Case report

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ABO incompatibility and glucose-6-phosphate dehydrogenase deficiency presenting as Hydrops Foetalis

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Abstract

ABO incompatibility and glucose-6-phosphate dehydrogenase deficiency G6PD are common haematological problems affecting the newborn. The resulting haemolytic disease of foetus and newborn (HDFN) caused by either of these pathologies generally follows a benign course. It is typically characterized by mild jaundice without significant anaemia. ABO incompatibility alone as a cause of foetal hydrops is extremely rare. We report a case of a newborn baby girl with an anti-B isoimmunisation and G6PD deficiency manifesting with hydrops foetalis, anaemia and hyperbilirubinaemia, born to a mother with blood group O. ***Clin Ter 2014; 165(3):151-154. doi: 10.7417/CT.2014.1714***

Key words: *ABO incompatibility, haemolytic disease of foetus and newborn, hydrops foetalis, glucose-6-phosphate dehydrogenase deficiency, neonatal jaundice*

Introduction

Haemolytic disease of the foetus and newborn (HDFN) is defined as a condition caused by the destruction of red blood cells in the foetus and newborn due to maternal alloantibody against the blood group antigens of the unborn child. With worsening anaemia, erythropoiesis expands to the liver and spleen for extramedullary haemopoiesis causing organ enlargement and portal hypertension. This results in impaired liver production of albumin which in turn leads to reduced plasma colloid osmotic pressure, thus causing generalized oedema, ascites, and effusions known as "hydrops foetalis". There are two types of hydrops: **immune** - when the red blood cells in the foetus are broken down by the mother's immune system, a condition known as HDFN. **Non-immune** - the more common type; occurs when diseases or complications affect the baby's fluid homeostasis.

This case report highlights the fact that ABO incompatibility should be considered to occur concurrently with other haematological conditions in babies who have haemolysis especially in geographic locations with increased genetic transmission of G6PD deficiency or alpha thalassaemias. In such cases, evidence for ABO incompatibility should be sought in conjunction with G6PD enzyme activity and thalassaemia traits. Furthermore, a diagnosis of ABO incompatibility should not halt the search for other causes that could contribute jointly to the severe haemolytic jaundice in a newborn. This is mainly because ABO HDFN rarely results in severe haemolysis and hydrop foetalis.

Case report

A baby girl was born prematurely at 33 weeks of gestation by emergency lower segment caesarean section following prolonged rupture of membranes. The mother was a 32-year-old lady, para 1+1. Antenatally, foetal ascites, oedema and pleural effusion were detected at 31 weeks of gestation [Fig. 1(a) and 1(b)]. Cordocentesis was performed, showing the foetal haemoglobin at 8.7 g/dL. An intra-uterine transfusion was performed two weeks before delivery. At birth, the newborn had features of hydrops foetalis with the presence of periorbital puffiness, ascites and oedema of the lower limbs and vulval area. The baby developed signs of respiratory distress and was on brief ventilatory support. At 20 hours of life, she developed jaundice. There were also features of ongoing haemolysis with a haemoglobin level of 9.3g/dL, reticulocytosis of 15.01% and unconjugated hyperbilirubinaemia of 131µmol/L. Full blood picture exhibited anisopoikilocytosis with presence of spherocytes, microspherocytes and fragmented red cells, with numerous nucleated red cells and polychromasia consistent with acute haemolysis [Fig. 2(a), 2(b) and 2(c)].

The glucose-6-phosphate dehydrogenase level at birth was low normal, 10.65 Unit/gHb (10.15-14.71 Unit/g Hb). However, it was acknowledged that at the time of the test, the baby's reticulocyte count was elevated and the baby had received intra-uterine transfusion about three weeks earlier, both conditions could cause transient and mildly elevated enzyme level. The thyroid stimulating hormone (TSH) level was normal. No organism was isolated from the blood culture or routine surveillance swabs.

Serologic evaluation using the standard methods as published in the American Association of Blood Banks Technical Manual demonstrated that the mother is blood group O Rh D

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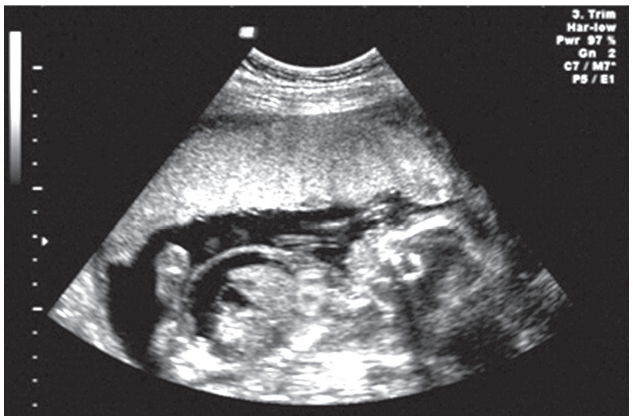

Fig. 1(a): Placentomegaly and ascites

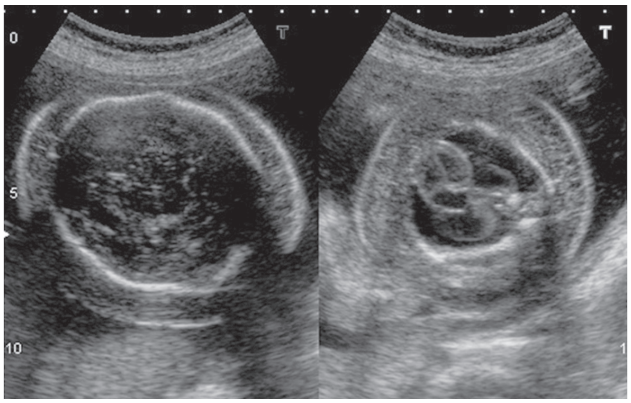

Fig. 1(b): Transverse ultrasonographic sections of the head (left) and chest (right) of the foetus with hydrops foetalis. Note the halo around the head due to oedema. The chest shows gross skin oedema and a large, bilateral pleural effusion.

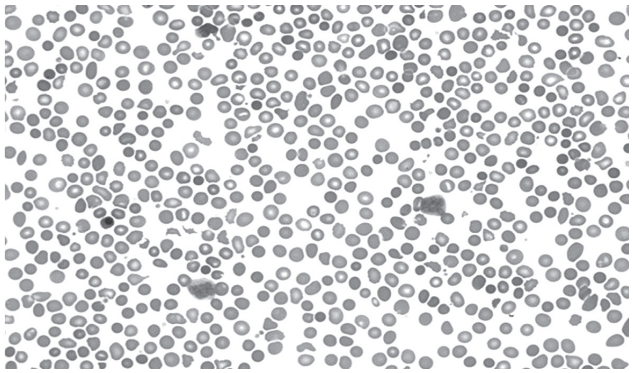

Fig. 2(a). Full blood picture with anisopoikilocytosis. The film exhibited presence of spherocytes, microspherocytes, fragmented cells and polychromasia (Wright stain x 20objective).

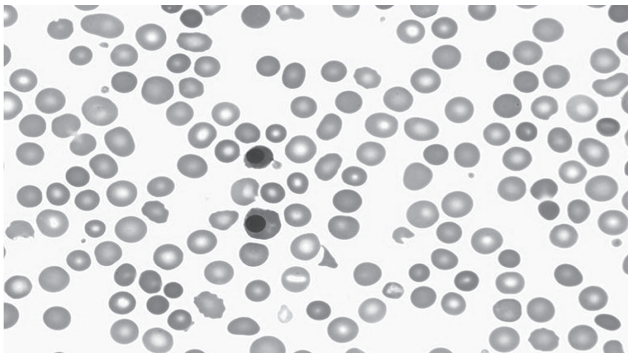

Fig. 2(b). Numerous spherocytes, microspherocytes, polychromasia and nucleated red cells. This blood film is consistent with ongoing haemolysis (Wright stain x40objective).

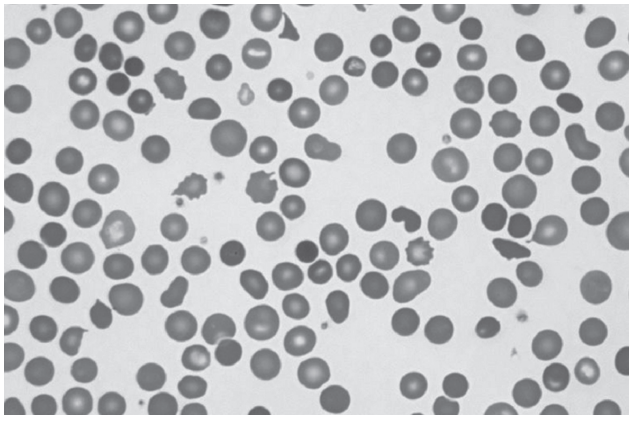

Figure 2(c): Similar blood film of haemolysis (Wright stain x40objective).

positive and the baby is blood group B Rh D positive. Mother's direct Coombs test (DCT) was negative. Study on the mother's serum demonstrated the absence of blood group antibodies to antigens in the Rh, Kell, Kidd, MNSs, Lewis, P, Lutheran, Duffy, or other high-incidence antigen systems. However, dithiothreitol (DTT) test showed presence of IgG anti-B with a significant titer of more than 1:64. Testing the maternal's serum directly against the paternal's red cell to rule out other or unknown low-incidence antigens was not feasible because the paternal's blood group is group B and would definitely react with the anti-B antibodies in the mother's serum.

The DCT on the baby's red cell was negative. Elution done on the baby's sample using the Freeze and Thaw technique was unable to detect presence of any antibody. This was partly due to inadequate baby's blood sample collected. Other possible causes for hydrops such as thalassemia or infectious causes (Toxoplasmosis, Rubella, Cytomegalovirus and Herpes simplex virus 1 and 2) were excluded. Nevertheless, the baby responded well with phototherapy and was discharged well after 1 week.

At 3 months of life, the baby's G6PD enzyme level was repeated and found to be low, 8.22 Unit/g Hb but no evidence of haemolysis was found. The molecular study for G6PD was not done and the baby was lost to follow up.

Discussion

Hydrops foetalis is Latin standing for oedema of the foetus. It is a severe, life-threatening problem in the affected

foetus due to an imbalance in fluid homeostasis, with more fluid accumulating than can be resorbed.

ABO incompatibility has rarely been reported to cause significant foetal diseases. Additionally, only about 5% of all ABO incompatible newborn infants show some signs of ABO HDFN (1). The presenting features can range from asymptomatic to rarely, severe haemolysis. Mild ABO HDFN is characterized by jaundice only, occurring in 1 in 150 births, whereas moderate to severe cases could cause significant haemolysis leading to severe jaundice and anaemia but these are seen in only 1 in 3000 neonates (1, 2). Hydrops foetalis resulting from a foeto-maternal ABO incompatibility is even rarer (2-4). In ABO incompatibility, Group A or B infants born to group O mothers are those at greatest risk of HDFN, as group O mothers have higher levels of IgG anti-A, -B, -A,B in their plasma compared with group A or B mothers (2, 3). In this case of ABO incompatibility, the mother's blood group was O Rh D positive and the baby was grouped as B Rh D positive. The high maternal IgG anti-B titers and the baby's blood film that showed changes typical of ABO HDFN support the diagnosis of ABO incompatibility as a cause of the haemolytic anaemia (Fig. 2). Voak and Bowley (5) found that 66% and 90% of the sera from the mothers delivering babies with HDFN due to anti-A and anti-B, respectively, contain IgG antibodies with a titer greater than 256. They also found that 100% of the sera from group O mothers who previously had delivered a group A or group B baby contained IgG2; 97% of the sera contained IgG1, 41% contained IgG4, and 38% contained IgG3 anti-A/B. Destruction of red cells occurs when the sensitized red cells adhere to the Fc receptors of phagocytic cells, such as the splenic macrophages in the foetus. The IgG1 and IgG3 antibodies are known to have the strongest adhering activity (6). The rate of haemolysis and severity of disease are determined by the IgG subclass, amount of antibody, and the number of antigenic sites on the red cells (2, 6, 7). The subclasses IgG1 and IgG3 are more efficient at causing haemolysis than IgG2 and IgG4. As IgG1 is transported across the placenta earlier and in larger amounts than IgG3, IgG1 is associated with more severe disease (7). However, the IgG subclass for this case was not ascertained due to limited resources. The IgG subclass would have been very useful in this case to ascertain the stand-alone contribution of ABO incompatibility to the clinical presentation of our case.

There has been much discussion in the literature regarding why the DCT in ABO HDFN is often weakly positive or even negative. Suggestions on the negative DCT in the baby includes pinocytosis of antigen-antibody complexes, low number of A and B antigenic sites in the fetal RBCs and deficiency of branched chains on the foetal RBC membrane which reduce the antibody binding strength (3, 8). It was also found that blood drawn after 24 hours of age, when the baby begins to show symptoms of disease, usually shows a negative direct Coombs test (8, 9). This is due to the maximum haemolysis occurring at the time of birth and this subsequently diminishes when the maternal antibody concentration in the infant's circulation begin to decline (10). Negative DCT at delivery can also occur if the diseased baby has received an intrauterine transfusion (9).

Although neonatal hyperbilirubinaemia may develop with ABO incompatibility, hydrops is not noted to occur and anaemia at birth is usually mild (4). Therefore, the diagnosis of hydrops foetalis resulting from ABO incompatibility requires that the other aetiologies of non-immune hydrops be considered and to look for other co-existing haematological conditions. In this case, the baby girl had an initially low normal G6PD enzyme activity level. Her cord blood screening with the fluorescence spot test (FST) was normal. Our lab has commenced routine screening of female newborn infants for G6PD deficiency in view of the limitations of the FST method (11). G6PD functions to oxidize glucose-6-phosphate and reduces NADP at the same time. The G6PD gene is expressed in all tissues but the effect of its deficiency is most severe in the erythrocytes, rendering them susceptible to oxidative damage (12). Therefore, the most common clinical manifestation of G6PD deficiency is hyperbilirubinaemia. This condition alone has not been associated with significant neonatal anaemia or hydrops foetalis.

However, both ABO blood group incompatibility and G6PD deficiency are frequently associated with neonatal hyperbilirubinaemia. We speculate that a combination of these two conditions in a newborn would result in a higher rate of haemolysis and hyperbilirubinaemia than in neonates with only one of these conditions. This may explain the hydrops foetalis that occurred in this baby. Conversely, Kaplan et al. (13) found that neonates with combined ABO incompatibility and G6PD deficiency had a similar incidence of haemolysis and hyperbilirubinaemia when compared to neonates with either one of these conditions: ABO-incompatible and G6PD deficient group (13/29, 45%), ABO-incompatible only (44/82, 54%) and G6PD deficient only (45/121, 37%). They postulated that other independently acting icterogenic mechanisms were most likely responsible for the lack of the additive effect. However, this observation could be affected by the lack of patients with combined ABO-incompatibility and G6PD deficiency. The G6PD enzyme activity and genotype of their patients were also not determined.

In summary, the instructive nature of this case report was to highlight that 1) ABO blood group incompatibility causing significant haemolysis *in utero* resulting in hydrops foetalis should lead the clinician to explore other co-existing haematological conditions commonly occurring in that locality such as G6PD deficiency and thalassaemias. 2) A negative direct Coombs test in a baby does not exclude ABO haemolytic disease 3) Resources permitting quantification of the subclass IgG involved in the incompatibility could predict the more severe haemolytic type. This could be an adjunct supportive result to assist the clinician to consider the use of intravenous immunoglobulin in the treatment of these cases in addition to the close monitoring and aggressive phototherapy to be instituted. 4) Borderline G6PD enzyme activity in patients who are actively haemolysing or those who had prior blood or exchange transfusions may be spuriously elevated to the low normal range, suggesting that clinicians be wary of this and repeat or genotyping tests, if available, are warranted.

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