

## **A Case of Haemolytic Disease of the Newborn Due to Maternal Anti-E and Anti-c**

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**Hemolytic disease of the fetus and newborn (HDN) is a condition in which the lifespan of an infant's red blood cells (RBCs) is shortened by the action of specific IgG antibody (ies) derived from the mother. These antibodies may be directed against Rhesus or other blood group antigens on fetal RBCs that are inherited from the father but are not expressed by the mother. The widespread use of Rh immune globulin has dramatically decreased occurrence of anti-D HDN among D-Negative pregnant women, but alloimmunization and importance of antigens other than D has increased. We report a case of HDN due to maternal Anti-E and anti-c in an O positive mother. The newborn received double phototherapy and exchange transfusion followed by a top up transfusion and was discharged with no further problems.**

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Hemolytic disease of the newborn, (HDN) first described in the 1600s has unfortunately not become extinct, it is still with us<sup>1</sup>. Levine and Stetson reported the first human antibody against one component of the Rh system, later called D antigen in 1939<sup>2</sup>. The antibody was found in the serum of a woman with HDN. The Rh blood group system is the most polymorphic of the human blood groups, consisting of at least 45 independent antigens and next to the ABO system is the most clinically significant in transfusion medicine<sup>3</sup>. The widespread use of Rh immune globulin has dramatically decreased the occurrence of anti D-HDN among D negative pregnant women, but has not eliminated the problem. No measures are available to prevent sensitization to other blood groups, most notably other Rhesus (C,c,E,e), Kell and Duffy antigens, and the corresponding maternal antibodies may cause severe HDN<sup>3</sup>.

### **THE CASE**

A live baby boy was born on 30 July 2004; the 4<sup>th</sup> child of 27 year old Saudi lady. It was an uncomplicated normal spontaneous vaginal delivery. On examination, the baby was active, jaundiced, not in respiratory distress and there were no dysmorphic features. His vital signs and systemic examination were within normal limits. Laboratory investigations showed: A rising indirect bilirubin level (6.2 to 19.7 mg/dl), hemoglobin level dropped from 14.8 g/dl to 9.3 g/dl, with an increasing reticulocyte count (5.3 to 7.6 %), despite a trial of double phototherapy for 42 hours. The Baby's blood group was O positive and the direct antiglobulin test (DAT) was strongly positive (4+). Screening for G6PD deficiency and sickle cell anemia was negative and hemoglobin electrophoresis was normal. Antibody screen of the mother was positive

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with anti-E and anti-c, which were identified in both serum and eluate of baby's red blood cells (RBCs). The baby was transferred to the neonatal intensive care unit (NICU) and an exchange blood transfusion using 300 ml of fresh group O positive packed red blood cells (PRBCs) negative for E and c antigens, sickle cell test negative, and compatible with the mother's serum was given. The total bilirubin decreased to 8.8 mg/dl and hemoglobin level increased to 11.9 g/dl.

A top up simple blood transfusion with 55 ml of fresh group O positive, E and c antigens negative, sickle cell negative packed RBCs, match compatible with the mother's serum, was transfused. The baby tolerated both exchange and simple blood transfusion well. Single photon phototherapy was continued for two more days, and the baby was discharged on the sixth day of life in a good condition.

Obstetric history of the mother revealed that this was her fourth child. She had three other living children and her first pregnancy was aborted. The third child, 4 year old boy had indirect hyperbilirubinemia at birth which responded to phototherapy. He was blood group O positive, DAT positive, anti - E and anti - c was found in the eluate from cord blood cells. Her other two children, 7 year old girl and 6 year old boy did not have jaundice at birth nor positive DAT. Laboratory investigations of the mother showed that her blood group was O positive; antibody screen was negative after abortion of her first pregnancy. After delivery of her third and fourth babies, anti-E and anti-c were identified in her serum. She had no history of blood transfusion or any chronic illness. Antibody titre was not done because the mother showed up the first time at labor in this hospital; she did not have proper antenatal care previously.

## DISCUSSION

Many of the red blood cell (RBC) alloantibodies of the Rh system have been associated with HDN; however, the severity of the disease is usually the greatest with anti-D<sup>4</sup>. Prevention of RhD HDN became feasible in the late 1960s after pioneering research by Finn Clarke and Freda; there was a dramatic decline in Rh HDN<sup>5,6,7</sup>. Since then, other Rh and non Rh red cell alloantibodies have become relatively more important and are now responsible for the greater proportion of HDN cases. Anti-c and anti-E are the most commonly implicated non DRh antibodies in the pathogenesis of HDN<sup>8</sup>. Another study assessed the outcomes of anti-E in pregnancy, and they concluded that a substantial proportion of infants are sufficiently affected by anti-E and suffer from clinically significant HDN. In that study, 21% of the affected infants required exchange transfusion and 10% had severe or very severe disease, and they concluded that anti-E titres are insensitive and poor predictor of HDN severity. Another study also showed that anti-E was a cause for moderately severe HDN in a baby who had jaundice and anemia; he required phototherapy and blood transfusion<sup>9</sup>. Anti-c is an important Rh antibody that may cause severe HDN, and in some cases may be as severe as anti-D HDN<sup>10,11,12</sup>.

In a series of 1022 cases of non RhD alloimmunization<sup>13</sup> Kenneth found that only anti-c was associated with severe HDN that ended in hydropic stillbirth or necessitated intrauterine blood transfusion. He also noted that anti-E is half as likely to require neonatal treatment, and clinical manifestations are more variable and usually less severe, than other Rh antibodies. In this case, a live born male neonate had HDN of

moderate severity, which required exchange blood transfusion on the second day of life in addition to double phototherapy.

Some Points to be Considered in This Case Are:

Is the severity of HDN affecting this baby attributed to anti-c only or is it enhanced by the combination with anti-E? Most likely it is a combination of both. This question may be partially answered if the two antibodies are separately titrated and cellular assays employed to predict the clinical behavior of each alloantibody (which unfortunately was not done). Assays which used anti-D to predict the severity of HDN were developed and evaluated<sup>14</sup>. The other point to be considered is the identical ABO groups of mother and both babies (all O positive) may have potentiated the severity of HDN: This point may be true in this case due to the absence of the protective effect of feto/maternal ABO incompatibility. ABO incompatibility between the mother and fetus has a substantial but not absolute protective effect against maternal immunization to other antigens, by virtue of increased rate of fetal RBC destruction by maternal anti-A or anti-B<sup>3</sup>. The most probable genotype of the baby inferred from his RBC phenotyping results (Table 1) is DCe / DcE, therefore he is most likely heterozygous for the c & E antigens and this heterozygosity may have slightly ameliorated the severity of the HDN in this case. It is not clear whether these antibodies separately or in combination, have any suppressive effect on erythropoiesis, similar to anti-K (anti- KELL), for example, as the baby did not have significant reticulocytosis for the degree of anemia (normal reticulocyte range for neonates is 2.5-6.5%). Anemia in Kell HDN may be severe and appears to be due to suppression of erythropoiesis rather than immune destruction<sup>15,16</sup>. Studies have shown that noninvasive methods for antenatal care of pregnant women with alloantibodies like ultrasound(U/S) and Doppler(U/S) were in favor of invasive techniques (amniocentesis and cordocentesis) for monitoring the condition of the fetus and further management (obstetric intervention)<sup>17</sup>.

In addition, prenatal diagnosis of fetal RhD status and Rh CcEe phenotype by molecular analysis of maternal plasma using polymerase chain reaction is useful for the obstetricians to start the management of high risk pregnancies as early as possible<sup>18,19</sup>.

**Table 1: Rh Phenotype of Mother's and 4<sup>th</sup> Baby's RBCs**

Tested RBCs	Anti-e	Anti-E	Anti-c	Anti-C
Mother's RBCs	3+	0	0	3+
Baby's RBCs	2+	2+	2+	2+
Positive Control	3+	3+	3+	3+
Negative Control	0	0	0	0

## CONCLUSION

**In this case, a moderately severe type of HDN was detected in a neonate, which was caused by a combination of anti-E and anti-c. The severity of HDN due to this blend of antibodies is found to be increasing in successive pregnancies with E and/or c antigen positive babies. Proper antenatal follow up of all pregnant women who are Rh D positive with a positive antibody screen and/or a history of previous babies with signs of HDN is required. Further investigations are needed to clarify the behavior of these alloantibodies in the variable clinical picture of HDN, for example, the antibody titre at which invasive obstetric intervention and management is necessary.**

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