

RECURRENT HYDROPS FETALIS DUE TO KELL ALLO-IMMUNIZATION

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We report a case of recurrent hydrops fetalis caused by Kell allo-immunization. The peculiar features of hemolytic disease of the newborn (HDN) due to anti-Kell allo-immunization are described, discussed and contrasted with those of anti-D allo-immunization. The ideal management protocol is outlined and discussed. It is suggested that a team comprising an obstetrician, a neonatologist and a hematologist or blood transfusion expert should manage pregnancies complicated by Kell allo-immunization.

Case Report

A 33-year-old gravida 12 para 11+0 mother presented unbooked, in active labor at 31 weeks of gestation. Her obstetric history was remarkable: two of her previous pregnancies (10th and 11th) had ended in fetal deaths at 24 and 26 weeks of gestation, respectively, due to fetal hydrops. She had undergone cesarean section on two occasions (5th and 6th pregnancies), during the first of which she received blood transfusions at another hospital. Her blood group was "A" Rh negative, and she had been identified to have anti-Kell antibodies in two previous pregnancies (10th and 11th) at Prince Salman Hospital (PSH), Riyadh. No anti-D antibodies were detected then or have been detected since.

Delivery was by cesarean section, during which marked polyhydramnios was noticed. The infant weighed 2.75 kg, had an Apgar score of 2 at 1 minute, and was hydropic with gross ascites, scalp edema and severe pallor. He was actively resuscitated with endotracheal intubation, positive pressure ventilation, volume expansion and abdominal paracentesis of 100 mL of ascitic fluid to facilitate ventilation.

The initial investigations of the infant revealed severe anemia (hemoglobin 35 g/L), macrocytosis (MCV 165 fl), low reticulocyte count (0.4%), normal white blood cell count ($8.6 \times 10^9/L$) and platelet count ($216 \times 10^9/L$). The serum transaminases were normal as was serum bilirubin, but total serum proteins (33 g/L) and serum albumin (17 g/L) were low.

Cord blood analysis revealed the infant's blood group as "O" Rh positive, and the direct Coombs' test (DCT) was strongly positive. The maternal blood was positive for anti-Kell antibodies in a titer of 1:512, but no anti-D antibodies were detected. The infant and his father were heterozygous Kell positive (K1K2), as indeed was the fourth child, who was born before the mother received her first blood transfusion.

The infant received a single-volume exchange transfusion with packed "O" Rh negative, Kell (K1) negative red blood cells, followed by a top-up transfusion after 12 hours, as well as supportive treatment. He also required phototherapy for three days for moderate hyperbilirubinemia (maximum serum bilirubin 190 $\mu\text{mol/L}$). The infant did well until the age of seven days, when he was noticed to be hypertensive (BP 106/62 mm Hg). Antihypertensive treatment with hydralazine was started. On the 8th day, he was lethargic, the anterior fontanelle was full and tense, and brain CT scan showed a large intracerebral hemorrhage on the right side, causing compression of the brain stem and the lateral ventricle. The infant died at the age of 10 days.

Discussion

The incidence of rhesus hemolytic disease of the newborn (HDN) has diminished significantly due to anti-D prophylaxis. At the same time, HDN caused by other irregular antibodies is being increasingly recognized. After anti-D and anti-c, anti-Kell antibodies can cause moderate to severe hemolytic disease in the fetus and the newborn. Blood transfusion to a Kell-negative woman is an important cause of allo-immunization.

Isolated reports of Kell allo-immunization have appeared in the literature from 1965, and the earliest large series were published by Caine and Mueller-Heubach in 1986,¹ and by Leggat et al. in 1991.² Kell allo-immunization in women can be caused by pregnancy with a Kell-positive fetus or, more commonly, following transfusion with Kell-positive blood. In white populations, only 0.2% of the people are homozygous Kell positive, 8.7% are heterozygous and 91.1% are Kell (K1) negative. The frequency of anti-Kell antibodies differs in different countries and different populations. The studies from the U.S. quote figures from 3.1% to 22%.³ The prevalence of K1 phenotype in Saudi Arabia is 18%,⁴ and the prevalence

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of K1 phenotype in Saudi blood donors in Prince Salman Hospital is 14.7% (Bruce-Tagoe, unpublished data).

Kell antigens are strong immunogens; they are well developed in the red blood cells of the fetus that inherits the gene, and are present at an early stage of red cell maturation. One remarkable feature of anti-Kell hemolytic disease is that there is selective inhibition of erythroid progenitor cells, resulting in a lack of reticulocytosis and erythroblastosis.⁵ Another remarkable feature is that the red cell precursors are destroyed at the primitive stage of maturation when they are still poorly hemoglobinized. Their destruction does not, therefore, produce a significant increase in amniotic fluid bilirubin levels.⁶ The granulocyte-macrophage and megakaryocytic progenitor cells are not affected.

Anti-Kell and anti-D hemolytic diseases differ in some other important aspects. In the former, unlike the latter, the previous obstetric history is not always predictive of outcome in the index pregnancy, and there is poor correlation between the antibody titers and the outcome. Severe fetal hydrops has been reported with an antibody titer of 1:2.⁵ Furthermore, in anti-Kell disease amniotic fluid spectrophotometry for bilirubin concentration correlates poorly with disease severity and hyperbilirubinemia is not a prominent feature in the affected newborns.

The ideal management of Kell hemolytic disease involves a multidisciplinary team effort by Obstetrics, Neonatology, Hematology and Transfusion Services personnel. Efforts are directed at: 1) identifying which fetus is severely affected; 2) treating fetal anemia; and 3) determining optimal time for delivery. Once anti-Kell antibodies are identified in a pregnant woman, the titers should be measured, history of previous pregnancies and blood transfusions ascertained, and the Kell status of the husband determined. If the husband is Kell negative, the fetus will be Kell negative, and no further investigations are required. But if the husband is Kell positive, the Kell status of the fetus needs to be determined. This can be done by DNA analysis of fetal cells obtained by chorionic villus sampling as early as 10-12 weeks of gestation. Otherwise, maternal antibody titers need to be monitored every two to four weeks, and ultrasonography performed to identify signs of fetal affection. At 20 weeks of gestation, fetal blood sampling (FBS) is carried out to determine fetal blood group, hematocrit, DCT, reticulocyte count and bilirubin.

Once allo-immunization has occurred and the fetus has developed severe erythroblastosis, its healthy survival depends on active intrauterine management. If fetal hematocrit on FBS is below 30%, this indicates a need for either intraperitoneal transfusion (IPT) or intravascular transfusion (IVT). IVT is the preferred management modality. It allows direct entry of transfused cells into the fetal circulation and can be performed as early as 20 weeks of gestation. The fetal blood group can be confirmed, pre-

and post-transfusion hematocrit can be measured, and reversal of hydrops can be achieved irrespective of gestational age. It also allows continuation of pregnancy until 37-38 weeks of gestation, and the timing of transfusion and the delivery can be decided more rationally. IVT can either be a top-up transfusion or an exchange transfusion. A second transfusion should be performed within two weeks of the first transfusion, as it is difficult to predict the rate of fall of hemoglobin initially. Some institutions employ a combination of transfusions, i.e., IVT followed by IPT, as this approach diminishes the frequency of transfusions. Affected infants need top-up transfusions in the early months of life because they are born with virtual absence of reticulocytes and a red cell population consisting mainly of transfused adult red cells.

The outcome in allo-immunized pregnancies has improved greatly in recent years. With IPT alone, the overall survival rate is 80%. Following IVT, the survival in some centers is 90%, and the survival in hydropic fetuses is 66%. In a recent series, the reversal of hydrops following IVT was about 60%, and the survival in this group was about 86%.⁷ The long-term follow-up following intrauterine transfusions has shown normal neurological and developmental outcome in 84%-93% of cases.⁸

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