Severe fetal and mild hemolytic disease of newborn: a paradoxical presentation of maternal anti-E antibody

Joshi Rajan, Kalane Shilpa, Kulkarni Aparna

Maternal antibody production is stimulated when fetal red cells are positive for an antigen absent onmother's red cells. Alloimmune hemolytic disease of fetus and newborn due to anti E is uncommon. We report a case of anti-E hemolytic disease in a neonate who had severe fetal and mild neonatal hemolytic manifestations. The neonate was treated with phototherapy. He also received intravenous immunoglobulin and single PCV transfusion.

Egypt J Haematol 2022 47:158–159

Egyptian Journal of Haematology 2022 47:158–159

Keywords: anti-E antibody, fetus, hemolytic disease, neonate

Department of Pediatrics, Division of Neonatology, Deenanath Mangeshkar Hospital, Pune, Maharashtra, India

Correspondence to Shilpa Kalane, DNB, Department of Pediatrics, Division of Neonatology, 3rd Floor, Superspeciality Building, Deenanath Mangeshkar Hospital, Pune 04, Maharashtra, Postal Code: 411004, India.
Tel: 02049153379;
e-mail: drshilpakalane@gmail.com

Received: 06 September 2015 **Revised:** 13 September 2015
Accepted: 21 March 2021 **Published:** 07 October 2022

Introduction

Maternal red cell alloimmunization occurs when the fetus is positive for an antigen that is absent on maternal red cells. The mother is stimulated to produce immunoglobulin G antibodies against the positive fetal red cells, which pass through the placenta and destroy the antigen-positive fetal red cells. Clinically significant alloantibodies other than anti-D, such as anti-E, anti-K, and anti-C, occur in 1 : 300 pregnancies, and the risk for hemolytic disease of the fetus and newborn caused by these antibodies is 1 : 500. We report here the case of anti-E hemolytic disease of the fetus and newborn.

Case

A 34-year-old woman, gravida 4, was under regular antenatal follow-up. She had undergone cesarean sections for earlier pregnancies without a history of blood transfusion. The first baby was a term live-born. Second and third fetuses experienced intrauterine death. Both babies had hydrops. However, she was not investigated. For the fourth pregnancy, she was referred to our hospital and was under regular follow-up. Sonography of the fetus revealed marked skin edema, cardiomegaly, hepatosplenomegaly, pleural effusion, ascites, placentomegaly, and polyhydramnios. Doppler peak systolic velocity (PSV) in the middle cerebral artery (MCA) was 0.8 m/s (>2.0 multiples of median), indicating severe fetal anemia. Studies on karyotype, thalassemia, parvovirus B19, cytomegalovirus, toxoplasmosis, and antinuclear antibodies were all normal. Fetal echocardiography was normal. Both parents had A and D+ blood type. Indirect Coombs' test (ICT) was negative. The baby received two intrauterine transfusions (O-negative blood) and was delivered at 36 weeks of gestation. Birth weight was 2.8 kg. At birth, he was active, pink, with mild hepatosplenomegaly. In view of significant history in previous siblings, history of fetal hydrops in this baby, and negative maternal ICT, he was investigated further: blood group was indeterminate; direct Coombs' test was positive; TORCH infection titers were negative; G6PD was negative; osmotic fragility was normal; and parvovirus PCR was negative. His hemoglobin and bilirubin trend is mentioned in Table 1. On day 3 of life, he developed hyperbilirubinemia, which was not responding to intensive phototherapy. In view of hyperbilirubinemia and positive direct Coombs' test (++), he was investigated for minor blood group incompatibility and was given intravenous immunoglobulin 1 g/kg. Initially, the three-cell antibody panel test was performed. It was negative. Thereafter, the 10-cell antibody panel test was performed, which showed a positive test against anti-E. The mother was screened for the presence of antibody. Her anti-E titers were positive. The baby is 6 months old now, under regular follow-up, and did not require a repeat transfusion. Written consent has been taken from the patient.

Discussion

Antibodies with anti-E specificity are detected in 14–20% of pregnant women and it is one of the most common non-D Rhesus antibody in the pathogenesis of neonatal hemolytic disease [1,2]. However, anti-E is rarely associated with severe hemolytic anemia in the fetus [3,4]. Anti-E alloimmunization can cause fetal anemia, and the incidence could be underestimated [5]. This condition is caused by the father's passing of a low-frequency antigen to the fetus, usually during a prior

Table 1 Laboratory investigations

Day of life	Hb (g/dl)	PCV	Reticulocyte count (%)	Serum bilirubin (mg/dl)	Peripheral blood smear
1	14.6	45.3	3.02	2.86	Normal
3	15.4	46.6		7.9	
4				17.3	
6–10				16–17	Microspherocytes and schistocytes
12	8	24.2	3	6.15	
20	5.6	16.8	4	10	Microspherocytes and schistocytes
24	13.2	38.6		2.5	

Hb, hemoglobin; PCV, packed cell volume.

pregnancy, whose red cells sensitize the mother to the antigen. During the current pregnancy, with a second fetus that has also inherited the paternal antigen, maternal antibodies cross the placenta and sensitize the fetus' red cells. Only a few reports of pregnancy loss due to anti-E have been described [4,6]. Unlike anti-D alloimmunization, anti-E titer is less sensitive in detecting the severity of hemolysis in the subsequent pregnancy – like in the present case in which the mother's ICT was negative. Therefore, a high level of suspicion and early recognition of these cases is crucial even with low titers. A critical titer of 1 : 16 has been considered in anti-E alloimmunization [4]. Joy and colleagues reported that six of 16 fetuses with maternal titer greater than 1 : 16 had fetal hemoglobin less than 10 g/dl. Two fetal hydrops resulted in perinatal death despite intrauterine treatment. Extremely elevated titer coupled with very severe fetal anemia is scarce [4,6]. Using a cutoff of 1.5 multiples of median in the MCA of PSV Doppler studies, 100% sensitivity in the prediction of moderate-to-severe fetal anemia was reported [7]. If MCA PSV is added, fetal anemia is treatable with a favorable outcome of over 90% before hydrops [8]. Fetal hydrops combined with very low cord blood hemoglobin (2.1 g/dl) is a late and ominous presentation of hemolytic disease. As we encountered this adverse clinical setting, blood transfusions in our case were futile.

In present case, the baby was severely affected antenatally; however, postnatal course was mild. This was a paradox in the present case. This may be because the baby received two intrauterine transfusions. Repeated intrauterine transfusions are associated with a reduction in fetal hemolysis by the replacement of fetal red blood cells by Rhesus-negative donor red blood cells. Most fetal red blood cells have disappeared at the second intrauterine transfusion [9,10]. The replacement of fetal cells by donor red cells should theoretically result in a less-active neonatal alloimmune hemolysis and therefore reduce the need for neonatal intensive treatment as in the present case.

Conclusion

We advocate that, in D women who have had previous unexplained fetal loss (fetal hydrops), screening of maternal serum alloantibodies against red blood cells is important in the early trimesters of pregnancy, followed by regular Doppler studies and treatment strategies if an alloimmune cause of hemolysis is identified.

Acknowledgements

The authors thank Dr Arti Rajhans for her guidance.

Author contributions: Kalane S.: search of the literature, partial English editing, and correction; Joshi R.: final editing and correction; and Kulkarni A.: editing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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