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Case Series

Variable manifestations of minor blood group incompatibility

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ABSTRACT

In settings with adequate coverage of anti-D immunoglobulin, minor blood group incompatibility has become an important cause of hemolytic disease of the newborn (HDN). We presented a series of cases of HDN of varying severities caused due to presence of anti-E and anti-C antibodies. Two neonates with anti-E antibodies developed jaundice requiring intensive phototherapy, while the course of the third neonate born to mother with Rh D isoimmunization was complicated by presence of anti-C antibodies, who needed double volume exchange transfusions for jaundice and packed red cell transfusions for anemia. Hearing screening and neurological examination at discharge were normal for all three neonates. These cases highlighted the need for appropriate testing for minor blood group incompatibility in unusual cases of HDN to initiate timely therapy and prevent neonatal morbidity and mortality.

Keywords: Hemolytic disease of newborn, Neonatal hyperbilirubinemia, Rh incompatibility, Anti-C, Anti-E antibodies

INTRODUCTION

Hyperbilirubinemia is a common morbidity in the early newborn period. Rh incompatibility is one of the causes of severe hyperbilirubinemia that may result in bilirubin induced neurological dysfunction (BIND).[1] Rh blood group system is highly immunogenic and complex. It consists of up to 45 antigens with D, C, c, E and e being the most relevant ones to clinical practice.[2] These antigens are coded by RHD and RHCE genes on chromosome 1. Over the years, hemolytic disease due to Rh D incompatibility have reduced due to widespread use of anti-D immunoglobulin for Rh D negative mothers leading to increasing reports of isoimmunization with other Rh subgroups.[3] We reported a case series of HDN caused or complicated due to minor Rh blood group incompatibility.

CASE SERIES

Case 1

A 27 year old gravida 2 mother delivered a female baby weighing 3300 grams at 37^{+2} weeks gestation by lower segment caesarean section (LSCS) in view of previous LSCS. Antenatal period was uneventful. At 87 hours of life, transcutaneous bilirubin (TcB) was detected to be 14.5 mg/dl on routine screening. Both the mother's and neonate's blood group were B positive. The corresponding total serum bilirubin (TSB) was 12.6 mg/dl for which phototherapy was administered for 18 hours. After the resolution of hyperbilirubinemia, baby was discharged.

On follow up, at day 9, neonate was icteric till palms and soles, TSB was 20.3 mg/dl, so phototherapy was initiated and continued for 36 hours. Work up for

hyperbilirubinemia revealed: hemoglobin: 16.3g/dl, total leucocyte count: 11990 /mm^3, platelet count: 245000 /mm^3, peripheral smear: reticulocytosis, direct antiglobulin test (DAT): 4+ and anti-E antibody was identified in both mother and baby. The titer of anti-E antibodies in the mother was found to be 1:64 by conventional tube technique (CTT) and serial tube dilution. Hence, a diagnosis of hemolytic disease of newborn was established. The neonate did not develop any signs of BIND and was discharged on day 13 of life, with a normal neurological examination and hearing assessment using automated brainstem evoked response audiometry.

Case 2

A 33 year old gravida 2 mother delivered a female neonate at 30^{+5} weeks gestation by emergency LSCS in view of severe pre-eclampsia, with birth weight of 1356 grams. The antenatal period was uneventful and mother's blood group was AB positive. The baby developed respiratory distress soon after birth, which was managed with non-invasive ventilation. At 40 hours of life, neonate was found to be icteric till thighs without any other abnormalities on examination.

Work up for hyperbilirubinemia revealed baby blood group: B positive, hemoglobin: 20.4g/dl, total leucocyte count: 7630 /mm^3, platelet count: 1,65,000 /mm^3, peripheral smear: no features of hemolysis, DAT: 2+ and anti-E antibody was detected in both mother (titer 1:4) and baby. TSB was 10.7 mg/dl; hence phototherapy was initiated.[4] It was continued for 48 hours following which there was no rebound hyperbilirubinemia. During hospitalization and at discharge, neurological examination and hearing assessment stayed normal.

Case 3

A 29 year old gravida 2, para 1 mother delivered a male newborn weighing 2450 grams at 34^{+4} weeks gestation by LSCS due to previous LSCS with spontaneous onset of labour. Her blood group was B negative but she did not receive anti-D immunoglobulin in the previous pregnancy. In this pregnancy, her indirect antiglobulin test (IAT) revealed a titre of 1:64. Antenatal period was uneventful. The newborn cried immediately at birth, with Apgar scores of 9 and 9 at 1 minute and 5 minutes. The investigations in the newborn revealed B positive blood group, positive DAT (3+), cord bilirubin 4.2 mg/dl and Hb 11.7 gm/dl. Intensive phototherapy was initiated since birth.

While arranging and cross-matching blood in anticipation of an exchange transfusion, mother's blood was found to be positive for anti-D and anti-C antibodies by column agglutination technique (CAT). Anti-D and anti-C titres were detected to be 1:512 and 1:2 respectively. Neonate's peripheral smear revealed normocytic normochromic and microcytic red blood cells (RBC), polychromatophilia, few spherocytes, 90 nucleated RBCs for every 100 white blood cells and anisocytosis. Reticulocyte count was 28.74%.

At 7 hours of life, TSB increased to 13.4 mg/dl (above the cut-off for exchange transfusion), despite intensive phototherapy, necessitating a double volume exchange transfusion (DVET).[5] The procedure was completed without complications and post procedure TSB was 6.4 mg/dl. Intensive phototherapy was continued. By 24 hours of life, TSB again increased to 14.6 mg/dl necessitating a second DVET. Post exchange TSB was 6.2 mg/dl. A packed red blood cell (PRBC) transfusion was given due to low post exchange hematocrit of 30%.[6] Intravenous immunoglobulin (IVIG) was given, after the second DVET, at 28 hours of life in view of rising bilirubin trend to prevent further hemolysis. A repeat PRBC transfusion was given on day 5 of life for significant anemia. The neonate required intensive phototherapy, on and off, till day 8 of life. The neonate was discharged at 9 days with a normal hearing screening and neurological examination. On last follow up at 25 days of life, the neonate was gaining weight well and did not require any intervention.

DISCUSSION

The Rh system of blood group was intriguing due to its complexity and its clinical relevance, which was next only to the ABO system.[2] Most commonly encountered antigens were D, C, c, E, e which were implicated in HDN. Mothers who were negative to these antigens got sensitized in pregnancy with a fetus positive for these antigens and mounted an immune reaction in subsequent antigen positive pregnancies leading to HDN.[7] HDN may vary in severity from mild hyperbilirubinemia, anemia to severe hydrops fetalis and intrauterine death.

In a prospective study from South India, the frequency of C, c, E, e antigens in D positive donor population were reported as 91%, 50%, 17% and 97% respectively while in D negative donor population was reported 5%, 99%, 1%, 100% respectively.[8] Similar frequency of other Rh antigens in donors had been reported by other multicentric studies in India.[8,9] Hence, Rh subgroup screening would explain clinical incompatibility between blood samples, in both D positive and negative individuals, thus having implications for perinatology, obstetrics and transfusion medicine.

A retrospective analysis of hospitalised neonates who developed indirect hyperbilirubinemia due to minor blood group incompatibility was reported in 2012 from Turkey. The authors reported that out of the 106 such neonates, most (37.7%) had C incompatibility, followed by E (28.3%), c (20.8%), e (8.5%) and Kell (4.5%) incompatibility. Positive coombs test was reported in 28.3% patients and 20.8% patients required exchange transfusion. Hydrops fetalis was reported in 5 (4.7%) neonates.[10]

A few cases of hemolytic disease due to varying combinations of Rh antigens have been reported.[11,12] The clinical spectrum varied from asymptomatic and mild cases to severe disease and intrauterine death (rarely). One of our cases developed severe hemolytic anemia necessitating DVET and requiring PRBC transfusion twice. This highlighted the clinical scenario of Rh D incompatibility which was further complicated by minor Rh group incompatibility in low-income settings, where antenatal care, universal screening for Rh isoimmunization and prophylactic anti-D immunoglobulin administration were poor.[13]

CONCLUSION

This case series highlights the distinct presentations of minor blood group incompatibility with varying severity in newborns, which needs to be kept in mind in unusual cases of hemolytic disease of newborn to facilitate appropriate testing and timely therapy and prevent neonatal morbidity and mortality.

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