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Olgu / Case Report

Congenital Hypofibrinogenemia or Afibrinogenemia?; A Diagnostic Dilemma in Neonatal Period

Konjenital Hipofibrinojenemi veya Afibrinojenemi? Yenidoğan Döneminde Tanısal Bir İkilem

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Abstract

Congenital Afibrinogenemia/Hypofibrinogenemia (OMIM, 202400) (CA/CH) is one of the rare causes of hereditary hemostasis and is inherited in an autosomal-recessive. Spontaneous bleedings are not common unless the fibrinogen level is below 0.7-1 g/L. Congenital afibrinogenemia is characterized with prolonged Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR), Thrombin Time (TT), and very low or unmeasurable fibrinogen levels. Here, we presented a newborn who was initially diagnosed as CH according to fibrinogen level but we confused with genetic examination which revealed a homozygote deletion in the whole FGA gene compatible with CA. Fibrinogen level (<35 mg/dL) of the infant decreased during follow up and the diagnosis of CA became clear. We want to take attention of clinicians to that laboratory findings may not correlate with genotype leading to a diagnostic dilemma in neonatal period,and sometimes diagnostic puzzle completes during follow up.

Keywords: Newborn, Congenital afibrinogenemia/hypofibrinogenemia, Bleeding Diathesis

Özet

Konjenital Afibrinojenemi / Hipofibrinojenemi (OMIM, 202400) (CA / CH), kalıtsal hemostazın nadir nedenlerinden biridir ve otozomal resesif olarak kalıtılır. Fibrinojen seviyesi 0.7-1 g / L'nin altında olmadığı sürece spontan kanamalar yaygın değildir. Konjenital afibrinojenemi, uzamış Protrombin Süresi (PT), aktive Parsiyel Tromboplastin Süresi (aPTT), Uluslararası Normalize Oranı (INR), Trombin Süresi (TT) ve çok düşük veya ölçülemeyen fibrinojen seviyeleri ile karakterizedir. Burada fibrinojen düzeyine göre başlangıçta CH tanısı konmuş ancak genetik analizi CA ile uyumlu tüm FGA geninde homozigot delesyon saptanan bir yenidoğanı sunulmuştur. İzlemde bebeğin fibrinojen düzeyi azalmış ve hatta çok düşük seyretmiştir (<35 mg / dL) ve CA tanısı izlemde netleşmiştir. Laboratuvar bulguları yenidoğan döneminde klinisyenler için yanıltıcı olabilir, sonuçlar genotip ile uyumlu olmayabilir ve tanısal ikilem yaşanabilir. Bu olgu ile izlem sırasında tanısal bulmacanın çözümlenebildiğine dikkat çekmek istiyoruz.

Anahtar Kelimeler: Yenidoğan,Konjenital afibrinojenemi/hipofibrinojenemi,Kanama diatezi

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1. Introduction

Hereditary fibrinogen diseases are rare and have a spectrum of genetic fibrinogen disorders that develop consequence of the mutations in the components of the fibrinogen secretion caused by errors in transcription, mRNA processing, translation, polypeptide processing, and accumulation. They may be divided into two groups as Type I and Type II. In Type I, the quantitative features of the fibrinogen in the circulation are affected, and there is hypofibrinogenemia (<150 mg/dl) and afibrinogenemia that is characterized with complete deficiency of fibrinogen (<10 mg/dl) [1,2]. As congenital afibrinogenemia/hypofibrinogenemia (CA/CH) has an autosomal recessive transition, its frequency has increased in the communities where marriages among relatives are common [3].

The average plasma fibrinogen concentration is 150-350 mg/dL, and its half-life is approximately four days [1]. The fibrinogen molecule is a homodimer which is produced in the liver, and each of its half parts consists of three pieces of non-identical polypeptide chains (α-, β- and γ chains). Three genes encode these three chains in the fibrinogen molecule (FGA, FGB, and FGG), and all of them are in the long arm of the 4^{th} Chromosome (4q31.3-4q32.1) [1,4].

The clinical phenotype and genotype do not always show parallelism, and the bleeding patterns of two different patients who have the same genotype may show differences [5]. A total of 85% of the cases present with bleeding in the umbilicus in neonatal period. Muscle, joint, CNS, oral cavity bleedings and menorrhagia are reported later in life. Mucosal hemorrhage and hematomas are the most common bleeding findings [6].

The cases who have CH are usually asymptomatic and are diagnosed with routine laboratory tests. Bleeding might develop if there is a different bleeding disorder following or accompanying invasive intervention. The bleeding pattern is similar to that of the CA in symptomatic cases; however, it is milder [7,8,9]. We presented a newborn who has homozygote deletion in the whole FGA gene compatible with CA. The natural course of the congenital fibrinogen disorders and management strategies were reviewed.

2. Case Report

Three-days-old female newborn referred to our clinic for suspect of congenital hemostasis disorder. She was treated for jaundice and had poor feeding in the referring hospital when long-lasting bleeding from veni puncture sites was detected. Complete blood count was normal but the coagulation tests repeated for two times were too long to measure. She was born at 37^{+3} weeks to a G3A1P1 40 years old mother with C-section who had gestational diabetes mellitus and bipolar affective disorder and was under the therapy of multiple antipsychotic medications. 2^{nd}degree consanguinity was present between the 36-year- old father and they had a healthy nine years old daughter.

On admission, the infant appeared well, had normal vital signs and good perfusion. Body weight was 2465 g (25-50 percentile); height was 43 cm (<10percentile); head circumference was 32 cm (25-50percentile); her skin and sclera appeared jaundiced. There were bruises and bleeding in the form of leakage from the venipuncture and injection sites in the arms and legs. Her examination findings were otherwise unremarkable.

The initial laboratory findings were as follows; RBC 5x 10^{12}/L, Hb 19.1 g/L, Htc 56%, MCV 85 fL, WBC 18.3 x 10^{9}/L, Plt 228 x 10^{9}/L. On X100 amplification peripheral smear examination, erythrocytes were normocromicnormocytic and had 76% polymorphonuclearleukocytes, 24% lymphocytes, 15 normal sized clustered platelet are as each, CRP 1 mg/dl (normal range). PT and aPTT were immeasurable; the INR was prolonged to maximum, and fibrinogen was 106 mg/dl, d-dimer was 0.17 (normal). The biochemical analysis, all the values were normal other than the total bilirubin: 9.62 mg/dL; direct bilirubin: 0.19mg/dL; lactate dehydrogenase: 1314 U/L. The abdominal and cranial ultrasonography

were normal. The PT, aPTT, INR, and fibrinogen levels of the parents were found to be normal.

After the septic screening and take blood culture, we introduced empirical antibiotics (ampicillin and amikacin) for early neonatal sepsis; and started fresh frozen plasma infusion, and injected 1 mg intravenous vitamin K. Bleedings stopped after FFP administration, and control PT was 14 seconds; aPTT was 36 seconds; INR was 1.3, and the level of fibrinogen was 69 mg/dl. Blood culture was negative and no relation was found with the mother's drugs and low fibrinogen concentration in the literature. The replitase time and the TT could not be examined in our hospital.

Within three days after the interruption of the FFP support, the following results were obtained; PT: maximum; aPTT: maximum, INR: maximum, fibrinogen: 37 mg/dl. FFP support was continued until normal fibrinogen concentrate was obtained. In a few days bleeding repeated again and controlled with 100 mg/kg fibrinogen concentrate (Haemocomplettan P). One day after the administration of fibrinogen concentrate, PT, aPTT, INR was normal and fibrinogen level was measuredas 69 mg/dL. The genetic examination revealed Whole Gene Homozygote Deletion in the FGA gene (Figure-1). The genetic analysis was compatible with CA. Fibrinogen level of the baby during follow up decreased and our laboratory reported the fibrinojen level <35 mg/dL repeatedly. The diagnosis of CA became clear during follow-up.

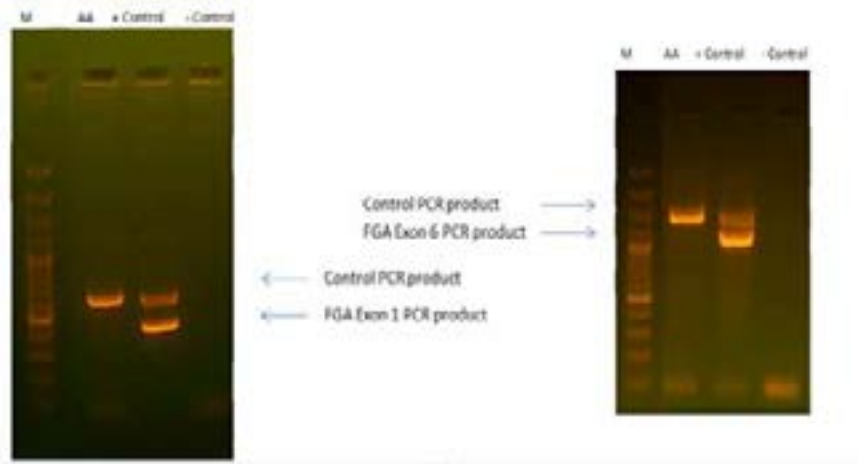

Figure-1: *Whole Gene Homozygous Deletion in FGA gene.*

3. Discussion

A complete history (including family history) and physical examination is necessary for the diagnosis of neonatal bleeding disorders. Bleeding disorder in relatives is a valuable data but a negative family history does not exclude a congenital condition. Bleeding sites does not precisely differentiate primary hemostasis defects from secondary hemostasis defects [orcoagulationtype-bleeding] especially in newborns. In our patient initial studies showed prolongation of PT, PTT, and INR with low fibrinogen level [6]. After exclusion of other conditions that may cause low fibrinogen level, healthy appearance of our patient with bleeding disorder leads us to consider the diagnosis of congenital factor deficiencies.

In our case, on admission, the PT, aPTT and INR were determined to be too long to be measured; and the fibrinogen level was determined to be low (106 mg/dl). According to the fibrinogen level, we thought that the diagnosis was compatible with CH. In the CH, the fibrinogen level is below 150 mg/dl; and

the coagulation tests are prolonged, and TT is the most sensitive test in diagnostic terms [1,4,14]. However, the clinical findings, the early initiation of the disease and the genetic analysis were similar to CA. The laboratory examination of CA is characterized by an unmeasurable low fibrinogen level of less than 10 mg/dl and significantly prolonged PT, aPTT, INR, TT and replitase time. Although we could not show the quantitative level clearly, the fibrinogen level of the infant reported repeatedly low [<35 mg/dL]. The diagnosis of CA became clear during follow-up. The differential diagnosis could be difficult in neonatal period, fibrinogen level decreases in the time. We experienced that diagnosis according to fibrinogen level can be misleading.

These cases usually refer to clinics with bleedings milder than the patients who have hemophilia [10]. In general, CH may appear in the form of prolonged bleeding from medical intervention or operation areas [11]. Akelma et al. [12] shared the results of 105 cases who had congenital factor deficiency, four cases (3.8%) were reported to be diagnosed with CH; one case was reported to have umbilical bleeding, one case had gastrointestinal bleeding and two other patients had prolonged PT and aPTT as the initial findings. All cases had consanguinity between their parents, and half of them had a family history. In this report, CA cases were below the age of one, there were bleedings from the injection sites, and it was also determined that CH cases were diagnosed later. In a multicenter study conducted by Fışkın et al. [13], fibrinogen deficiency (CA/CH) was determined in 15 (9.6%) of the 156 cases who had rare coagulation disorders. The average age of the cases during diagnosis was one month, and the most frequent complaint was intracranial hemorrhage that appeared following traumas or bleedings in the nose [13]. In our patient, the hemorrhage from the medical intervention areas in the form of leakage on the 5thday of life seems atypical for CH amongst the other reported cases. The clinical presentation and genotype were compatible with CA in neonatal period, during follow up fibrinogen level decreased and the diagnostic puzzle completed.

In nearly half of the autosomal recessively inherited CA/CH cases, consanguinity was reported among the parents [14]. Similarly, second degree consanguinity was determined in the parents of our patient. Until now, more than 200 different mutations were defined affecting the quantitative level of the fibrinogen in FGA, FGB and FGG genes [15]. However, new mutations are still reported. In two articles that were published in 2017, a new mutation in the FGB gene was defined in a case from China; and a total of 16 mutations were defined in 15 patients as 10 in the FGA gene; 3 in the FGB gene and 3 in the FGG gene were reported in a study from Pakistan 12 of which were new [16,17]. Defining these mutations, diagnosing and confirming the potential carriers, and characterizing them for a familial diagnosis are important. While the most common mutations resulting with the absence of fibrinogen appear in the gene that encodes the α chain (FGA), patients with CH have mutations in the gene that encodes the γ-chains (FGG) [1, 5, 18]. The genetic analysis of our patient revealed Whole Gene Homozygote Deletion in the FGA gene which was not previously identified in the literature. While the frequently expected mutation in CH is in the FGG gene, the mutation was detected in the FGA gene in our patient which is detected mostly in CA cases.

As a result, although not so frequent as CA or hemophilia, CH cases are among the very rare hemostasis disorders which may appear with abnormal bleedings in various parts of the body especially bleeding in the umbilicus in neonatal period. As for the laboratory works, the fibrinogen levels and TT must be examined to differentiate from hemophilia patients who have long PT and aPTT. In cases who have low fibrinogen levels, the reasons for secondary deficiencies must be excluded before the congenital deficiency is diagnosed; and fibrinogen concentrate must be preferred as the first choice in urgent bleeding control, and if this is not possible, bleeding control must be carried out with FFP or CP. The conventional treatment for fibrinogen deficiencies [in case of bleeding] is episodic treatment, and Fibrinogen Concentrate (FC) must be administered as soon as possible during bleeding. With the 100 mg/kg

fibrinogen concentrate replacement to our patient, the fibrinogen level was 69 mg/dl after 24 hours, and the bleeding was taken under control. Since the administration of FFP or FC will increase the risk of thrombosis when there are no active bleedings, the prophylactic administration is not recommended [18].Our case has become an index case for the family; if the mother becomes pregnant again, the antenatal diagnosis is possible by examining the genetic mutation.

- ✓ *Permission was obtained from the family to make a case report.*

REFERENCES

1. S.S.Acharya and D. M. Dımıchele. Rare inherited disorders of fibrinogen. *Haemophilia* 2008; 14, 1151–58.
2. Shannon L. Meeks MD. Transfusion Medicine and Hemostasis (Second Edition), 2013; 711-15.
3. Mannucci PM, Duga S, Peyvandi F. Recessively in herited coagulation disorders. *Blood* 2004; 104: 1243–52.
4. Casini A, de Moerloose P, Neerman-Arbez M. Clinical Features and Management of Congenital Fibrinogen Deficiencies. *Semin Thromb Hemost*. 2016;42: 366-74.
5. Asselta R, Duga S, Tenchini ML. The molecular basis of quantitati ve fibrinogen disorders. *J Thromb Haemost*. 2006; 4: 2115–29.
6. Turkish Hematology Association National diagnosis and treatment guide 2013,Part 1Fibrinogen (Factor 1) deficiency.
7. Suzanne Shusterman, Catherine S. Manno. Blood Banking and Transfusion Medicine (Second Edition), 2007, 467-82.
8. Acharya SS, Coughlin A, Dimichele DM. North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost* 2004; 2: 248–56.
9. Giovanni Luca Tiscia, Maurizio Margaglione. Human Fibrinogen: Molecular and Genetic Aspects of Congenital Disorders. *Int. J. Mol. Sci*. 2018 ; 19: 1597.
10. Lak M, Keihani M, Elahi F et al. Bleeding and thrombosis in 55 patients with in herited afibrinogenaemia. *British Journal of Haematology*. 1999;107:204-6.
11. de Moerloose P, Neerman-Arbez M. Congenital fibrinogen disorders. *Semin Thromb Hemost*. 2009, 35: 356-66.
12. Akelma Z, Işık P, Yararlı N et al. Kalıtsal Pıhtılaşma Faktör Eksiklikleri: Tek Merkez Deneyimi. *Turkish J Pediatr Dis* / 2016; 1: 1-6.
13. Fışgın T, Balkan C, Celkan T et al. Rare Coagulation Disorders: A Retrospective Analysis of 156 Patients in Turkey. *Turk J Hematol* 2012; 29: 48-54.
14. Pati S, Kombogiorgas D, Anwar A et al. Spontaneous extra-axial intracranial hemorrhage followed by thrombosis in congenital afibrinogenemia: perioperative management of this rare combination. Surg Neurol 2009 ;71:689-92.
15. Neerman-Arbez M, Casini A. Clinical Consequences and Molecular Bases of Low Fibrinogen Levels. *Int. J. Mol. Sci*. 2018, 19, 192.
16. Chiaki Taira, Kazuyuki Matsuda, Shinpei Arai et al. A Novel Mutation in the Fibrinogen B_ Chain (c.490G>A;d of Exon 3) Causes a Splicing Abnormality and Ultimately Leads to Congenital Hypofibrinogenemia. *Int. J. Mol. Sci.* 2017, 18, 2470.
17. Arshi Naz, Arijit Biswas, Tehmina Nafees Khan et al. Identification of novel mutations in congenital afibrinogenemia patients and molecular modeling of missensemutations in Pakistani population. *Thrombosis Journal* 2017; 15:24.
18. Miguel A Escobar, Harold R Roberts. Consultative Hemostasis and Thrombosis (Third Edition), 2013, 60-79.