17] The short half-life of these proteins may necessitate multiple infusions to maintain hemostasis. Patients with FXIII deficiency can be treated easily since 0.5-2% of the normal FXIII level corrects clot solubility and minor bleeding, and 30-50% of the normal FXIII level both increases clot tensile strength

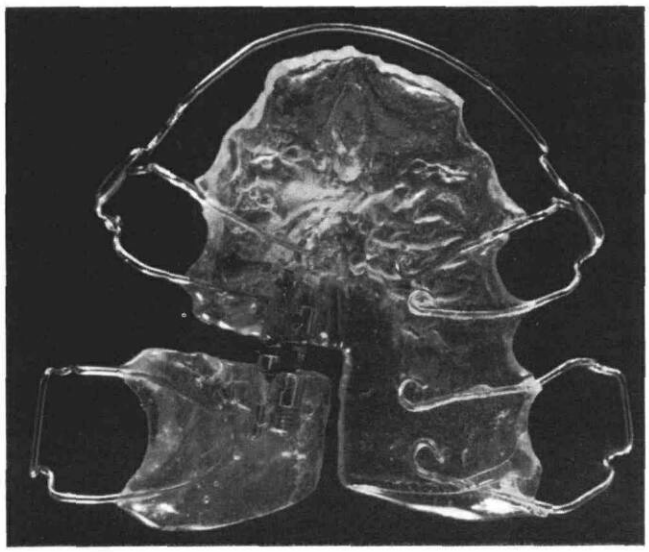

FIG 3. Removable sagittal appliance used to move distally the maxillary right first permanent molar.

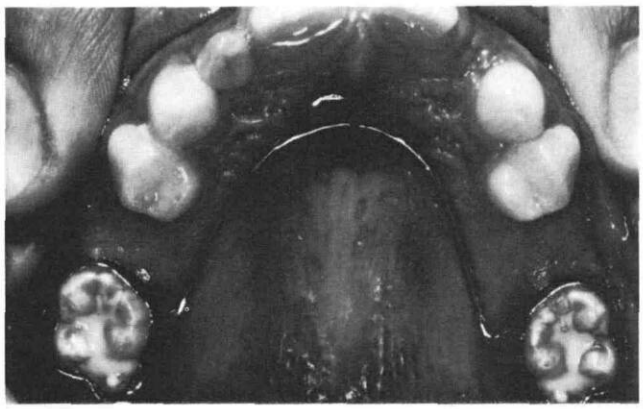

FIG 4. Fixed bilateral maxillary space maintainer in place.

and prevents major bleeding episodes.[8] Additionally, FXIII has a relatively long half-life (8.4 days) compared to other factors such as FVIII (12 hr);[18,19] therefore, only a single dose of a small amount of FFP needs to be infused prior to dental treatment that otherwise may have resulted in bleeding. A single infusion of FFP concentrate would provide protection to an FXIII patient needing dental extractions, both at the time of surgery and well into and beyond the postoperative healing phase. The authors' observations on this patient reinforce previous reports of the need for minimal amounts of FFP (approximately 200 cc) for adequate hemostasis for dental extraction in FXIII-deficient patients.[7-11]

Noncross-linked clots that are present in FXIII patients are characterized by decreased mechanical stability as well as increased susceptibility to lysis.[8] These properties may account for the fact that EACA alone has not been found effective in controlling bleeding in patients with FXIII deficiency. Nevertheless, the authors attempted to control bleeding in this FXIII-deficient patient with EACA alone since it is relatively safe. The most typical untoward effects are reported to be dizziness, diarrhea, nausea, vomiting, and abdominal pain. Theoretically, using EACA to inhibit the fibrinolytic factors responsible for the lability of the noncross-linked fibrin clot with antifibrinolytic agents seemed appropriate; however, it was unsuccessful.

The multiple signs and symptoms of FXIII deficiency may be potentiated by several basic cellular phenomena other than the defect of clotting.[1] FXIII or at least FXIII-like activity purportedly enhances cell-to-substrate adhesion. This is hypothesized to occur by cross linking of the adhesive glycoprotein fibronectin to connective tissue. Fibronectin cross linking theoretically would increase wound strength and wound healing.[8] If, in fact, FXIII-deficient tissue is more labile, this could account for the decreased wound strength and delayed healing independent of its fibrin cross-linking function.

Conclusion

Based on the authors' observations, EACA therapy alone was ineffective for the hematologic management of this FXIII-deficient patient, which confirms previous reports. EACA probably also was not needed after FXIII replacement because FXIII is unique in having a relatively long half-life (8.4 days) and requires a very low plasma concentration for clotting activity (approximately 1%). This is unlike other clotting factors, which have a short half-life FVIII—12 hr, require higher plasma concentrations, and hence may require multiple factor infusions or the addition of EACA to the regime. This fact stresses the need for a cross-linked fibrin clot substrate, the lysis of which EACA can prevent. FXIII-deficient patients have an intrinsic lack of fibrin cross linking; hence EACA could not prevent clot lysis because an adequate clot had not formed. In summary, patients with FXIII deficiency can be managed successfully for routine dental care and/or superficial surgical treatment with a small infusion of fresh frozen plasma.

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