

CASE REPORT

Massive acute haemolysis in neonates with glucose-6-phosphate dehydrogenase deficiency

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Three neonates with glucose-6-phosphate dehydrogenase (G6PD) deficiency are described. All three patients suffered an episode of massive acute haemolysis, in the absence of blood group incompatibilities, infection, or ingestion of oxidising agents known to trigger haemolysis. One patient died, but the other two survived after an exchange transfusion. This highlights that G6PD deficiency in the neonatal period may present with severe anaemia in association with hyperbilirubinaemia.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic enzymatic disorder that affects hundreds of millions of people world wide.^{1,2} Severe hyperbilirubinaemia and kernicterus, the most health threatening consequences of this disorder in the newborn period, have been well documented in many population groups.^{2,3}

Hyperbilirubinaemia in neonates with G6PD deficiency is thought to be secondary to reduced hepatic conjugation and excretion of bilirubin^{1,2,4,5} rather than increased bilirubin production resulting from haemolysis.³ Anaemia is often not reported in G6PD deficient neonates who develop hyperbilirubinaemia or even kernicterus. Massive acute haemolysis is thought not to occur in the absence of trigger factors^{2,6} in the newborn period.

We describe three neonates with G6PD deficiency who developed severe hyperbilirubinaemia requiring exchange transfusion because of massive acute haemolysis, in the absence of any obvious blood group incompatibilities, infection, or ingestion of oxidising agents known to trigger haemolysis by either the mother or infant.

CASE REPORTS

Cases 1 and 2 were monozygotic twins of non-consanguineous Indian parents with an unremarkable medical history. The pregnancy was uncomplicated until spontaneous onset of labour at 28 weeks gestation. Although the mother (blood group O positive) had taken chloroquine (Nivaquine; Rhone-Poulenc Rorer, West Malling, Kent, UK) as malaria prophylaxis in the first trimester, there was no other history of drug or fava bean ingestion.

Twin 1 was a 970 g boy of blood group O positive, direct Coombs test (DCT) negative, and haemoglobin (Hb) concentration 139 g/l at birth. He required intubation, ventilation, and exogenous surfactant for classical respiratory distress syndrome. Vitamin K₁ (Konakion MM; Roche; 0.1 mg) was given intramuscularly. By day 3 his condition had improved sufficiently to be extubated and total parenteral nutrition (TPN) started. Jaundice developed within 24 hours of age requiring phototherapy from day 3. On day 5 there was a sudden fall in Hb from 139 to 95 g/l and a rise in serum bilirubin concentration from 227 to 311 µmol/l despite phototherapy. His condition deteriorated rapidly, so that six

hours later he was anaemic (Hb 45 g/l, white cell count (WCC) $5.6 \times 10^9/l$, and platelet count $325 \times 10^9/l$) with hepatomegaly and poor perfusion. He suffered a profound apnoeic episode from which he did not recover despite full cardiopulmonary resuscitation. Blood film showed fragmented red blood cells but no Heinz bodies. Urinalysis was negative. Before the collapse he was well saturated (oxygen saturation 98%) and not acidotic (pH 7.38). G6PD assay performed on the pre-transfusion blood showed reduced enzyme activity of 56.9 U/ 10^{12} red blood cells (normal = 260–650; Cobas Fara method using Sigma kit; Sigma Diagnostics). At postmortem examination, a small amount of blood was present in the subarachnoid space which was not sufficient to explain the anaemia. There was no evidence of bleeding from any other sites. Full infection screen taken at the time of the collapse—including cultures of blood, cerebrospinal fluid, urine, oropharyngeal secretions for bacteriology—and all cultures taken at the postmortem examination (including umbilical and central venous line catheter tips) was sterile.

Twin 2 was a boy weighing 990 g of blood group O positive with a negative DCT. He also required intubation, ventilation, and surfactant for respiratory distress syndrome. He was extubated on day 4, and TPN was given from days 3 to 8. Cranial ultrasound scans were normal, and a full infection screen was negative. G6PD enzyme assay result showed reduced enzyme activity (33 U/ 10^{12} red blood cells; Cobas Fara method using Sigma kit). Within 24 hours of age he developed jaundice and was given phototherapy for 5 days (maximum serum bilirubin 286 µmol/l). Hb remained stable until day 11 when there was a sudden fall to 78 g/l. Although the infant remained well, a decision was made to perform an exchange transfusion. Before the exchange, the blood counts were Hb 43 g/l, WCC $7.9 \times 10^9/l$, platelet count $174 \times 10^9/l$, with normal blood film morphology. Double volume exchange using whole blood (O negative) was uneventful. Blood cultures performed before and after the exchange were negative. In view of his brother's fate, it was felt that twin 2 was at a high risk of death from an acute episode of haemolysis. Therefore, his Hb was closely monitored. He was started on a regimen of regular blood transfusions to maintain a high proportion of his blood volume as transfused blood and thereby minimise G6PD deficient red blood cells. In spite of this, he required three further transfusions because of haemolysis (increased reticulocytosis of 7.5%; absolute count $243 \times 10^9/l$ (normal (2.0–100.0) $\times 10^9/l$)) in the first 4 months of life. He has subsequently remained well and transfusion free, with no further episodes of haemolysis up to the age of 4 years. Further haematological investigations performed at 1 year of age confirmed G6PD deficiency

Abbreviations: DCT, direct Coombs test; G6PD, glucose-6-phosphate dehydrogenase; Hb, haemoglobin concentration; TPN, total parenteral nutrition; WCC, white cell count

in twin 2 and carrier status of the mother (level = 5.6 U/g Hb (normal 7.0–20.4; Cobas Fara method using Sigma kit), but absence of any other erythrocyte abnormality. This twin subsequently behaved like a G6PD deficient patient with no evidence of chronic haemolysis by 4 years of age.

Drugs administered to both twins were konakion (intramuscular), benzylpenicillin (intravenous), gentamicin (intravenous), cefotaxime (intravenous), vancomycin (intravenous), aminophylline (intravenous), and caffeine citrate (oral).

Case 3 was a term female infant (birth weight 3300 g) of consanguineous Pakistani parents. Maternal blood group was A positive with no abnormal antibodies detected. Pregnancy was unremarkable. Postnatal examination was normal and she was discharged home the next day having received an oral dose of vitamin K₁ (Konakion MM; 1 mg) and established on formula milk feeds. She received no other drugs. She was readmitted on day 6 with increasing jaundice for 48 hours. Clinical signs were negative except the presence of pronounced jaundice. Initial blood results were Hb 118 g/l, WCC $16.8 \times 10^9/l$, platelet count $410 \times 10^9/l$, packed cell volume 0.34, red cell count $3.03 \times 10^{12}/l$, blood group O positive, DCT negative, total serum bilirubin 468 $\mu\text{mol}/l$, and direct serum bilirubin 0. Total serum bilirubin fell gradually over the next 24 hours and the Hb remained stable at 112 g/l, on a regimen of oral and intravenous fluids and phototherapy. Forty eight hours after admission, the Hb suddenly dropped to 52 g/l, the packed cell volume was 0.14, the red cell count $1.25 \times 10^{12}/l$, WCC $20.1 \times 10^9/l$, platelet count $495 \times 10^9/l$, and the blood film showed red cell fragmentation, burr cells, nucleated red blood cells, and Howell-Jolly bodies, and total serum bilirubin increased to 408 $\mu\text{mol}/l$. Heinz bodies were absent and urinalysis was normal. She had received no drugs, and an infection screen performed at the time, including blood and urine cultures, malarial screen, and surface swabs, was sterile. Renal function was normal and there was no evidence of disseminated intravascular coagulation or blood loss. A single volume exchange transfusion was performed. Subsequent course was uneventful and she was discharged home at 12 days of age with an Hb of 124 g/l and serum bilirubin of 115 $\mu\text{mol}/l$. Bloods results taken before the exchange transfusion confirmed the severe G6PD deficiency (G6PD activity was 0.2 U/g Hb (normal 7.0–20.4; Cobas Fara method using Sigma kit). Haemoglobin electrophoresis showed no evidence of haemoglobinopathy, and pyruvate kinase activity was normal. She was reviewed at 2 months of age having remained well with a stable full blood count and normal blood film morphology.

DISCUSSION

G6PD is required for the generation of NADPH, which maintains glutathione in the reduced form, to counteract the day to day oxidant stresses on the erythrocyte. Although G6PD deficiency affects all cells, its primary effects are haematological because the erythrocyte has no alternative source of NADPH. It is inherited in an X linked fashion with, male hemizygotes and female homozygotes invariably more severely affected than female heterozygotes.¹

Hyperbilirubinaemia resulting from G6PD deficiency is well documented in the newborn period²; however, its pathogenesis is not completely understood. Although, deficiencies in the hepatic bilirubin conjugation and elimination process play a major part in the pathogenesis of hyperbilirubinaemia,^{1 2 4 5} haemolysis of G6PD deficient erythrocytes also has a role.^{7–9} The absence of frank anaemia in G6PD deficient infants with severe neonatal jaundice is often interpreted as indicating absence of increased rates of haemolysis. However, there is no doubt from reports of trigger factor induced acute haemolysis^{10 11} and studies on haematological markers of haemolysis^{7–9} that haemolysis occurs at

higher rates in neonates with G6PD deficiency than in G6PD normal neonates. Haemolysis in neonates with G6PD deficiency is usually reported to be secondary to trigger factors and often mild to moderate in relation to the degree of hyperbilirubinaemia,^{7 12} and not commonly associated with anaemia. Massive acute haemolysis in the newborn period, resulting in sudden anaemia, in the absence of trigger factor(s) in either the mother or the infant, is rare.

Although most newborn infants with G6PD deficiency will be free of haemolytic problems, a few are potentially at risk for development of severe hyperbilirubinaemia and anaemia. Certain G6PD mutation variants, seen in some racial groups, may increase the susceptibility to severe haemolysis,^{13–15} although this genetic analysis was not performed in our three cases. G6PD deficiency in a premature infant is especially handicapping. Normal premature infants have shortened erythrocyte survival,¹⁶ which, coupled with G6PD deficiency, makes the erythrocyte particularly vulnerable to oxidative injury.

Furthermore, factors other than oxidising drugs and infections may precipitate haemolysis in G6PD deficient newborns. Neonatal haemolysis in G6PD deficiency has been well documented with exposure to fava beans¹⁷ and with naphthalene in mothballs.¹⁸ In our three cases, thorough questioning revealed no history of fava bean ingestion by any of the mothers or exposure to mothballs in any of the babies. Furthermore, neither the infants nor their mothers had received any agents associated with haemolytic episodes in G6PD deficient subjects, except vitamin K.¹⁹ It is impossible to state with certainty whether the doses of vitamin K received by these patients influenced the course of the haemolysis. This is unlikely,²⁰ however, as the episodes of severe haemolysis did not occur until 5–11 days after the vitamin K dose. None of the three patients received supplementary vitamin C, and none had evidence of Heinz bodies or haemoglobinuria, making this as cause of haemolysis extremely unlikely.²¹ In case 2 the persistent anaemia in the first 4 months of age was associated with increased reticulocytosis (7.5%) and not due to erythropoietic shutdown which occurs in premature infants, although this may have contributed to the severity and acuteness of the anaemia as a consequence of haemolysis. As all three patients were healthy neonates, with no evidence of gastrointestinal disease or infection, haemolysis associated with T cell activation^{22–24} would have been highly unlikely, although this was not specifically tested. None of the infants were acidotic or hypoxaemic at the time of acute haemolysis. No other obvious factors that may have precipitated the episodes of haemolysis could be identified. The likelihood that such factors were present but not detected is very small, because the infants were observed in hospital and perinatal drug ingestion was known.

These three cases give support to the theory that massive haemolysis, although rare, does occur in neonates with G6PD deficiency, even in the absence of obvious precipitating factors. G6PD deficiency is no longer a condition limited to the boundaries of developing countries. Current ease of travel, migration of population groups, and intermarriage has allowed the penetration of the G6PD deficiency gene into populations and geographical areas far away from its places of origin and has resulted in cosmopolitan neonatal nurseries. It is in these populations where both the doctors and public are unfamiliar with the clinical manifestations and dangers of G6PD deficiency that catastrophic complications of G6PD deficiency are likely to occur.

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