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Short Report

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Factor VII Deficiency Presenting With Menometrorrhagia:

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A thirty-two years old female was admitted to the hospital because of anemia and menometrorrhagia. She had experienced intermittent palpitation and fatigue for many years which were relieved by blood transfusions and oral iron medication. She was quite well until she was 8 years old. Then she began to experience recurrent epistaxis attacks lasting for two years which caused her parents to seek medical attention. We learned that epistaxis attacks ceased spontaneously at the age of 10. She had no definite diagnosis regarding her complaints until admission to our hospital. Although her menstrual cycles were usually regular (every 25-28 days), she had enduring vaginal bleeding lasting for about 8-10 days. She additionally suffered from metrorrhagia which she experienced at every 2-3 cycles and lasting 3-4 days. In the last 10 years, menometrorrhagia continued with varying intervals and intensity causing severe anemia. Nine units of blood transfusion was needed during this period. She had been treated with oral iron medication for her anemia without any apparent success and neither an organic nor hormonal problem had ben detected. She had no history of gastrointestinal bleeding, hematuria, hemarthrosis or bleeding caused by tooth extraction.

Five months before admission, she had a pregnancy of eight weeks which was terminated by dilatation and curettage. Vaginal bleeding of 15 days duration followed this and stopped spontaneously. Her last menstruation had ended 3 days before admission and lasted 8 days. In the last 6 months, she took no medication containing iron.

Her skin and mucosae were pale at the time of admission. Her blood pressure was 100/60 mm Hg, pulse rate 116/min and respiratory rate 22/min. A painless right anterior cervical 0.3-0.4 cm mobile lymphadenopathy was palpated. Heart sounds were rhytmic and tachycardic and a slight systolic murmur over the left sternal border was heard. Her respiratory system was normal. There was no organomegaly, and examination of other systems revealed no pathologic findings.

Laboratory findings on admission were as follows: Hemoglobin 5.2 g/dl, white blood cell 5600/mm^3, hematocrit 17.8%, sedimentation 60 mm/h, platelet count 280.000/mm^3, BUN 18 mg/dl, creatinine 0.9 mg/dl, ALT 20 IU/L, AST 24 IU/L, fasting serum glucose 90 mg/dl, total bilirubin 0.8 mg/dl, direct bilirubin 0.4 mg/dl, total protein 7.2 g/dl, albumin 3.9 g/dl, bleeding time 4 minutes (normal value: 4-7 min) and clotting time 6 minutes (normal value :5-8 min), prothrombin times 26 seconds (normal value: 12-14 sec), and aPTT 38 second (normal value: 35-45 sec.). Blood smear examination showed microcytosis and hypochromia and hepatitis markers were all negative. Abdominopelvic ultrasonographic examination showed no abnormality. FSH, LH and prolactin mesurements were all in normal limits. Serum iron was 25 µg/dl (normal value: 50-140 µg/dl), iron binding capacity was 340 µg/dl (normal value: 150-300 µg/dl) and ferritin was 8 ng/ml (normal value: 15-200ng/ml). Vitamin B12 and folic acid levels were in the normal range. Factor VII activity was measured as 30% (normal: 60-100%). Factor VII activity was determined by performing a modified PT test using a plasma, deficient in a single extrinsic factor (IL Test™ , Factor

VII deficient plasma, Instrumentation Laboratory Co, Lexington, MA, USA). Chest x-ray was normal and an ECG showed sinus tachycardia.

Clinical follow-up: At the time of her admission to the hospital, there was not any active bleeding site. Gyncological examination revealed no organic pathology that might cause menometrorrhagia. Hormonal measurements were all in the normal range. Her anemia was consistent with iron deficiency. Prolonged PT and normal aPTT suggested Factor VII deficiency and this was confirmed by the laboratory test that showed a factor activity of 30%. As she had no active bleeding, we did not transfuse factor concentrates or fresh frozen plasma. Three units of erythrocyte suspension were transfused to correct severe anemia and oral iron therapy was started afterwards at an hemoglobin level of 8.9g/dl. In order to prevent recurrent menometrorrhagia, menstruation suppression therapy was adminestered. The patient had no brother or sister and her parents had died because of cardiac diseases. Therefore we could not screen them with regard to factor VII deficiency. The patient was informed about the nature and consequences of her disease.

Factor VII deficiency is a rare otosomal recessive disorder. Incidence is about 1 in 500.000 (1). It is also known as hypoproconvertinemia. As the first Factor VII deficiency case was reported by Alexander in 1951, the entity is also known as Alexander's disease (2). Factor VII has a distinct place among coagulation factors, as it is present in circulation in active form (3). Factor VII is composed of 406 aminoacids. Genetic material coding factor VII is located on the 13th chromosome. A qualitative defect or decreased production rate may elicit clinical factor VII deficiency (4,5). Factor VII is the initial protein involving the extrinsic pathway of the coagulation process. Tissue factor has an important role in accelerating the activation of factor VII. Tissue factor is a lipoprotein in nature, and is present in membranes of vascular endothelium, monocytes and fibroblasts (6,7). After celluler injury, tissue factor moves out of cells and binds to calcium which causes an increase in the activation rate of factdr VII (6,7,8).

Factor VII production by liver depends on vitamin K. A vitamin K dependent carboxylase catalyses a posttranslational modification and by doing so catalyses glutamic acid residues (9,10).

Factor VII deficiency may cause important bleeding episodes. The bleeding tendency is generally recognized during infancy or early childhood. Mucous membrane bleedings, epistaxis, intramuscular hematomas, hemarthosis and menometrrorhagia are the mostly encountered problems (11). After tooth extraction bleeding may be severe. Central nervous system bleeding is very rare.

Interestingly, factor VII level, duration, frequency and the intensity of the bleeding may not show correlation. While on the one hand, some patients with a factor activity of 30-40% may experience severe bleeding, on the other hand, some patients with a factor level of about 10% or less may not experience important bleeding and even, can tolerate major surgery well. The cause of this paradox is not clear. Generally, patients with factor VII levels below 5% have severe bleeding episodes that may be fatal if not treated vigorously. (12). Differential diagnosis include vitamin K deficiency, warfarin intoxication and diseases that destroy the synthesis ability of the liver.

There are some factor VII deficiency cases related to homocystnuria, Gilbert syndrome and Dubin Johnson syndrome (13,14). Our case presented with recurrent epistaxis during childhood but afterwards epistaxis did not recur. The most important clue for the diagnosis was the presence of menometrorrhagia that could not be attributed to organic reasons. A bleeding disorder was considered and bleeding parameters were investigated. The only abnormal finding was prolonged prothrombin time. Other diagnositc possibilities including warfarin intoxication, malabsorbtion and liver diseases were ruled out. A unique clotting factor abnormality that causes prolonged PT and normal aPTT is factor VII deficiency which motivated us to measure the factor VII level. Consistent with our presumptive diagnoiss, the level was lower than normal. Presenting this case, we aim to emphasize the importance of searching for coagulation abnormalities in patients presenting with long lasting bleeding disorders.

References

1. Cleton F.J. Two typical heredtary charts of congenital actor VII deficiency. Thromb Diath Haemorr; 5:87-90, 1980.
2. Alexander G, Goldstin R. Congenital SPCA deficiency, a new hitherto unrecognized defect with hemorrhage rectified by serum and serum fractions. J Clin Invest; 30.596-98, 1951.
3. Triplett D A, Brandt J, Batarol M A. Hereditary factor VII deficiency defined by combined functional and immunochemical analysis. Blood; 66: 1284, 1985.
4. Lawn R. The molecular genetics of hemophilia. Sci Am; 254:48, 1986.
5. Lutchman J L, Broze GJ. The current status of coagulation. Ann Med; 27: 47-52, 1995.
6. Weiss H J, Turitto V T. Evidence for the presence of tissue factor activity on subendothelium. Blood; 73: 968-75, 1989.
7. O'Brien D P, Kemboll-Cook G, Hutchinson A M, Martin D M, Johnson D J. Surface plasmon resonance studies of the interaction between factor VII and tissue factor. Demostration of defective tissue factor binding in a variant FVII