Post-tonsillectomy hemorrhage due to factor XIII deficiency

Sameer Albahkaly, Arwa Alkhunaizi and Fawaz Makki

Department of Surgery, King Abdulaziz Medical City, King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia

Correspondence to Arwa Alkhunaizi, MD, ENT intern, Department of surgery, King Abdulaziz Medical City, King Fahad National Guard Hospital, P.O. Box 46863, Riyadh 11442, Kingdom of Saudi Arabia
Tel: +966 125 2008 x14119;
e-mail: arwa.alkhunaizi@hotmail.com

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Factor XIII deficiency is a very rare disorder, which represents a significant threat to life and can result in significant morbidity. Factor XIII is the final enzyme in the coagulation cascade and is essential for normal homeostasis. There is a very high rate of bleeding in patients who do not receive appropriate prophylaxis. We report a case of patient who presented with profuse secondary post-tonsillectomy hemorrhage few days after the operation.

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Introduction

Plasma factor XIII (FXIII) is a heterotetramer consisting of two A-subunits and two B-subunits (A2B2) held together by noncovalent forces [1], (Fig. 1). Although it was described as a fibrin stabilization factor, knowledge continues to evolve regarding this protein, and it is becoming evident that FXIII plays a role throughout the clotting process [4].

In 1960, Duckert *et al.* [5] published the first case report on FXIII deficiency describing a 7-year-old Swiss boy with a so far unknown bleeding disorder. Today, more than 60 mutations in the FXIII A-subunit and B-subunit genes are known that lead to congenital FXIII deficiency. Because of this low incidence and, in part, unawareness, and also because of the fact that FXIII deficiency is not diagnosed by the routinely applied tests of coagulation, the disorder is certainly under diagnosed [1].

Case report

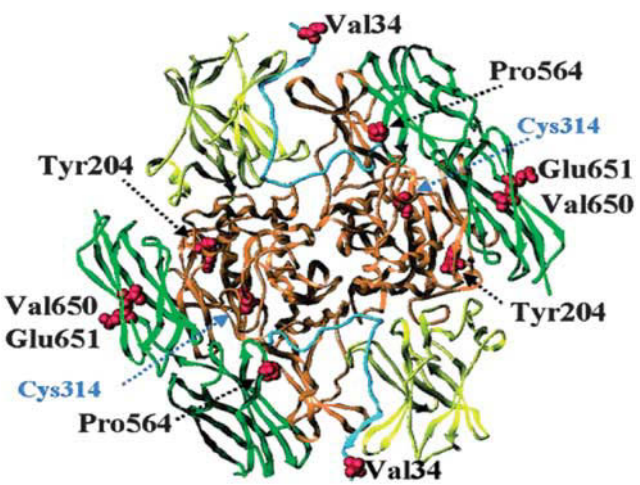
A 4-year-old girl admitted as an emergency case with severe post-tonsillectomy bleeding at day 7 was included in the study. The patient presented to the Emergency Room with profuse active bleeding. On examination, the child was pale, in a semiconscious state following a febrile, and tachycardic – heart rate 130–140. Throat examination showed profuse active bleeding. A blood sample was sent for analysis of complete blood count, prothrombin time, partial thromboplastin time; all values were within normal limits except for hemoglobin (Hgb), which was 90 g/l. The patient was taken immediately to the operating room and bleeding points were cauterized in the left tonsillar fossa. After surgery the patient was clinically and vitally stable. On the fifth day after the operation, the patient coded because of profuse mouth bleeding and her heart rate was low – in the 40 beats/min range. The patient was sent to the operating room after stabilization and the vocal cords and stomach were found to be covered in blood; however, no clear source of bleeding was traced. An antifibrinolytic agent was prescribed as the treatment of choice (fresh frozen plasma) if the she continue to bleed.

Carotid angiography was performed to locate any bleeding source, the results of which were negative.

On the same day a blood sample from the patient was analyzed for FXIII, factor XI, serum fibrinogen, and thrombin/reptilase time. All results were within normal limits except for FXIII, which was 0.37, and the normal limits are between 0.7 and 1.4 U.

The patient was administered with 10 ml/kg of fresh frozen plasma and was continued on the antifibrinolytic agent. Three days later the FXIII level was 86% and the patient had no more bleeding. The plan was to discharge the patient on treatment with antifibrinolytic agent for 4 more days. Parents were instructed to return to

Figure 1



Factor XIII A-subunit structure and locations of common coding polymorphisms. The structure shown is that of the recombinant factor A-subunit dimer, modeled using X-ray crystallography coordinates from Weiss *et al.* [3]. The catalytic core region is colored orange; the β sandwich, yellow; the 2β barrels, green; and the activation peptide, cyan. Highlighted are the active-site cysteine residue and five residues (Val34, Tyr204, Pro564, Val650, and Glu651) that show common variation in the general population [2].

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Emergency Department if the patient developed any source of bleeding. A follow-up appointment with the Hematology Clinic was fixed for 1 month later. Unfortunately, 2 days later, the patient presented to the emergency room with profuse throat bleeding.

On examination, the patient was pulseless, breathless, had O_2 saturation of 0%, fixed and dilated pupils, and had no cardiac rhythm. The patient was intubated, cardiac massage was started, and intravenous epinephrine was administered; however the patient did not respond. Resuscitation continued for 11 min after which a decision was made to discontinue resuscitation and the patient was pronounced dead.

Discussion

Adenotonsillectomy remains the most common surgical procedures in otorhinolaryngology. Post-tonsillectomy hemorrhage is the most common and significant complication following tonsillectomy, occurring in about 5% of all patients, most often within 24 h (primary hemorrhage), although it can occur at any time after this period (secondary hemorrhage) [6]. Primary bleeding is considered to be related to the surgical technique, with a decreasing incidence, and to be more dangerous because of the possible risk of aspiration, laryngospasm, and invisible swallowing of blood with a consequent collapse in blood circulation [7,8]. Secondary bleeding is not considered to be related to the surgical technique; it is usually due to fibrinolysis aggravated by infection [7]. Secondary bleeding occurs rarely and is predominantly observed within the first 10 postoperative days [6]. The incidence of secondary tonsillectomy hemorrhage increases with age, peaking at 30–34 years in both men and women, with no statistically significant difference between the two sexes [9].

It has been repeatedly stated that tonsillectomy and adenoidectomy can safely be performed on an outpatient basis after careful patient selection. Exceptions are accepted for risk factors such as age less than 3 years, sleep apnea, underlying diseases, distance from the hospital, and coagulation disorders; however exceptions for other risk factors are still a matter of debate [10]. Hemorrhage following tonsillectomy and adenoidectomy is rare and predominantly occurs early after surgery. Delayed hemorrhage has the potential to be life threatening [7]. Moreover, secondary hemorrhage usually peaks at day 6 and its occurrence after day 10 is an extremely rare finding [11].

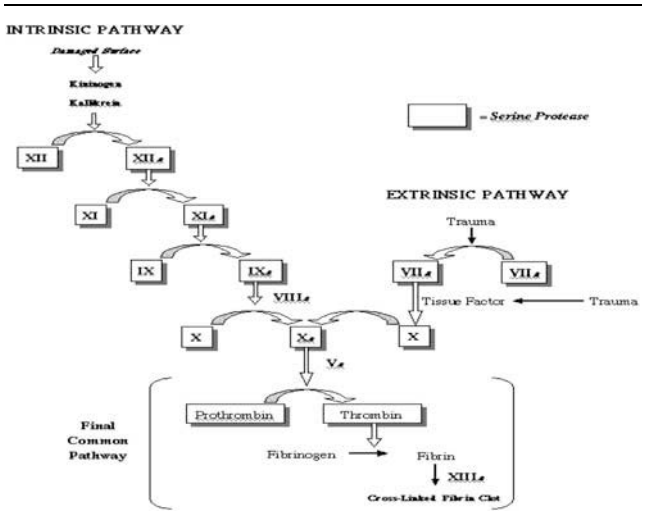
The hemostatic system, consisting of blood vessels and blood, plays a crucial role in human survival. The importance of the plasma coagulation system in protecting life and preventing further blood loss after transection of a blood vessel has been understood for a long time. Blood is normally maintained in a fluid state, without evidence of bleeding or clotting. The presence of bleeding diathesis in families with an X-linked pattern of inheritance of the disorder has been recognized for hundreds of years.

Factor XIII is an enzyme, a transglutaminase, that stabilizes fibrin clots in the presence of calcium [3]. Thus, FXIII alters the quality but not the amount or rate of clot formation, hence affecting the secondary phase, but not the primary phase, of homeostasis. The hallmark of FXIII deficiency is umbilical cord bleeding and delayed separation of the umbilical cord, which are often diagnosed in the neonatal period [12]. Other clinical features include delayed bleeding after trauma, cutaneous bruising and hematomas, intramuscular and joint hemorrhage, postoperative hemorrhage, impaired wound healing, spontaneous abortions during early pregnancy, and intracranial hemorrhage (the major cause of death). The manifestation of the disorder represents a significant threat to life and can result in significant morbidity. There is a very high rate of recurrence in patients who do not receive appropriate prophylaxis. Mucous membrane bleeding and surgical bleeding have also been observed, but are often delayed, probably because of poor clot stability [13].

The importance of FXIII in the process of coagulation is underscored by symptoms borne by patients who are homozygously deficient in FXIII or who produce antibodies that disrupt FXIII function. Paradoxically, alterations in FXIII may predispose patients to thrombosis. On the basis of all the available data, FXIII is clearly involved in the clot preservation side of the delicate balance between clot formation and stability and clot degradation. FXIII participates in other physiologic processes, including wound repair and healing. The many functions of FXIII and the disruptions of those functions by mutations in the genes coding for FXIII are the subjects of ongoing investigations [14–16] (Fig. 2).

Laboratory evaluation of FXIII deficiency is characterized by a normal coagulation screening test despite a definite history of bleeding. The most useful diagnostic test is the clot solubility test because the fibrin clot in FXIII deficient samples is soluble in 5 mol/l urea or weak organic acid [13].

Figure 2



Coagulation cascade.

Conclusion

Repeated episodes of bleeding are a warning sign of excessive hemorrhage and certainly needs further analysis and comments from the literature. Nevertheless, we strongly suggest overnight observation of patients with repeated episodes of bleeding after tonsillectomy. Moreover, because the diagnosis of FXIII deficiency may be missed by the usual screening coagulation tests that evaluate prothrombin time or activated partial thromboplastin time, the clot solubility test must be included as a routine screening test in the workup of patients with bleeding diathesis. Although death following tonsillectomy may be rare and acceptable from a statistical point of view, it will always be difficult to accept for individuals undergoing the procedure.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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