Hemolytic disease of the newborn due to isoimmunization with anti-E antibodies: a case report*

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Minor blood group hemolytic disease is extremely rare, since the overall potency of minor blood groups in inducing antibodies is significantly lower when compared with that of Rh (D) antigen. We hereby report a very rare case of severe neonatal anti-E hemolytic disease due to E minor blood group incompatibility. A term newborn born to a 27-year-old, gravida 3, para 3 mother was referred due to a high and increasing serum bilirubin level despite phototherapy on the 4th day of life. On admission physical examination was normal except for the jaundice, and results of the laboratory investigation demonstrated a moderate-to-severe anemia (hemoglobin 7.8 g/dl) and a severe hemolytic hyperbilirubinemia (serum total and indirect bilirubin levels 36 mg/dl and 32.8 mg/dl, respectively; reticulocyte count 15%; and a positive direct antiglobulin test). As there was no apparent cause of the hemolytic disease such as Rh or ABO incompatibilities, further investigation (a positive indirect antiglobulin test and a positive irregular anti-E antibody in both the patient and mother, and minor blood group antigen profiles in family members compatible with E minor blood group isoimmunization) revealed the presence of anti-E hemolytic disease due to E minor blood group incompatibility. Two exchange transfusions with a 12-hour-interval were performed with minor blood group compatible fresh whole blood, and the patient was discharged in a healthy condition on the 10th postnatal day. If the most common causes of severe neonatal hemolytic disease such as Rh and ABO incompatibilities cannot be demonstrated in a newborn with significant hemolytic hyperbilirubinemia, anti-E hemolytic disease should strongly be considered in differential diagnosis. It should be kept in mind that a very severe from of minor group antibody hemolytic disease characterized by anemia and severe hyperbilirubinemia many exchange transfusions may be encountered during the course of the disease.

Key words: anti-E hemolytic disease, E minor blood group isoimmunization, hyperbilirubinemia, minor blood group incompatibility, newborn.

Hemolytic disease of the newborn due to minor blood group incompatibilities has been a greater problem since the decline of Rh (D) hemolytic disease with widespread use of prophylactic anti-D gamma globulin therapy. Of these minor blood groups, Kell, Duffy, Diego, Kidd, MNS, P, C, c and E in particular may cause neonatal hyperbilirubinemia[1]. Minor blood group hemolytic disease is extremely rare, as the overall potency of these minor groups in inducing antibodies is significantly lower when compared with that of Rh (D) antigen[1,2]. In this article a very rare case of severe neonatal hemolytic disease due to anti-E antibodies is presented and discussed.

Case Report

A 4,000 g male newborn was born at 40 weeks' gestation to a 27-year-old, gravida 3, para 3 mother by spontaneous vaginal delivery at a peripheral hospital. The baby was referred to our Division of Newborn Medicine due to increasing serum bilirubin level despite a

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phototherapy treatment of 50 hours at 72 hours of life.

In detailed family history the parents and first sibling were normal whereas the second sibling and undergone three exchange transfusions because of high (>35 mg/dl) serum bilirubin levels in the first 72 hours of life. Physical examination of the baby on admission at 90 hours of life was normal except for the jaundice. His weight was 3,830 g, and his length and circumference were 50 cm and 34.5 cm, respectively. Renal function tests, transaminases, and serum electrolyte and blood sugar levels were within normal limits. Serum total and direct bilirubin levels were 36 mg/dl and 3.2 mg/dl, respectively. Results of the complete blood count were hemoglobin 7.8 g/dl, hematocrit 23.6%, white blood cell $10.1\times10^3/\mu l$, and platelets $347\times10^3/\mu l$, and reticulocyte count was 15%. Further investigation to determine the exact etiology of the neonatal hemolytic disease revealed the following: blood groups of 0 Rh (+) and B Rh (+), respectively, in the patient and mother, a positive direct antiglobulin test in the patient, and a positive indirect antiglobulin test and a positive irregular antibody (anti-E) in both the patient and mother. To confirm the type of the hemolytic disease in the patient, minor blood group antigen profiles were studied in family members, and were as follows: CcEeCw(–) Kell(–) in the patient, CceeCw(–)Kell(–) in the mother, ccEECw(–)Kell(–) in the father, ccEeCw(–)Kell(–) in the first sibling, and ccEeCw(–)Kell(–) in the second sibling. Anti-E hemolytic disease due to E minor blood group incompatibility was diagnosed in view of the clinical and laboratory findings. Two exchange transfusions with a 12-hour-interval were performed with minor blood group compatible E(–) fresh whole blood. The case was discharged in a healthy condition on the 10th postnatal day.

Discussion

The most common causes of red blood cell hemolysis in the fetus and newborn are Rh (D) and ABO blood group incompatibilities. In cases of isoimmune hemolytic hyperbilirubinemia in which neither of these incompatibilities can be demonstrated in the etiology, the diagnosis of a minor blood group incompatibility should strongly be suspected[1,2]. We excluded other causes of both early neonatal hyperbilirubinemia and anemia such as infection, sepsis, and autoimmune diseases based on the clinical findings and results of laboratory investigations, and finally established the diagnosis of an isoimmune minor blood group incompatibility in our case.

The pathophysiology of fetal and neonatal isoimmunization in minor blood group incompatibilities is very similar to that in Rh (D) incompatibility and erythroblastosis fetalis. Initial maternal antibodies appearing in response to antigenic stimulation are primarily immunoglobulin-M (IgM) antibodies, and these are of no importance in the pathogenesis of hemolytic disease of the newborn since they cannot cross the placenta to enter the fetal circulation. Following repetitive antigenic stimulations as in subsequent antigen-positive pregnancies, however, the titer of immunoglobulin-G (IgG) antibodies increases, and these antibodies cause a positive indirect antiglobulin test in the mother can cross the placenta, thus leading to a hemolytic disease in varying degrees in the fetus and newborn[2,3]. The indirect antiglobulin test positivity in the mother of our case is due to the irregular antibody (anti-E) titration in maternal circulation. That the first sibling of the family with "E" minor blood group incompatibility has not had, but the second and third (present case) siblings have had a severe neonatal hemolytic disease is also in accordance with the pathophysiology of minor blood group isoimmunization.

The majority of minor blood group incompatibilities causing a significant hemolytic disease occur with anti-c, anti-E, or anti-Kell antibodies[4,7]. Minor blood group incompatibilities usually cause a neonatal hemolytic disease with slight-to-moderate severity[1,2,8], and of the minor group antibodies, anti-c causes virtually the most severe form of hemolytic disease of the newborn[1,4]. Even though our case did not have the classical findings of hydrops fetalis such as ascites, edema, and effusions, anemia and severe hemolytic hyperbilirubinemia requiring two exchange transfusions were in favor of the presence of a very severe form of a minor group antibody (anti-E) hemolytic disease. Severe

forms of fetal and neonatal anti-E hemolytic disease requring intrauterine transfusions are rare in the literature[8-11]. Transfusion of E antigen negative blood products in treatment of anti-E hemolytic disease would help in preventing further hemolysis that might be caused by transfusion of E (+) red blood cells.

If neither Rh (D) nor ABO incompatibilities can be demonstrated as the cause of anemia and hemolytic hyperbilirubinemia in a newborn, anti-E isoimmune hemolytic disease should strongly be considered in the differential diagnosis. It should be kept in mind that the pathophysiology of E minor blood group isoimmunization is very similar to that of Rh (D) incompatibility. A very severe form of minor group antibody hemolytic disease characterized by anemia and severe hyperbilirubinemia requiring many exchange transfusions may be encountered during the course of the disease.

REFERENCES

1. Gruslin-Giroux A, Moore TR. Erythroblastosis fetalis. In: Fanaroff AA, Martin RJ (eds). Neonatal-Perinatal Medicine, Diseases of the Fetus and Infand (3rd ed) Vol 1. St. Louis: Mosby; 1997: 300-311.
2. Zipursky A, Bowman JM. Isoimmune hemolytic diseases. In: Nathan DG, Oski FA (eds). Hematology of Infancy and Childhood (4th ed). Vol 1. Philadelphia: WB Saunders; 1993: 44-73.
3. Turner TL. Hematological problems of the newborn. In: Campbell AGM, McIntosh N (eds). Forfar and Arneill's Textbook of Pediatrics (5th ed). New York: Churchill Livingstone; 1998: 221-235.
4. Bowman JM, Resnick R. Hemolytic Disease (Erythroblastosis Fetalis) (3rd ed). Philadelphia: WB Saunders; 1994.
5. Kornstad L. New cases of irregular blood group antibodies other than anti-D in pregnancy. Acta Obstet Gynecol Scand 1983; 62: 431.
6. Polesky HF. Blood group antibodies in perinatal sera. Minn Med 1983; 22: 537.
7. van Dijk BA, Hirasing RA, Overbeeke MA. Hemolytic disease of the newborn and irregular blood group antibodies in the Netherlands: prevalence and morbidity. Ned Tijdschr Geneeskd 1999; 143: 1465-1469.
8. Moncharmont P, Juron-Dupraz F, Rigal D, Vignal M, Meyer F. Haemolytic disease of two newborns in a Rhesus anti-e alloimmunized woman. Review of literature. Haematologia (Budap) 1990; 23: 97-100.
9. 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: 533-536.
10. Liu YJ, Lee BF, Lin YZ, Chen W, Wu KW, Lin MC. Hemolytic disease of the newborn caused by maternal irregular antibody anti-E: report of one case. Chung Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih 1990; 31: 332-335.
11. Strohm PL, Iams JD, Kennedy MS. Hemolytic disease of the newborn from anti-E. A case report. J Reprod Med 1988; 33: 404-406.