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Case report

CONGENITAL AFIBRINOGENEMIA IN A NEWBORN

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Abstract: **Introduction:** Congenital afibrinogenemia is a rare coagulation disorder characterized by a deficiency in the fibrinogen molecule. Fibrinogen is a hexameric glycoprotein consisting of a polypeptide chain encoded by FGB, FGA, and FGG and is required for normal hemostasis. Changes in FGA, FGB, and FGG may affect fibrinogen at different levels. As a result of these changes, fibrinogen cannot be detected in the blood. Clinical manifestations of such changes range from asymptomatic to life-threatening bleeding or thromboembolic events. Since it is an autosomal recessive disease, the risk is higher in children whose parents are related. Therefore, the disease is more common in regions where consanguineous marriage rates are high. Diagnosis is made by laboratory tests that show the absence of fibrinogen. These patients need to be treated with fibrinogen replacement therapy.

Case presentation: This study reports the case of a newborn with congenital afibrinogenemia. The baby born from a first-degree consanguineous marriage was referred to our hospital due to bleeding and ecchymosis, and afibrinogenemia was diagnosed after coagulation tests were performed. Blood samples of the patient and his parents were sent to the Genetic Diseases Diagnosis Center for a genetic diagnosis of afibrinogenemia. A new homozygous mutation of FGB exon 7: c.1220c > t (p.t407 m) (p.thr407 met) was identified in the patient. The patients' parents were heterozygous for the same mutation. Prophylaxis was not recommended for our patient who was asymptomatic in the follow-up.

Conclusions: We present the case of a hemorrhagic neonatal patient diagnosed with congenital afibrinogenemia and emphasize that fibrinogen testing should be included in the evaluation of such patients. Furthermore, congenital fibrinogen disorders may be more severe when caused due to unknown specific mutation genes. Therefore, a more center-involved genetic analysis is required to identify undiagnosed fibrinogen and fibrinogen mutations.

Keywords: Congenital Afibrinogenemia, Fibrinogen Beta Chain, Newborn.

INTRODUCTION

Congenital afibrinogenemia is a rare hematological disorder in which fibrinogen (factor I) is absent, and the patient has a tendency to bleed. It is an autosomal recessive disorder in which most patients have a history of consanguineous marriage (1). The severity of bleeding varies among patients with afibrinogenemia. The most common symptom was umbilical cord bleeding. Hemarthrosis, hematoma, and mucosal bleeding are the other types of bleeding (2).

Congenital afibrinogenemia is an autosomal recessive disease described in 1920. More than 150 cases have been reported in the literature to date. The genes responsible for this disease are located on chromosome 4 (q26-q28) and are associated with different mutations (3). So far, more than 250 mutations have been reported in online databases. A total of 1215 mutations were reported in 2016, including 626 α, 154 β, and 435 γ (http://site.geht.org/base-fibrinogene/).

In the present study, a newborn with a new homozygous mutation of FGB c.1220c > t (p.t407 m) (p.thr407 met) has been presented.

CASE REPORT

The baby was born from a consanguineous marriage by normal spontaneous vaginal delivery at a gestational age of 39 weeks and 3 days and was referred to our hospital because of ecchymosis and bleeding at the blood draw sites. The baby appeared healthy and had normal vital signs. His body weight was 3650 g (75–90p), length was 52 cm (90p), and head circumference was 35 cm (90p). Bleeding and ecchymosis were observed in the form of vascular access and injection site leakage in the arms and legs. Other ex-

amination findings were normal. History revealed no specific disease in the mother, drug use history during and before pregnancy, and no family history of similar diseases. Initial laboratory findings revealed hemoglobin of 15.5 g/dl, white blood cell of 18 000/µl, and platelet count of 220 000/µl. Prothrombin time (PT) (out of range, upper limit,16 s), pt/international normalized ratio (INR) (out of range, upper limit, 1.3), activated partial thromboplastin time (PTT) (out of range, upper limit, 35 s), and thrombin time (outside range, upper limit, 21 s). Liver and kidney function test results were normal. No evidence of hemolysis, infection, or thrombocytopenia was observed in the peripheral blood smear. The values were normal in biochemical analyses. Abdominal and cranial ultrasound findings were normal. Fresh frozen plasma (FFP) was administered to the patient, and bleeding in the form of leakage decreased. The patient's fibrinogen level was < 20 mg/dl (245–400 mg/dl). The mother's fibrinogen level was 256 mg/dl, PT was 15 s, aPTT was 28.6 s, and INR was 1.15, whereas the father's fibrinogen level was 118mg/dl, PT was 15 s, aPTT was 28.4 s, and INR was 1.17. After a definitive diagnosis, fibrinogen concentrate was administered. The test results after fibrinogen concentrate administration were as follows: PT of 14s, INR of 1, and PTT of 26s.

Blood samples taken from our patient and his family were sent to the Genetic Diseases Diagnostic Center for genetic analysis. FGB exon 7: c.1220c > t (p.t407 m) (p.thr407 met) homozygous mutation was detected in our patient. To our knowledge, this mutation has not been identified before and the parents were found to be heterozygous for the mutation.

The child was recommended vaccination following the schedule with special precautions in the use of small-diameter needles and the application of adequate pressure after injections. Our patient was told to apply to us in cases of trauma or surgery and never to use drugs that increase bleeding tendency. Vaccination was carried out in accordance with the vaccination schedule in our country. Prophylaxis was not recommended for our patient who was asymptomatic in the follow-up.

DISCUSSION

Congenital afibrinogenemia is characterized by the absence or very low levels of fibrinogen in the plasma. Partial fibrinogen deficiency (hypofibrinogenemia) is a more benign disease than afibrinogenemia. While afibrinogenemia mostly occurs in homozygous conditions, hypofibrinogenemia occurs in heterozygous conditions (4). In the genetic examination of our patient, homozygous change in the fibrinogen beta chain (FGB) gene, c.1220c > t (p.t407 m) (p.thr407 met) was detected. The FGB gene in our patient's parents was c.1220c > t (p.t407m) (p.thr407met), and a heterozygous change was detected. The relationship between the detected change and the disease has not been previously reported.

Patients with afibrinogenemia have undetectable fibrinogen levels < 10 mg/dl(200–400 mg/dl). Without consumptive coagulopathy, unmeasured fibrinogen levels diagnose afibrinogenemia (5). Bleeding may occur in patients with a fibrinogen level of < 50 mg/dl (6). According to Lak et al. 45 (85%) out of the 55 patients with congenital afibrinogenemia presented with umbilical cord bleeding (2). The fibrinogen level of our patient was < 20 mg/dl, and fresh bleeding was noticed in the places where the vascular access was opened.

The primary treatment for fibrinogen disorders is human fibrinogen concentrate. In patients with fibrinogen disorders, the target fibrinogen level is 100 mg/dl for treating minor bleeding, while the target is 150 mg/dl in patients with major bleeding (6, 7). Five fibrinogen concentrates are commercially available. In the absence of fibrinogen-containing drugs, cryoprecipitate or FFP can be administered as an emergency alternative (8). Fibrinogen concentrate was used for treating our patient, and the bleeding stopped after its infusion.

Various measures have been proposed to prevent spontaneous bleeding in patients with congenital afibrinogenemia. Weekly infusion prophylaxis is a generally accepted regimen, but monthly or biweekly infusion prophylaxis has also been used (9). Prophylaxis is not recommended in patients without spontaneous bleeding due to the high risk of blood-borne diseases, allergic reactions, and thrombotic complications. Secondary fibrinogen prophylaxis should be started after the first life-threatening bleeding event in patients with afibrinogenemia, and the target fibrinogen level should be 50mg/dl during prophylaxis (5). We did not recommend prophylaxis because our patient did not experience spontaneous bleeding during the follow-up.

In summary, prenatal diagnosis or preimplantation genetic diagnosis can help prevent disease recurrence in pedigrees. In patients experiencing bleeding from any part of the body, afibrinogenemia should be considered in the preliminary diagnosis. This case highlights the importance of testing fibrinogen levels in newborns with bleeding. Congenital fibrinogen disorders have been reported worldwide but may be higher with unknown specific mutation genes. Therefore, genetic analysis involving more centers is required to identify undiagnosed fibrinogen and fibrinogen mutations.

Abbreviations

FFP — Fresh frozen plasma
FGB — Fibrinogen beta chain
INR — International normalized ratio
PT — Prothrombin time
PTT — Partial thromboplastin time

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Sažetak

KONGENITALNA AFIBRINOGENEMIJA KOD NOVOROĐENČETA

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Uvod: Kongenitalna afibrinogenemija je redak poremećaj koagulacije koji karakteriše nedostatak molekula fibrinogena. Fibrinogen je heksamerni glikoprotein koji se sastoji od polipeptidnog lanca kodiranog sa FGB, FGA i FGG i neophodan je za normalnu hemostazu. Promene u FGA, FGB i FGG mogu uticati na fibrinogen na različitim nivoima. Kao rezultat ovih promena, fibrinogen se ne može otkriti u krvi. Kliničke manifestacije takvih promena kreću se od asimptomatskih do životno opasnih krvarenja ili tromboembolijskih događaja. Pošto se radi o autozomno recesivnoj bolesti, rizik je veći kod dece čiji su roditelji u srodstvu. Zbog toga je bolest češća u regionima u kojima je visoka stopa brakova u srodstvu. Dijagnoza se postavlja laboratorijskim testovima koji pokazuju odsustvo fibrinogena. Ovi pacijenti moraju biti lečeni zamenom fibrinogena.

Prikaz slučaja: Ova studija prikazuje slučaj novorođenčeta sa urođenom afibrinogenemijom. Beba rođena iz prvostepenog krvnog braka upućena je u našu bolnicu zbog krvarenja i ekhimoze, a afibrinogenemija je dijagnostikovana nakon urađenih testova koagulacije. Uzorci krvi pacijenta i njegovih roditelja poslati su u Centar za dijagnostiku genetskih bolesti na genetsku dijagnozu afibrinogenemije. Kod pacijenta je identifikovana nova homozigotna mutacija FGB eksona 7: c.1220c > t (p.t407 m) (p.thr407 met). Roditelji pacijenta su bili heterozigoti iz iste mutacije. Profilaksa nije preporučena za našeg pacijenta koji je bio asimptomatski u periodu praćenja nakon što je dijagnostikovan poremećaj.

Zaključci: Predstavljamo slučaj hemoragičnog novorođenčeta sa dijagnozom kongenitalne afibrinogenemije i naglašavamo da ispitivanje fibrinogena treba da bude uključeno u evaluaciju takvih pacijenata. Štaviše, kongenitalni poremećaji fibrinogena mogu biti teži kada su uzrokovani nepoznatim specifičnim mutacijskim genima. Stoga je potrebna centralno orijentisana genetska analiza kako bi se identifikovali nedijagnostikovani fibrinogeni i mutacije fibrinogena.

Ključne reči: kongenitalna afibrinogenemija, beta lanac fibrinogena, novorođenče.

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