



Case Report

Hemolytic Anemia Due To Anti-c Incompatibility in The Newborn Period: A Case Report

Ilkay Ozmeral Odabasi,¹ Sinan Uslu,¹ Evrim Kiray Bas,¹ Ali Bulbul,¹ Ebru Turkoglu Unal,¹
 Duygu Besnili Acar,¹ Ahmet Tellioglu,¹ Mehmet Fatih Ileri²

¹Department of Neonatology, Health Sciences University, Sariyer Hamidiye Etfal SUAM, Istanbul, Turkey

²Department of Pediatrics, Health Sciences University, Sariyer Hamidiye Etfal SUAM, Istanbul, Turkey

Abstract

Hemolytic disease of the fetus and newborn is a disease that is caused by maternal alloantibodies to the fetus. In the literature, the frequency of hemolytic disease of the newborn due to Rh (D) sensitization decreased inversely with the increase in the use of anti-D gammaglobulin. However, the importance of minor blood group incompatibilities has increased in the etiology. Clinical presentation in patients with minor blood group incompatibility may vary from subclinical hemolysis findings to active hemolysis and hyperbilirubinemia requiring blood exchange. In this case study, we present a patient with hemolytic anemia due to anti-c antibody incompatibility.

Keywords: Anti-c antibody incompatibility; anemia; newborn.

Please cite this article as "Ozmeral Odabasi I, Uslu S, Kiray Bas E, Bulbul A, Turkoglu Unal E, Besnili Acar D, et al. Hemolytic Anemia due to anti-c Incompatibility in the Newborn Period: A Case Report. Med Bull Sisli Etfal Hosp 2020;54(4):502-504".

Hemolytic disease of the fetus and newborn refers to the hemolysis of fetal or neonatal erythrocytes by maternal alloantibodies. Maternal alloantibodies against erythrocyte antigens other than Rh (D) may rarely cause clinically significant hemolysis in the fetal and neonatal period. The frequency of hemolytic disease of the newborn due to Rh (D) incompatibility decreased with the increase in the use of anti-D gammaglobulin. However, the importance of minor blood group incompatibilities in etiology has increased.^[1] In this article, a case with anti-c antibody incompatibility, which is a rare cause of anemia, is presented and neonatal hemolytic diseases due to subgroup incompatibilities are reviewed.

Case Report

The baby, who was born from the second pregnancy of a 23-year-old mother at 38 weeks of gestation through a normal vaginal route, with a weight of 2650 g and who did not develop postnatal adaptation problems, had normal vital signs in the physical examination performed immediately after birth, but the skin color was clearly pale. Complete blood count revealed hemoglobin: 6.6 g/dL, hematocrit: 24%, MCV: 109.1 fL, platelet count: 302.000/mm³ and white blood cell count: 26.000/mm³. The reticulocyte count was 11%. There were target cells, teardrop erythrocytes and anisocytosis in the peripheral blood smear. Mother and baby blood types were A Rh (+) and Direct Coombs test was (-).

Address for correspondence: Ilkay Ozmeral Odabasi, MD. Saglik Bilimleri Universitesi Neonatoloji Anabilim Dalı, Sariyer Hamidiye Etfal SUAM, Istanbul, Turkey

Phone: +90 506 336 30 26 **E-mail:** ilkayozmeral@gmail.com

Submitted Date: April 16, 2019 **Accepted Date:** July 09, 2019 **Available Online Date:** December 11, 2020

©Copyright 2019 by The Medical Bulletin of Sisli Etfal Hospital - Available online at www.sislietfaltip.org

OPEN ACCESS This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).



The baby was taken to the neonatal intensive care unit due to anemia.

Glucose-6-phosphate dehydrogenase, pyruvate kinase enzyme levels, thyroid hormones and hemoglobin electrophoresis were normal in the etiological examinations of the baby who had no signs of insufficiency. TORCH and Parvovirus serology was negative. Cranial and abdominal ultrasonographies were normal. Tandem mass spectrometry test was normal. When the mother and baby minor blood groups were evaluated, Kell (-) E (+) e (+) C (+) c (-) and Kell (-) E (+) e (+) C (+) c (+) were determined, respectively. With the current clinical and laboratory findings, the patient, who was thought to have the hemolytic disease due to c minor blood group incompatibility was transfused with a subgroup-compatible erythrocyte suspension on the postnatal first day. No decrease in hematocrit level was observed in the follow-up. The patient, who did not develop hyperbilirubinemia and the need for transfusion, was discharged on the postnatal fifth day for outpatient control. Hemolytic anemia did not develop in the outpatient clinic follow-up during the neonatal period.

Discussion

The Rh blood group system is one of the most complex human blood groups identified. At least 45 Rh antigens have been identified, and the most important ones are D, C, c, E and e antigens.^[2, 3] These antigens are encoded by the RHD and RHCE genes on the first chromosome.^[2] It has been reported that minor blood group incompatibility is responsible for 3-5% of haemolytic jaundice in the newborn.^[4] More than 70 red cell antigens may create antibodies. Among the minor blood group antigens, the most common causes of incompatibility between mother and baby are Kell, C, c, E, e, Diego, Duffy, Kidd and MNS.^[5] While multispecific antibodies are detected in 8-14% of the cases, the most common combination is an anti-c and anti-E combination.^[6] Anti-c alloimmunization, with or without anti-E, is present in 0.07% of all pregnancies, with few case reports with Rh antibodies other than anti-D (anti-c and anti-E) that cause hemolytic disease of the newborn.^[7, 8] In the study of Geifman-Holtzman et al. examining minor blood group incompatibility between mother and baby, anti-Kell incompatibility was reported as 22%, anti-D as 18.4%, anti-E as 14%, anti-c as 5.8% and anti-C as 4.7%.^[9] Anti-c antibody incompatibility was found in our case, which is a rare cause of anemia.

Anti-c antibodies may occur due to exposures, such as fetomaternal hemorrhage, abruptio placentae, spontaneous or therapeutic abortion, cesarean delivery, ectopic pregnancy or transfusion.^[10] They may cause acute or delayed hemolytic reactions. As with the D antigen, pregnant women are

sensitized to c-antigen during the first pregnancy and complications occur with re-exposure in subsequent pregnancies.^[11] Maternal IgM antibodies are formed in the first step in response to antigenic stimulation. However, since these antibodies cannot cross the placenta, they do not cause sensitization in the fetus. Ig G type antibodies formed by the continuation of antigenic stimulation transplacentally pass to the fetus and cause clinical symptoms in the newborn.^[1] Our case also suggested that the mother was sensitized in her first pregnancy.

Hemolytic disease due to minor blood group incompatibility may present a wide clinical presentation from hydrops fetalis and intrauterine losses during pregnancy to subclinical hemolysis, active hemolysis and hyperbilirubinaemia requiring exchange transfusion in the neonatal period.^[4, 5, 12] Anti-c antibodies are known to cause the heaviest hemolytic clinical picture.^[5, 13] In Dajak et al.'s study evaluating the relationship between maternal transfusion and fetal/neonatal hemolysis, 14 of 44 hemolysis cases except anti-D developed severe hemolysis, and eight of the cases with severe hemolysis were anti-c antibody positive.^[14] In Wenk et al.'s study evaluating 70 anti-c positive cases, eight of the cases ended with hydropic birth and perinatal death, 26% of the cases had a mild hemolytic disease that did not require transfusion after birth, and moderate hemolytic disease in need of transfusion was detected in 29%.^[15] Although our case presented with severe hemolytic anemia requiring transfusion, no hyperbilirubinaemia requiring phototherapy, intravenous immunoglobulin or blood exchange developed, which suggests that the severity of hemolysis and the time of the onset of the hemolytic process may be the cause of clinical variation.

The positivity rate of the direct Coombs test is not directly proportional to the severity of the disease. In a study conducted in the United States of America, the direct Coombs test was positive in 46 babies (84%) born from 55 anti-c alloimmunized pregnancies between 1967-2001, and only 12 (26%) of these babies developed severe hemolytic disease requiring exchange transfusion.^[10] Direct Coombs test positivity was reported in approximately one-third of cases with subgroup incompatibility. In cases with signs of hemolytic anemia, the direct Coombs test is not always positive, and a negative test does not indicate that incompatibility will not develop. The weak antigenic properties of minor red cell antigens may be the cause of this condition.^[1] Although our case was direct Coombs test negative, our case was in the group that developed clinical findings.

In conclusion, minor blood group incompatibilities should be kept in mind among the causes of hemolysis in cases with a negative direct Coombs test with hemolytic disease findings.

Disclosures

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – I.O.O., S.U.; Design – S.U., E.K.B., A.B.; Supervision – S.U., A.B.; Materials – A.T., M.F.I., E.T.U.; Data collection &/or processing – A.B., E.T.U., D.B.A.; Analysis and/or interpretation – M.F.I., A.T., D.B.A.; Literature search – E.T.U., D.B.A., M.F.I.; Writing – I.O.O., E.K.B.; Critical review – I.O.O., E.K.B.

References

1. Zipursky A, Bowman JM. Isoimmune hemolytic diseases. In: Nathan DG, Oski FA, editors. Hematology of Infancy and Childhood. 4th ed. Philadelphia: WB Saunders C; 1993. p. 44–73.
2. Avent ND, Reid ME. The Rh blood group system: a review. *Blood* 2000;95:375–87.
3. Westhoff CM. The Rh blood group system in review: a new face for the next decade. *Transfusion* 2004;44:1663–73.
4. Gökçe İK, Güzoğlu N, Öncel MY, Çalişici E, Canpolat FE, Dilmen U. A Hemolytic Disease due to Minor Blood Group (Anti-C and Anti-E) Incompatibility Leading to Symptomatic Anemia in the Neonatal Period. *Turk J Pediatr Dis* 2014;1:32–4.
5. Can E, Ozkaya H, Meral C, Suleymanoglu S, Aydinöz S, Karademir F, et al. Anti-C hemolytic disease of the newborn and prolonged jaundice: report of three cases. *Çocuk Sağlığı ve Hastalıkları Dergisi* 2009;52:88–90.
6. Farnault L, Garcia-Meric P, Cortey A, Arnaud F. Fetomaternal anti-RH3, -4 (anti-E and anti-c) rhesus isoimmunization: a case report. [Article in French]. *Arch Pediatr* 2011;18:176–82.
7. Babinszki A, Berkowitz RL. Haemolytic disease of the newborn caused by anti-c, anti-E and anti-Fya antibodies: report of five cases. *Prenat Diagn* 1999;19:533–6.
8. Moise KJ Jr. Non-anti-D antibodies in red-cell alloimmunization. *Eur J Obstet Gynecol Reprod Biol* 2000;92:75–81.
9. Geifman-Holtzman O, Wojtowycz M, Kosmas E, Artal R. Female alloimmunization with antibodies known to cause hemolytic disease. *Obstet Gynecol* 1997;89:272–5.
10. Hackney DN, Knudtson EJ, Rossi KQ, Krugh D, O'Shaughnessy RW. Management of pregnancies complicated by anti-c isoimmunization. *Obstet Gynecol* 2004;103:24–30.
11. George AA, Simon CD. Anti-c (Little c) IgM: An Uncommonly Observed but Expected Phenomenon. *Lab Med* 2014;45:e142–5.
12. Baş EK, Bülbül A, Uslu S, Arslan S, Çelik M, Nuhoğlu A. A rare condition: subgroup incompatibility due to anti-E. *Turk Pediatr Ars* 2013;48:80–1.
13. Liley HG. Immune hemolytic disease of the newborn. In: Nathan DG, Oski FA, editors. Hematology of infancy and childhood. 7th ed. Vol. 1. Philadelphia: WB Saunders; 2009. p. 89–92.
14. Dajak S, Culić S, Stefanović V, Lukačević J. Relationship between previous maternal transfusions and haemolytic disease of the foetus and newborn mediated by non-RhD antibodies. *Blood Transfus* 2013;11:528–32.
15. Wenk RE, Goldstein P, Felix JK. Alloimmunization by hr'(c), hemolytic disease of newborns, and perinatal management. *Obstet Gynecol* 1986;67:623–6.