A Case Presenting Massive Umbilical Hemorrhage with Previously Unrecognized Factor XIII Subunit A Mutation (Factor XIII A1 gene; NM_000129.3 c.1817_1817delA (p.H606Pfs*23) (p.His606Profs*23, homozygous)

*Masif Umbilikal Kanama ile Başvuran Daha Önce Tanımlanmamış Faktör XIII Subünit A Mutasyonlu Bir Olgu (Factor XIII A1 gen; NM_000129.3 c.1817_1817delA (p.H606Pfs*23) (p.His606Profs*23, homozygous)*

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Abstract

Congenital factor XIII deficiency is an autosomal recessive inheritance bleeding disorder. Usually, the cause of this disease is deficiency of factor XIII subunit A protein in plasma. Some symptoms of the disease support that the clinical suspicions related to FXIII deficiency. For example; prolonged umbilical cord bleeding which is started in the newborn period. Diagnose of Factor XIII deficiency is difficult, on the other hand it has important therapeutic implications. When cryoprecipitate or plasma-derived factor XIII concentrate is used prophylactically, the prognosis of the disease will be good. We report here a case related to factor XIII deficiency with presented a massive umbilical cord bleeding as the first manifestation of factor XIII deficiency. The patient was managed successfully with cryoprecipitate, fresh frozen plasma transfusion and supportive treatments.

Keywords: Factor XIII deficiency, umbilical cord bleeding, children

Öz

Konjenital faktör XIII eksikliği kalıtsal bir kanama bozukluğudur ve otozomal resesif geçişlidir. Hastalığın nedeni genellikle plazmada faktör XIII subünit A proteinin eksikliğidir. Bazı belirtiler FXIII eksikliği ile ilgili klinik şüpheleri desteklemektedir. Örneğin; yenidoğan döneminde başlayan uzamış göbek kordonu kanaması. Faktör XIII eksikliğinin teşhisi zordur, ancak önemli terapötik etkileri vardır. Kriyopresipitat veya plazmadan türetilen FXIII konsantresi profilaktik olarak kullanıldığında hastalığın prognozu iyi seyretmektedir. Burada FXIII eksikliği olan bir olgu ile birlikte faktör XIII eksikliğinin ilk belirtisi olarak masif umbilikal kord kanaması sunulmaktadır. Hastamız kriyopresipitat, taze donmuş plazma transfüzyonu ve destek tedavisi ile başarılı bir şekilde tedavi edildi.

Anahtar Kelimeler: Faktör XIII eksikliği, göbek kordonu kanaması, çocuklar

INTRODUCTION

Congenital factor XIII deficiency is an autosomal recessive inheritance bleeding disorder. Factor XIII (FXIII) deficiency is a rare hematologic disorder and the incidence of disease is 1/2000000 every live birth. Hereditary factor XIII (FXIII) deficiency may occur with umbilical bleeding in the newborn period, delayed soft tissue healing, mucosal bleeding and severe intracranial haemorrhage. Factor XIII deficiency can cause wound healing problems and recurrent miscarriages. FXIII deficiency may be present with different clinical manifestations. The cause of the disease is usually the absence of the factor XIII-A subunit protein in plasma (1-5).

Some symptoms of the disease support that the clinical suspicions related to FXIII deficiency. For example; prolonged umbilical cord bleeding which is started in the newborn period, severe life-threatening episodes of intracranial hemorrhage. The difficulty of laboratory diagnostics is emphasized related to factor XIII deficiency. Performing quantitative FXIII assay strengthened the clinical suspicion. Diagnose of Factor XIII deficiency is difficult, on the other hand it has important therapeutic implications. The patients who have FXIII deficiency should be treated regularly with factor XIII concentrates. When cryoprecipitate or plasma-derived factor XIII concentrate is used prophylactically, the prognosis of the disease will be good ,although FXIII deficiency is always a risk of bleeding (2,4,5).

We report here a case what Factor XIII deficiency in a child that presented a massive umbilical cord bleeding as the first manifestation of the factor XIII deficiency. The patient was managed successfully with cryoprecipitate, fresh frozen plasma transfusion and supportive treatments.

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CASE REPORT

7-day-old neonate was admitted to our clinic for umbilical cord bleeding. Our patient was born from a primigravid woman (19 years old from Syria) during the 39th gestational week. Her parents were first-degree cousins (paternal aunt and uncle's child). Her father was diagnosed previously related to factor XIII deficiency and was receiving treatment for factor XIII deficiency. The newborn was previously healthy and she received 1 mg vitamin K (intramuscular) at birth. She was just taking breast milk. The blood tests showed that her hemoglobin was 14.9 g/dL, platelet count was 512x103/ µL. International Normalised Ratio (INR), fibrinogen, prothrombin time (PT) and partial thromboplastin time (PTT) were normal. The coagulation tests were repeated and the results were normal again. Pressed dressing was made to the patient's umbilical cord. Elaborate coagulation tests showed factor XIII-deficiency. There was a significant decrease in hemoglobin (9.2 g/dL) due to massive hemorrhage (Fig.1). The patient received a blood transfusion and a second dose of vitamin K (1 mg). Coagulation tests showed that the level of factor XIII is %3 (normal range: %80-150). She would going to receive prophylactic treatment monthly with fresh frozen plasma or cryoprecipitate. She was discharged after four days. Family studies and molecular analysis were performed. Patient diagnosis and treatment have prevented further haemorrhaging successfully. Her development has been normal to this day.

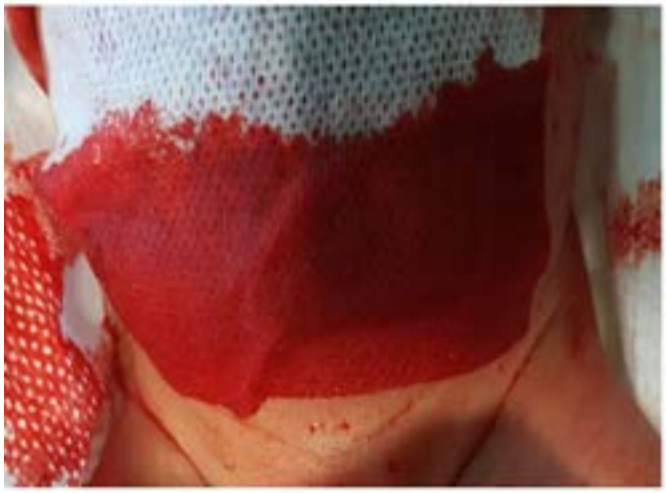

Figure 1. Our patients umblical cord bleeding.

DISCUSSION

Factor XIII deficiency first time defined by Duckert. It is inherited an autosomal recessive. Factor XIII creates covalent bond between fibrin molecules. Therefore, factor XIII is responsible for fibrin resistance. Factor XIII deficiency has three sub-types. Type 1 has deficiency of subunit A and B. Type 2 has deficiency of subunit A. Type 3 has deficiency of subunit B. Deficiency of subunit A is the form that seen the most frequently. Some drugs, such as isoniazid, phenytoin, penicillin, may also develop acquired factor XIII deficiency with IgG antibodies to factor XIII (6).

Factor XIII deficiency is a serious disease. It can not be understood by routine coagulation tests. The diagnosis of the disease based on clinicians doubts. Early diagnosis and treatment of the disease significantly prevent morbidity and mortality. This disease can be seen at any age and is detected mostly during the infant period. International normalised ratio (INR), prothrombin time (PT) and partial thromboplastin time (PTT) were usually normal. The umbilical cord bleeding is pathognomonic in the disease. It may be accompanied by findings such as ecchymosis, recurrent spontaneous abortions, postoperative bleeding (4).

Fresh frozen plasma and cryoprecipitate can be given for treatment of the disease. Cryoprecipitate (a form of fresh frozen plasma) concentrates contain cold insoluble proteins (fibrinogen, factor XIII, von Willebrand factor (VWF), factor VIII and fibronectin). In massive hemorrhages, cryoprecipitate is preferred in most parts of the world. Factor XIII can be found in most blood products, however it is found to be as 3 times more concentrated in fresh frozen plasma (7).

The amplification and sequencing of factor XIII A and factor XIII B is performed by molecular analysis. Subunite A is located on chromosome 6 and contains 14 introns with 15 exons. To date, 153 missense mutations have been identified in more than half of the cases. Subunit B is found on chromosome 1 and contains 11 introns with 12 exons. On less than 5% of cases, 16 mutations were detected (the majority are missense) (8).

Our case was also diagnosed because of the complaint of massive umbilical cord hemorrhage. A genetic examination of our case revealed a previously unrecognized factor XIII subunit A mutation (Factor XIII A1 gene; NM_000129.3 c.1817_1817delA (p.His606Profs*23, homozygous). The detected mutation has not been reported in association with the disease earlier. Mutation tester analyzes which are in the silico evaluation tools were evaluated to a new mutation as a cause of the disease due to frame shift and early stop codon formation. The mother and father of the patient were also genetically analyzed and showed that the father carries the same mutation as homozygous and the mother carries the same mutation as heterozygote.

The case emphasizes the importance of researching the family stories about bleeding disorders in the newborn period. If there is a newborn baby with persistent and massive umbilical cord hemorrhage, the newborn should be screened for factor XIII deficiency even if routine coagulation tests are normal.

There is no conflict of interest between the authors.

REFERENCES

1. Killick CJ, Barton CJ, Aslam S, Standen G. Prenatal diagnosis in Factor XIII-A deficiency. Arch Dis Child Fetal Neonatal Ed 1999;80: F238-9.
2. Von der Weid N, Furlan M, Siegenthaler I, Lämmle B. An infant with umbilical cord and intracranial hemorrhage--severe Factor XIII deficiency. Ther Umsch 1999; 56: 544-6.
3. Odame JE, Chan AK, Wu JK, Breakey VR. Factor XIII deficiency management: a review of the literature. Blood Coagul Fibrinolysis 2014; 25: 199-205.
4. Sawlani KK, Chaudhary SC, Roy A, Tripathi AK. Factor XIII deficiency presenting with intracerebral bleed. BMJ Case Rep 2013; 2013.
5. Hsieh L, Nugent D. Factor XIII deficiency. Haemophilia

2008; 14: 1190-200.

6. Öcek Ö, Bilgin RR, Bilgir O, Gedizlioğlu M. Recurrent spontaneous intracerebral haemorrhage due to Factor XIII deficiency. Turkish Journal of Cerebrovascular Diseases 2014; 20: 24-27.
7. Cushing MM, Fitzgerald MM, Harris RM, Asmis LM, Haas T. Influence of cryoprecipitate, Factor XIII, and fibrinogen concentrate on hyperfibrinolysis. Transfusion 2017; 57: 2502-2510.
8. Karimi M, Peyvandi F, Naderi M, Shapiro A. Factor XIII deficiency diagnosis: Challenges and tools. Int J Lab Hematol 2018; 40: 3-11.