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When bleeding does not stop after capillary blood sampling for the newborn screening test

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Hemophilia A and hemophilia B are the most common and most serious congenital coagulation factor deficiencies. The two types are clinically virtually indistinguishable. Hemophilia occurs in approximately 1:5'000-10'000 males, with 85% having factor VIII (FVIII) deficiency and 10-15% having factor IX (FIX) deficiency (1).

Why do hemophiliacs bleed? The old cascade hypothesis of coagulation consisted of an extrinsic and intrinsic pathway. This model does not explain why the extrinsic pathway is unable to produce sufficient amounts of FX to at least partially compensate for a deficiency of FVIII or FIX. The cell-based model of hemostasis highlights the importance of the location of FXa production (Fig. 1-4, movie: size 13 MB). In hemophilia, activation of FX by the TF/FVIIa-complex is intact. FXa activation by TF/FVII-Complex occurs on the surface of tissue factor (TF) bearing cells and converts the coagulation pathway from the initiation phase to the amplification phase. But FXa produced on the surface of TF bearing cells is unable to move to the activated platelet surface because of efficient inhibitors (antithrombin, TFPI). In the propagation phase, the tenase complex has to be formed to activate FX on the surface of platelets leading to the generation of the prothrombinase complex and the thrombin burst. Formation of the tenase complex is impaired in both types of hemophilia. Hemophiliac patients demonstrate relatively normal initiation and amplification phases, and are able to form an initial platelet plug at the bleeding site, but they cannot generate the burst

of thrombin necessary to stabilize the initial plug into a fibrin clot. Therefore rebleeding occurs after physiologic lysis of the clot or minimal additional trauma (2, 3).

CASE REPORT

This was the first pregnancy of an 31-year-old mother and the first child of the family. Family history was unremarkable (however, there was no contact at all to the maternal grandfather), and parents were non-consanguineous. Routine serologic examinations had been normal. A male infant was delivered at 38 5/7 weeks of gestation by vacuum-assisted vaginal delivery after maternal exhaustion sub partu and non-reassuring CTG pattern following an otherwise unremarkable pregnancy. Primary adaptation of the infant was good and the first days of life were uneventful. The family planned to leave the hospital on day 4 of life following blood sampling for the newborn screening test. For this purpose the infant's heel was punctured using a Quikheel® Lancet. The newborn had received two doses of vitamin K on day 1 and day 4 of life (Konakion MM ® 2 mg/dose). About one hour after the procedure, the mother noticed that there was a relevant amount of blood around the clad left foot of her son. Repeated cooling and compression did not stop the bleeding. Blood was slowly trickling from the tiny cut on the lateral aspect of the left heel. Another capillary blood sample was obtained from the other foot to rule out vitamin K deficiency bleeding and thrombocytopenia (platelet count 291 G/l and prothrombin time 74%).

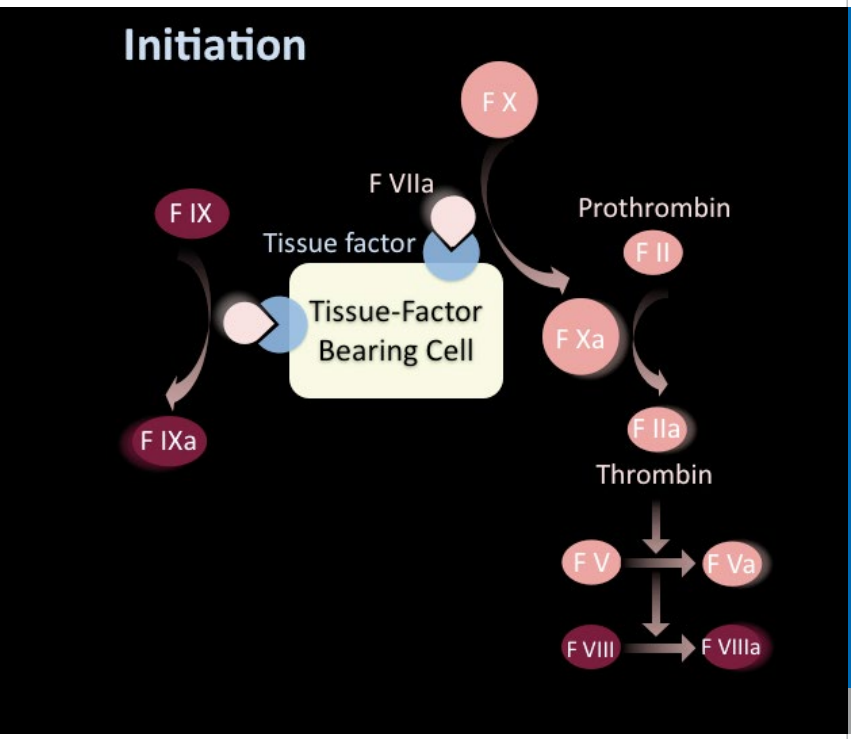

Fig. 1

Initiation phase: Tissue-factor (TF) bearing cells (i.e. fibroblasts, macrophages) activate FVII. The TF-FVIIa complex activates FIX and FX. FXa activates small amounts of prothrombin to thrombin.

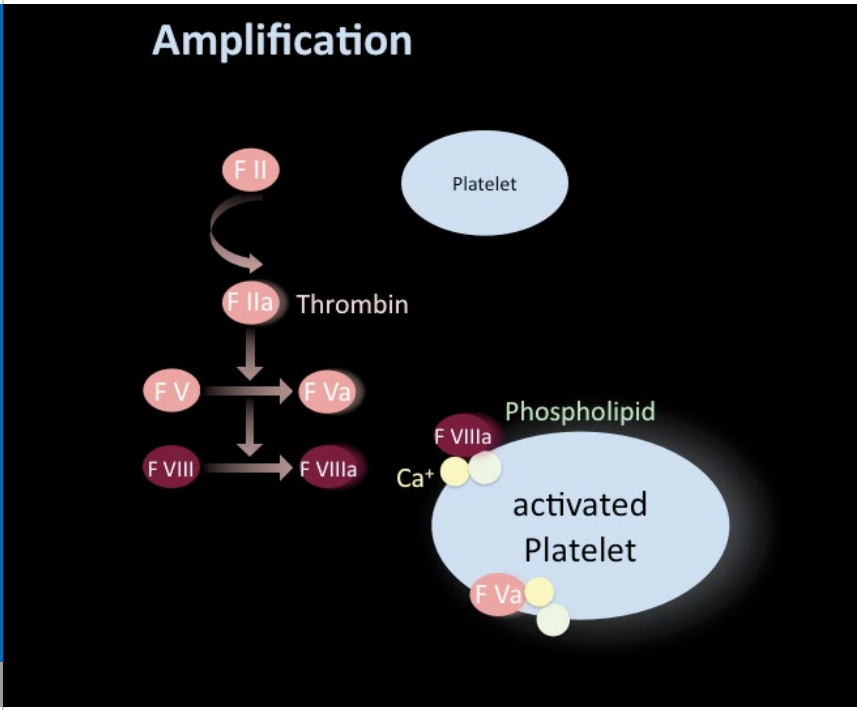

Fig. 2

Amplification phase: Platelets are activated by thrombin. FVIIIa and FVa bind to the activated platelet membrane.

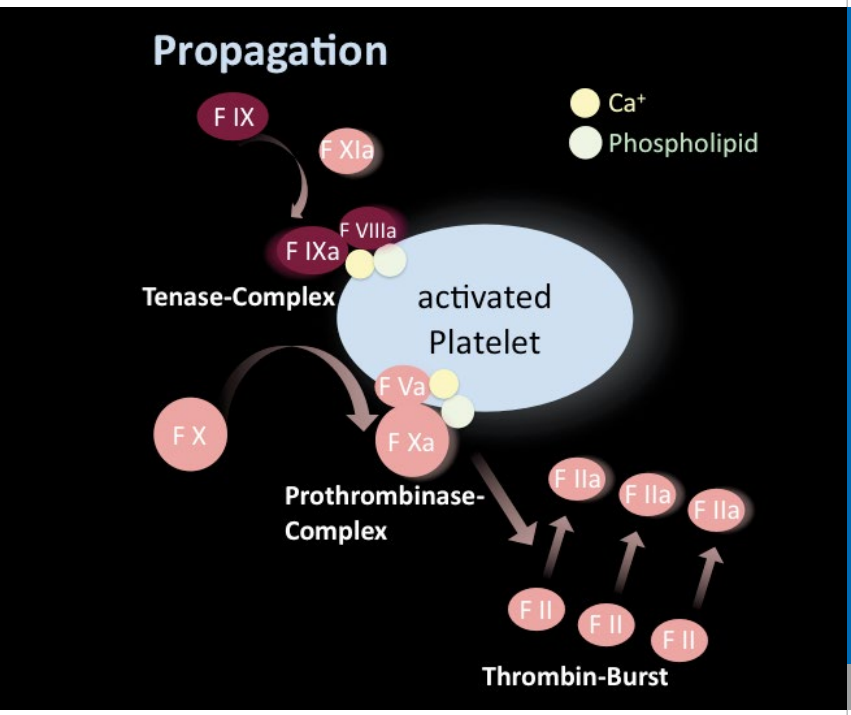

Fig. 3

Propagation phase: Activated FIX binds to the platelet membrane and together with FVIIIa forms the tenase complex. The latter activates FX that binds to FVa thus generating the prothrombinase complex. This complex is responsible for the thrombin burst. One molecule of FXa activates approximately 1000 molecules of thrombin.

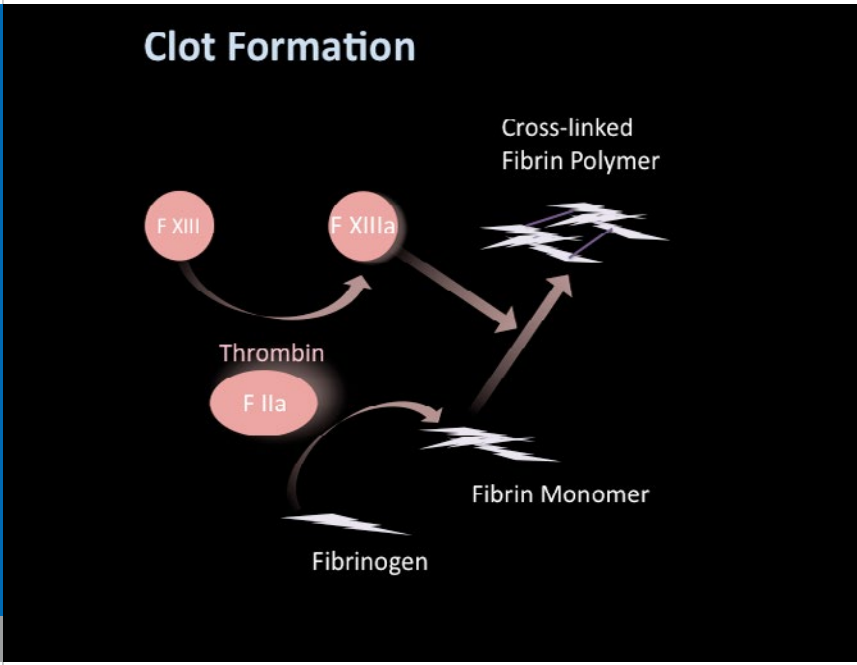

Fig. 4

Clot formation: Thrombin converts fibrinogen to fibrin. It also activates FXIII. This factor cross-links fibrin monomers.

The oozing from the left heel stick was stopped by the application of Dermabond®, a topical skin adhesive (2-octyl-cyanoacrylate). There was no bleeding from the right heel and after two hours of observation, the infant was discharged home. Unexpectedly, the parents returned to the hospital because of rebleeding from the right heel stick. There was no bleeding from the left „dermabonded" heel stick. The child appeared well, showed no bruising or hematomas. There was no cephalohematoma and a neurologic exam was unremarkable.

Comprehensive hemostasis studies revealed a prolonged aPTT of 105 s (normal 25-35 s), a PFA-Epinephrine of 230 s (normal 98-167s), a FVIII activity of 84% (normal 65-184%), a FIX activity < 1% (normal 70-129%) and vWF antigen Vidas of 90% (50-200%), establishing the diagnosis of severe hemophilia B. Fig. 5 depicts bruising of the left hand following venipuncture to obtain blood for the clotting tests.

DISCUSSION

The severity of hemophilia is classified on the basis of the individual patient's baseline level of FVIII or FIX. Severe hemophilia is characterized by less than 1% activity of the specific factor, and bleeding is often spontaneous and prolonged.

Hemophilia shows no apparent predilection and occurs in all ethnic groups. The genes for FVIII and FIX

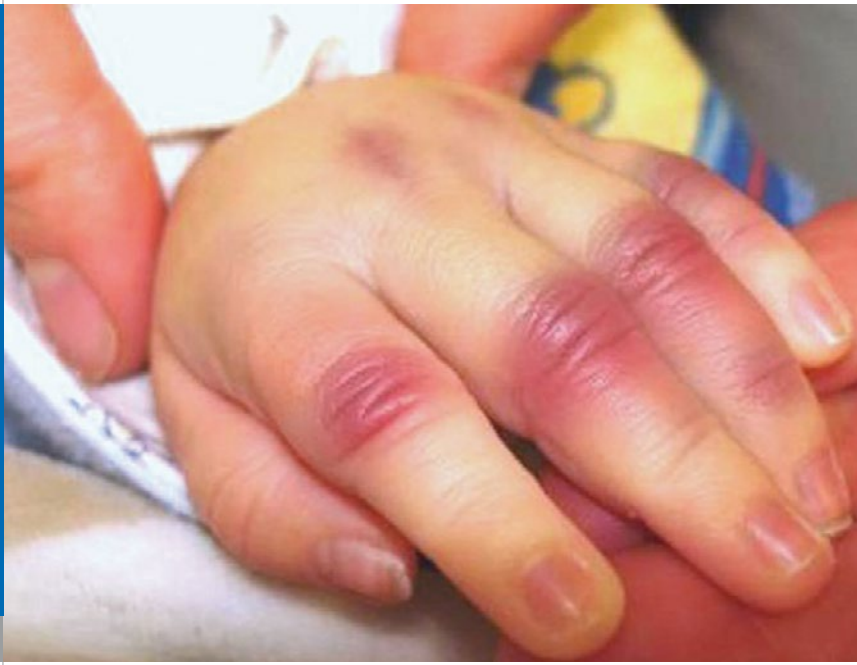

Fig. 4

Bruising of the left hand following venipuncture to obtain blood for the clotting tests.

are located near the terminus of the long arm of the X-chromosome. The mutation can be detected in the blood of patients (or female carriers) and in the amniotic fluid by molecular techniques. In the absence of a family history, diagnosis of hemophilia is usually made following a bleeding episode, 18-54% of which occur within the first month of life (4-5). Bleeding sites include cephalohematomas (particularly after vacuum extractions), venipuncture sites or muscle following intramuscular vaccination or drug administration. Excessive bleeding after circumcision, umbilical stump bleeding, intracranial hemorrhages and bleeds into the gastrointestinal tract or other major organs have also been reported (6-10). There is one case report of a massive intradermal hemorrhage in the immediate newborn period after difficult extraction at caesarean section (11). We have not come across of a report describing prolonged bleeding following blood sampling for the Guthrie newborn screening test.

Initiation of primary prophylaxis (regular administration of clotting factor concentrates) in young children remains challenging. The aim is to prevent bleeding, especially joint bleeds to achieve the best outcome (a perfect musculoskeletal status for age). The gold standard primary prophylaxis regimen (the Malmö protocol) was pioneered and tested in Sweden and involves the infusion of 20-40 IU of FVIII per kg body weight on alternate days (minimum three times per week) for haemophilia A cases, and 20-40 IU kg of FIX

twice weekly for haemophilia B cases. However, there are many variations of this protocol (e.g., dose escalation based on frequency of bleeding, starting before the age of 2 years, or starting before the third joint bleed, trials with discontinuing prophylaxis in adulthood).

The challenge is to optimize efficiency by individualizing prophylactic dose and frequency according to lifestyle and bleeding pattern. Inhibitors may develop in up to 30% of patients with severe haemophilia. Especially those with high titer inhibitors are at increased risk of developing target joints and severe arthropathy. The use of prophylactic treatment with bypassing agents (e.g., FEIBA: factor VIII inhibitor-bypassing activity, an activated prothrombin complex concentrate, and NovoSeven®, recombinant factor VIIa) in inhibitor patients is increasing. Early studies have described a significant reduction of bleeds, including intracranial bleeds, and an improved quality of life. The role of primary prophylaxis to prevent arthropathy in patients with inhibitors is not yet clear (12, 13).

The future of hemophilia treatment will involve the use of modified recombinant factors to achieve advantages such as decreased immunogenicity to avoid inhibitor formation and enhanced efficacy as a result of their longer half-life. Ultimately, gene therapy and cell therapy might succeed. Hemophilia is a very good candidate for the use of gene therapy protocols because

it is a monogenic disease, and even low gene expression would be able to modify a severe to a moderate phenotype (14).

ACKNOWLEDGEMENTS

We would like to thank the patient's parents for their consent to publish this case report including the depicted image.

See also: **COTM 11/2003**: Hemophilia A: presentation with neonatal circulatory collapse

REFERENCES

1. Chalmers EA: Haemophilia and the newborn. Blood Rev 2004;18:85-92

2. Hoffman M. Blood Reviews 2003;17:1-5

3. Hoffman M. J of Thrombosis and Thrombolysis 2003:16;17-20

4. Kulkarni R, Lusher J. Perinatal management of newborns with haemophilia. Br J Haematol 2001;112:264-274

5. Chalmers EA. Neonatal coagulation problems. Arch Dis Child Fetal Neonatal Ed 2004;89:F475-F478

6. Conway JH, Hilgartner MW. Initial presentations of pediatric hemophiliacs. Arch Pediatr Adolesc Med 1994;148:589-594

7. Pollman H, Richter H, Ringkamp H, et al. When are children diagnosed as having severe haemophilia and when do they start to bleed? A 10 year single centre PUP study. Eur J Pediatr 1999;158:S166-S170

8. Kulkarni R, Lusher J. Intracranial and extracranial hemorrhages in newborns with haemophilia A: a review of the literature. J Pediatr Hematol Oncol 1999;21:289-295

9. Barkat A, Kabiri M, Zaari Y, et al. Hemophilia in a newborn with an unusual clinical presentation; Arch Pediatr 2009; May 8 [Epub ahead of print]

10. Reish O, Nachum E, Naor N, et al. Hemophilia B in a neonate: unusual early spontaneous gastrointestinal bleeding. Am J Perinatol 1994;11:192-193

11. Hart AR, Wong CM, Gibson AT. Unusual presentation of neonatal haemophilia A. Arch Dis Child Fetal Neonatal Ed 2007;92:F324

12. Fischer K, Valentino L, Ljung R, et al. Prophylaxis for severe haemophilia: clinical challenges in the absence as well as in the presence of inhibitors. Hemophilia 2008;14:196-201

13. Blanchette VS, Manco-Johnson M, Santagostino E, et al. Optimizing factor prophylaxis for the haemophilia population: where do we stand? Haemophilia 2004;10:97-104

14. Liras A, Olmedillas S. Gene therapy for haemophilia...yes, but...with non-viral vectors? Hemophilia 2009;15:811-816