Anti-c Antibody mediated Hemolysis - A Rare cause of Neonatal Jaundice

SATHYAN V K KANAGAMBARANATHAN
Department of Neonatology,
MADRAS MEDICAL COLLEGE AND GOVERNMENT GENERAL HOSPITAL

Abstract:
Neonatal jaundice caused by hemolytic disease of the newborn is mostly due to Rh(D), ABO incompatibilities and rarely due to other minor blood group incompatibilities. There are very few case reports of Minor blood group incompatibilities causing neonatal jaundice. We hereby report a neonate who had severe neonatal hyperbilirubinemia due to maternal anti-c antibodies leading to acute bilirubin encephalopathy. Though Minor blood group incompatibilities are a rare cause of neonatal hyperbilirubinemia, they should always be kept in mind while evaluating neonatal hyperbilirubinemia especially in situations where there is a positive direct coombs test and there is no Rh (D) or ABO incompatibility between the mother and the neonate.

Keyword : Neonatal jaundice, Hemolysis, Anti-c antibodies

Introduction:
Hemolytic disease of the newborn (HDN) is one of the causes of severe neonatal hyperbilirubinemia. It is a condition in which the life span of an infant’s red blood cells (RBCs) is shortened by the action of specific IgG antibodies 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. This is mostly due to Rh (D) and ABO incompatibility. With the routine prophylaxis in Rh negative pregnant mothers, alloimmunisation has declined from 45 cases per 10,000 births to 10.2 cases per 10,000 births, with less than 10% requiring intrauterine transfusion, but importance of antigens other than D has increased. Minor blood group incompatibilities such as Anti-c, Anti-C, Anti-E, Kell, etc. are often overlooked during evaluation of neonatal hyperbilirubinemia.

Case Summary:
A 4 day old term neonate with severe jaundice was referred to our hospital in critically ill state with shock and respiratory failure. The baby also had signs of bilirubin induced neurological dysfunction (BIND). The baby was second born child to 23 year old mother from non-consanguineous marriage with past history.
of abortion at 3 months gestation which was not evaluated. Mothers blood group was O positive and had PROM for 48 hours. Baby weighed 2750 grams and had smooth transition but developed lethargy and refusal of feeds from day 2 of life with signs of shock which was treated with vasopressors and antibiotics. In view of deterioration baby was shifted to our hospital on day 4 of life in intubated condition. On examination the baby was found to be deeply jaundiced and also had signs of acute bilirubinencephalopathy. The baby was immediately commenced on intense double surface phototherapy, ventilator support and vasoppressors. The baby’s blood group was also O positive ruling out Rh or ABO incompatibilities. After sending preliminary investigations for neonatal jaundice Double volume exchange transfusion was performed. 2 exchange transfusions were performed in 24hrs. The bilirubin levels decreased from a total of 40 mg/dl to 18mg/dl in 48 hrs. Investigations revealed positive direct coomb’s test, anemia, reticulocytosis and severe hemolytic picture in peripheral smear. Work up for Minor blood group incompatibilities was performed since the direct coomb’s test was positive. Investigations revealed the presence of Anti-c antibodies in the mother and the neonate which was the cause of neonatal jaundice. During Rh phenotyping, father was found to be c antigen positive whereas the mother was c antigen negative. The baby was c antigen positive which led to production of Anti-c antibodies in the mother which got transferred to the baby causing hemolysis and severe jaundice.  

(Table 1) Though there was reduction in serum bilirubin levels (15mg/dl) the baby continued to be in encephalopathy and shock and succumbed at 80 hours of admission.

Discussion:
Hemolytic disease of the newborn is a well-recognised entity because of the isoimmunisation of Rhesus D negative mother bearing a Rh positive fetus. Although anti-Rh (D) was once the major etiology of haemolytic disease of the fetus and newborn (HDFN), the widespread adoption of antenatal and postnatal Rhesus immunoglobulin administration has resulted in a marked decrease in the prevalence of alloimmunisation due to the RhD antigen and has led to an increased interest in non–Rh D isoimmunisation\(^{(1, 2)}\). The Rh antigen system is mainly composed of the antigens C, c, D, E, and e. Out of 49 known Rhesus antigens, only 5 (c, C, D, e, E) are well known. Besides this, there are other rare blood group systems like Kell, Duffy (Fya and FYb), Kidd (JKa and JKB), and the M and N system. Though CDe is the most common haplotype in Caucasians (42%), Native Americans (44%) and Asians (70%), some case series and case reports have reported hemolytic disease of the newborn due to Anti-c antibodies. There are only very few case reports of neonatal jaundice due to Anti-c antibodies in India. The first case report of hemolytic disease of the newborn due to Anti-c antibodies reported from PGI Chandigarh India was published in 2007. Fetal affection was noted to be of a milder variety, where the baby was managed only with intravenous immunoglobulin and phototherapy \(^{(6)}\). Another case series from Fernandez hospital India reported 2 cases of neonatal jaundice due to Anti-c antibodies\(^{(8)}\). Isoimmunisation due to Rh c antigen is very similar to that of Rh D antigen. If the father is homozygous, the fetus will be affected. The fetus of a heterozygous father has a 50% chance of being affected. Similar to Rh D, the risk of isoimmunisation occurs due to fetomaternal haemorrhage, placental abruption,
spontaneous or therapeutic abortion as well as after caesarean delivery and ectopic pregnancy. The management of anti-c isoimmunisation is similar to the management of anti-D isoimmunised pregnancy, with a specification that blood used for fetal and/or neonatal transfusion should be negative for its respective antibody. In a series by Hackney et al.\(^5\) a critical titre of 1:32 without features of hydrops and a critical titre of 1:16 supplemented with ultrasonographic features of hydrops were considered significant. However, fetal and/or neonatal direct Coomb’s test (DCT) positivity does not necessarily correlate with a severe hemolytic disease. DCT may be negative in anti-c isoimmunisation as this antibody is often present in small titres in the neonate\(^3\). Serologic evaluation of maternal antibodies thus remains the cornerstone of management\(^5\). The blood used for intrauterine transfusion or exchange transfusion should ideally be c- negative, irradiated and compatible with baby’s blood type. Infants exposed to anti-c isoimmunisation have the risk of high bilirubin levels, bilirubin encephalopathy, auditory abnormalities and late anemia. These infants should be monitored with hemoglobin and reticulocyte count for the first 6–12 weeks of life. A brainstem evoked response audiometry (BERA) is advised at 3 months of age and also they need neuro-developmental assessment till 18 months of age.

**Conclusion:**
Direct coomb’s test is mandatory in neonates presenting with severe jaundice (Total Bilirubin>20mg/dl) or if hemolysis is suspected. A positive direct coomb’s test should alert the clinician to the presence of maternal antibodies against RBC antigens.

In the absence of major blood group incompatibilities such as Rh (D) and ABO incompatibilities, minor blood group incompatibilities should strongly be considered in the differential diagnosis neonatal jaundice

**References:**
6) Thakral B, Agrawal SK, Dhawan HK, Saluja K, Dutta S, Marwaha N: First report from India of hemolytic disease of newborn by anti-c and anti-E in Rh (D) positive mothers. Hematology 2007, 12:377-380


8) Srinivas Murki & Hemasree Kandraju & Surekha A. Devi Hemolytic Disease of the Newborn-Anti c Antibody Induced Hemolysis Indian J Pediatr (February 2012) 79 (2):265–266