SEVERE FACTOR VII DEFICIENCY IN A NEWBORN

A Case Study

Wendy Lumm, MHS, MLS, MB, Mary Jonah, MT, SH, Gloria Sloan, MS, MT, and Natasha Savage, MD

Clinical Laboratory Science Program, Augusta University, Augusta, Georgia and Augusta University Medical Center

Abstract

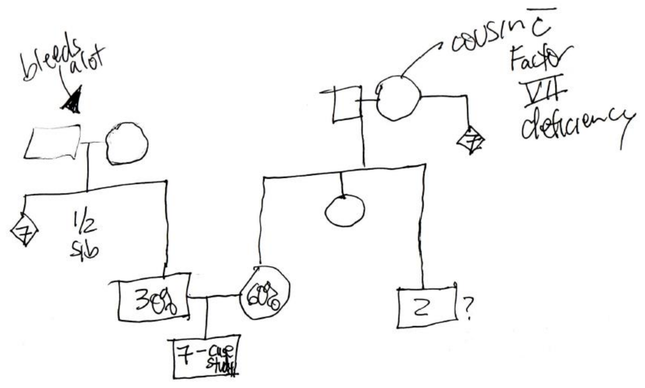
Factor VII deficiency is classified as a RBD, rare bleeding disorder. It is however the most common of all RBDs and is more prevalent than Hemophilia C. It is an autosomal recessive disease. Factor VII deficiency is unlike hemophilia or other bleeding disorders in that **genotype does not predict bleeding severity phenotype** in patients.

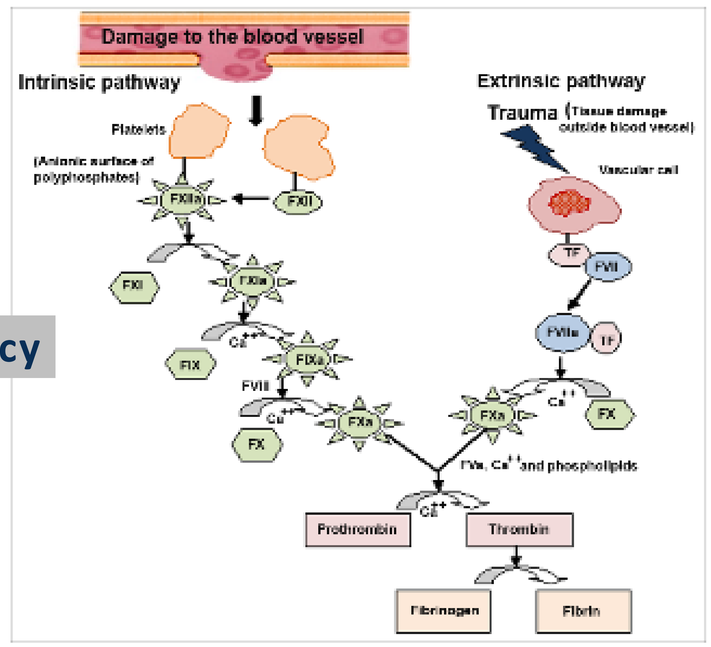
Severe bleeders with Factor VII deficiency are usually detected in the first 6 months of life. We report here a Factor VII deficient patient diagnosed at day 5 by the PT assay. His first symptom his first day of life was difficulty nursing and the physician ordered an IV of gentamicin in case of meningitis. The child's first blood work revealed only slightly low creatinine and BUN. A frenulotomy was performed to correct feeding issues. The next day the RN noticed blood on the pacifier and underneath the tongue; she applied pressure to stop the bleeding. She also noted swelling in the left groin and occipital area of the skull. The physician stopped the IV and ordered PT, aPTT and INR. PT was 53 seconds N (12-13 seconds). The newborn was transferred to AUMC on day 5. Lab tests revealed normal platelet function, a Factor VII level of 1% N (50-150%). Despite given NovoSeven@ RT regularly, at 3 months, the child was spitting up blood, at four months, his left arm was swollen; he was transfused with 65 mLs O negative blood. At 5 months, the infant was vomiting daily and underwent surgery because of intracranial bleeding. During surgery, the patient was transfused with 90 mLs of O negative blood and given 500 mcg/kg of NovoSeven@ RT. The patient was discharged 9 days later and receives NovoSeven@ injections twice a week. Gene therapy treatment maybe possible very soon.

Distinguishing Features of Factor VII Deficiency

- Most common RBD (rare bleeding disorder), 1 in 500,000 incidence
  Hemophilia C 1 in 1,000,000 incidence.
- A serine protease, circulates as a zymogen
- FVIIa circulates in plasma as 1% of total FVII, ready to start the coag cascade
- Normal plasma level is 0.5 mg/L
- Vitamin K dependent factor along with II, IX, X, PC, PS, PZ
- Factor VII is located on chromosome 13q34, 2.8 kb upstream from the FX gene
- Interacts with Tissue Factor, also known as thromboplastin, Factor III, or CD142 and Protein Kinase C
- Structurally similar to Factors IX, X, and Protein C.
- Component of intrinsic Xase and Ca++, and TF, extrinsic Xase=VIIa/TF complex
- Positive feedback loop when FVIIa activate itself, some autocatalytic activity.
- Expect gene therapy trials for F7 gene soon as F9 trials have been conducted in 2014
- Gene structures are similar:
  F7 has only 9 exons and is only 406 amino acids in length, 50 KDa in size
  F9 gene has only 8 exons and is 461 amino acids in length, 51778 Da in size.
- Recently, a gene therapy in dogs corrected a factor VII deficiency to 15% of normal levels. Published in Blood of February 2016 by researchers from CHOP and UNC Chapel Hill. The study used an adenoviral vector expressing the F7 gene.
- Expensive to treat due to short half life of the recombinant protein IM injections of Novoseven every 2-3 days
- Paradoxical ability of a factor deficiency to be associated with thrombotic tendencies.

RBD Autosomal Recessive





IN THE INTEREST OF SCIENCE AND MEDICINE IT SEEMS WISE TO DETERMINE THE GENOTYPE OF THE CHILD.

KNOWING WHERE THE MUTATION IS, CORRELATING THAT WITH THE CHILD'S CLINICAL HISTORY ALONG WITH WHAT MUTATIONS HAVE BEEN DOCUMENTED IN THE LITERATURE ON THE FACTOR VII GENE WILL SHED LIGHT ON THIS MOST COMMON OF RARE BLEEDING DISORDER'S PATHOGENESIS.

NovoSeven on an ACL TOP 500

- Once NovoSeven treatment was initiated, PT results for this patient on the ACL Top 500 were off the charts. Clotting was induced almost instantaneously. The read out on the ACL Top 500 was a graph of a straight line at about an 80 degree angle.
- The clotting process happened before the window period of recording for the instrument however. When NovoSeven levels are high then there is no result from the ACL Top 500.
- For bleeding episodes, the clinician has to take into account the half-life of the drug which is only **2 hours**
- **The half life of Factor VII in human plasma is the shortest of all Factors 5 hours**

Discussion

NovoSeven is the recommended factor replacement for severe Factor VII deficiency. It also is the treatment of choice in trauma situations where the patient is bleeding out. NovoSeven undoubtedly saved this child's life and is continuing to as the child is still alive.

One must realize however that this child would not be alive if it were not for the skilled and knowledgeable hands and minds of all the clinical staff. Kudos to the nursing staff, the first 5 days of this child's life; their detailed documentation provides clues to the nature of this child's bleeding tendency. The notation of the swelling in the groin region is also characteristic of hemophiliacs' hemarthroses signs and symptoms. The neurosurgeon who removed the excess blood in the child's brain and the necrotic tissue therein is absolutely astonishing.

What's most exciting is the future prospect of gene therapy with regards to Factor VII and IX replacement therapies. A Factor level of 15-20% is attainable today and that is probably enough to allow someone to live a normal life without overt bleeding crises.

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