Fatal course of ABO hemolytic disease associated with hydrops in a twin pregnancy

Filiz Tiker, Berkan Gürakan, Aylin Tarcan, Namık Özbek

Department of Pediatrics, Başkent University Faculty of Medicine, Ankara, Turkey

SUMMARY: Tiker F, Gürakan B, Tarcan A, Özbek N. Fatal course of ABO hemolytic disease associated with hydrops in a twin pregnancy. Turk J Pediatr 2006; 48: 73-75.

Hydrops fetalis associated with ABO incompatibility is an extremely rare condition. We report twin infants both afflicted with significant ABO hemolytic disease but showing different degrees of clinical severity, in which fatal hydrops developed in one of the twins. Hemolysis due to ABO incompatibility is usually difficult to diagnose. All causes of non-immune hydrops should be ruled out in order to identify hydrops due to ABO incompatibility.

Key words: ABO incompatibility, hydrops fetalis.

Hemolytic disease of the newborn due to ABO incompatibility is the most common type of materno-fetal blood group incompatibility. The severity of hemolysis in ABO hemolytic disease varies widely. Most affected infants develop a very mild condition that resolves without therapy, but a small proportion of patients develop life-threatening hemolysis. Hydrops fetalis associated with ABO incompatibility is extremely rare, and has only been documented in case reports[1-4]. We present a case of hydrops fetalis that developed due to ABO incompatibility in a twin pregnancy.

Case Report

A 28-year-old, gravida 3, para 1, blood type O-positive woman with a twin pregnancy was referred to our hospital at 22 weeks' gestation with the complaint of rapid enlargement of abdominal girth. Her medical background was unremarkable, and there was no history of previous blood transfusion or drug addiction. Ultrasonographic examination revealed fetal ascites in one fetus (twin A, a boy), but no pleural or pericardial effusion was noted. The other fetus (twin B, a girl) appeared normal on ultrasound. Maternal serology for toxoplasmosis, rubella and cytomegalovirus revealed that the woman was immunoglobulin G (IgG)-positive and IgM-negative for these diseases. She was also IgM-negative for herpesvirus types I and II. The woman declined cordocentesis and did not attend any routine prenatal visits.

The twins were born by spontaneous delivery at another center at 34 weeks' gestation. Both babies had respiratory problems, and they were referred to our hospital at three hours of age. On admission, twin A was edematous, cyanotic, pale and bradycardic. His breathing was insufficient, so he was intubated and placed on mechanical ventilation. Physical examination revealed growth-related parameters of 2040 g body weight (50th percentile), 43 cm length (25th percentile), and 30 cm head circumference (25th percentile). Cardiac findings were normal, his respiratory sounds were decreased, his abdomen was grossly distended with ascites, and the liver was palpated 2 cm below the right costal margin.

Initial laboratory investigation at four hours of age is shown in Table I. Investigation of red blood cell (RBC) morphology showed anisocytosis, with spherocytes and occasional acanthocytes and helmet cells. Chest radiography suggested pulmonary hypoplasia and massive ascites.

Twin A was treated with phototherapy, 500 mg/kg of intravenous immunoglobulin, and one transfusion of RBCs. The severity of the abdominal ascites decreased within

days, but the baby remained dependent on the ventilator. He died on the 20th day of life due to sepsis and pulmonary hypertension. Pathological examination of postmortem liver samples revealed centrilobular necrosis with white blood cell infiltration in the sinusoids, suggesting sepsis. Microscopic examination of lung tissue revealed pneumonia and pulmonary hypertension. Since the family did not give consent for a complete autopsy, it was not possible to confirm the diagnosis of pulmonary hypoplasia.

On admission, twin B was in mild respiratory distress. Her growth parameters were 1800 g body weight (25th percentile), 41 cm length (10th percentile), and 30 cm head circumference (25th percentile). Her cardiac findings and respiratory sounds were normal. Laboratory studies are shown in Table I. She was treated with 500 mg/kg of intravenous immunoglobulin, one transfusion of RBCs, and a three-day course of phototherapy. She responded well and was discharged after 10 days in hospital.

Table I. Laboratory Data of the Infants

	Twin A	Twin B
Hemoglobin (g/L)	100	110
Platelet count (x10^9/L)	199	388
Reticulocyte count (% of total RBCs)	19	13
Nucleated RBCs (/100 WBC)	18	16
Initial total bilirubin (mg/dl)	2.91	3.74
Conjugated bilirubin (mg/dl)	0.64	0.55
Bilirubin at 20 hours of age (mg/dl)	11.76	13.37
Albumin (mg/dl)	2.9	3.04
Blood group	A-positive	A-positive
Direct Coombs' test	Negative	Positive
Indirect Coombs' test	Negative	Negative
Maternal anti A titer	1:1024	1:1024
Maternal anti B titer	1:64	1:64
Infant's anti A titer	1:16	1:36

RBC: red blood cell, WBC: white blood cell.

In both infants, the results of serologic testing for congenital infection with toxoplasmosis, rubella, cytomegalovirus, Epstein-Barr virus, herpesvirus types I and II, Parvovirus B-19, hepatitis A, B, and C, and syphilis were all negative. Hemoglobin electrophoresis results and glucose-6-phosphate dehydrogenase levels were in the normal range. Additional studies were performed in the hydropic infant. Cardiac structure and rhythm were normal. Ultrasound and laboratory investigations revealed normal renal structure and function. Chromosomal analysis was not done, but the infant was morphologically normal.

Discussion

Implementation of Rh sensitization-prevention programs has significantly reduced the incidence of immune hydrops associated with Rh sensitization. As a consequence, the relative incidence of non-immune hydrops has risen. ABO and minor blood group incompatibilities are extremely rare causes of immune hydrops.

Although it is estimated that 20% to 25% of pregnancies are at risk for ABO incompatibility, the incidence of related hemolytic disease is considerably lower and varies among racial groups[5]. In the United Kingdom, the reported incidence of ABO hemolytic disease is 2% of all births, whereas severe hemolytic disease occurs in only 0.03% of all births[1]. In one study of a population of newborns in Turkey, there was a 14.8% incidence of ABO incompatibility, with 21.3% of these babies exhibiting significant hyperbilirubinemia (serum bilirubin concentration ≥17 mg/dl) and 4.4% exhibiting severe ABO hemolytic disease (serum bilirubin concentration >20 mg/dl, requiring intensive phototherapy, intravenous immunoglobulin or exchange transfusion)[6]. ABO incompatibility rarely results in significant fetal disease. The recent literature contains only four reports of ABO incompatibility associated with hydrops fetalis[1-4]. Anti-A and anti-B

antibodies are found in the IgA, IgM, and IgG fractions of plasma. Most maternal anti-A and anti-B antibodies are IgM type, and do not cross the placental barrier. However, naturally occurring anti-A and anti-B antibodies of IgG type can cross the placenta[7]. Blood group A and B antigens are not highly expressed on fetal RBCs. However, other fetal cells do express significant levels of A or B antigen, and these cells provide additional binding sites for anti-A or anti-B antibodies. Thus, the small amounts of anti-A IgG or anti-B IgG antibodies that cross the placenta have numerous antigenic sites other than RBCs to which they bind[5].

The twins we describe in this article were both afflicted with significant ABO hemolytic disease but showed different degrees of clinical severity. It is not possible to definitively diagnose hemolysis based on a positive direct Coombs' test, but this test is commonly used to identify newborns with isoimmunization. Still, the reliability of direct Coombs' testing for identifying isoimmunization in ABO incompatibility has been questioned. A negative result does not exclude sensitization, and a positive one does not confirm the diagnosis. In the majority of cases of ABO hemolytic disease, direct and indirect Coombs' tests are negative or weakly positive[5,7]. Also, as observed in our two cases, positive Coombs' status is not correlated with severity of disease.

Although levels of anti-A IgG or anti-B IgG are not highly specific or sensitive in the diagnosis of ABO hemolytic disease, this condition tends to occur in newborns whose mothers have high titers of these antibodies. With respect to the twins in this report, the maternal anti-B IgG titer was 1:64 positive and the anti-A IgG titer was 1:1024 positive, indicating very high levels of anti-A antibody. This high maternal anti-A titer may have contributed to the severity of the infants' disease. Concerning the babies' antibody levels, we found no correlation between anti-A titer and severity of hemolysis. ABO hemolytic disease is notorious for severe hemolysis despite negative or weakly reactive Coombs' test and low antibody levels. Hydrops developed in twin A, although direct Coombs' test was negative and antibody titer was lower than in the other twin. This could be explained by the numerous antigenic sites to which the antibodies can bind and the hemolysis of the antibody-coated RBCs. Severe anemia is not the sole cause of hydrops in isoimmunized fetuses[7]. The elevated venous pressure, portal and umbilical venous obstruction caused by excessive extramedullary erythropoiesis in the liver with severe hemolysis, and diminished albumin production associated with hepatic dysfunction can be contributory factors in this infant.

As noted above, ABO incompatibility is difficult to identify. In order to diagnose hydrops due to ABO incompatibility, all causes of non-immune hydrops must be ruled out and placental transfer of abnormal antibodies must be documented. Although ABO incompatibility is an extremely rare cause of hydrops fetalis, it should be considered in the differential diagnosis for this condition.

REFERENCES

1. McDonnell M, Hannam S, Devane SP. Hydrops fetalis due to ABO incompatibility. Arch Dis Child Fetal Neonatal Ed 1998; 78: F220-F221.
2. Gilja BK, Shah VP. Hydrops fetalis due to ABO incompatibility. Clin Pediatr 1988; 27: 210-212.
3. Sherer DM, Abramowicz JS, Ryan RM, et al. Severe fetal hydrops resulting from ABO incompatibility. Obstet Gynecol 1991; 78: 897-899.
4. Stiller RJ, Herzlinger R, Siegel S, Whetham JC. Fetal ascites associated with ABO incompatibility: case report and review of the literature. Am J Obstet Gynecol 1996; 175: 1371-1372.
5. Doyle JJ, Schmidt B, Blanchette V, Zipursky A. Hematology. In: Avery GB, Fletcher MA, Macdonald MG (eds). Neonatology: Pathophysiology and Management of the Newborn (5th ed). Philadelphia: Lippincott Williams and Wilkins; 1999: 1045-1091.
6. Sarici SU, Yurdakok M, Serdar MA, et al. An early (sixth hour) serum bilirubin measurement is useful in predicting the development of significant hyperbilirubinemia and severe ABO hemolytic disease in a selective high risk population of newborns with ABO incompatibility. Pediatrics 2002; 109: e53.
7. Koenig JM. Evaluation and treatment of erythroblastosis fetalis in the neonate. In: Christensen RD (ed). Hematologic Problems of the Neonate. Philadelphia: WB Saunders; 2000: 185-207.