Severe late onset anaemia following intrauterine transfusion

Introduction

Rhesus (Rh) incompatibility is known to cause severe haemolysis and hyperbilirubinaemia of prenatal onset. The pathological process occurs when an Rh-negative mother is exposed to Rh-positive fetal red blood cells, and develops Rh antibodies. Maternal Rh anti-D antibodies cross the placenta into the fetal circulation and attach to Rh antigen on fetal erythrocytes. This results in various pathophysiological manifestations ranging from mild haemolytic anaemia through to fetal hydrops or stillbirth. Prolonged haemolysis leads to severe anaemia, which stimulates fetal erythropoiesis in the liver, spleen, bone marrow, and extramedullary sites including the skin and placenta (McMillan et al, 2006).

With the availability of anti-D immunoglobulin and intrauterine transfusion these severe sequelae are far less commonly seen in current neonatal practice (Smits-Wintjens et al, 2008). This article presents a case of a Rh-sensitized neonate, treated by intrauterine transfusion, who developed profound and prolonged late onset postnatal anaemia associated with transient suppression of haematopoiesis.

Discussion

This infant was born with a normal haemoglobin level subsequent to intrauterine transfusion. There was evidence of ongoing haemolysis within the first 3 weeks. Beyond this point the main clinical issue was falling haemoglobin levels caused by continuing haemolysis combined with failure of erythropoiesis, not detected until blood testing became possible at 6 weeks of age. Prolonged suppression of reticulocyte response of up to 15 weeks has been described in infants who received intrauterine transfusion (Dorn et al, 2010).

This so-called 'hyporegenerative anaemia' is characterized by an ineffective erythropoiesis of the newborn, as evidenced by a lack of fetal red blood cells in peripheral blood and low or absent reticulocytes. This condition is mainly seen in patients who have received several intrauterine transfusion,

Table 1. Prenatal anti-D titres

Time of gestation	Anti-D titres
14 weeks	13.20 IU/litre
15 weeks	13.40 IU/litre
18 weeks	12.10 IU/litre
20 weeks	13.60 IU/litre
30 weeks	11.50 IU/litre
33 weeks	10.80 IU/litre

Table 2. Prenatal haemoglobin levels

Timing of intrauterine transfusion	Pre-transfusion haemoglobin (g/litre)	Post-transfusion haemoglobin (g/litre)
22+3 weeks	107	159
25+4 weeks	65	184
29+1 weeks	82	170
32+4 weeks	103	148
Anti-D was not given at any point		

CASE REPORT

A female infant was delivered by elective caesarean section at 35 weeks' gestation because of severe rhesus incompatibility. She had normal Apgar scores of 9 (1 min), 9 (5 min) and 10 (10 min). Her birth weight was 2.74 kg.

The mother was G_3P_{1+1} blood group B Rh-negative; anti D+ antibodies were detected. Her previous pregnancy ended following delivery of a stillborn baby at 31 weeks' gestation following severe complications of rhesus isoimmunization despite receiving anti D-prophylaxis during that pregnancy. In the current pregnancy, intrauterine transfusion had been given on four separate occasions for severe fetal anaemia. Anti-D antibody titres and timing of intrauterine transfusion are shown in *Tables 1* and *2*.

The haemoglobin level at birth was 143 g/litre. She was noted to be jaundiced on the first postnatal day, and the bilirubin level remained just below the exchange transfusion line for the first 24 hours of life. The infant was commenced on phototherapy immediately after birth; serum bilirubin levels settled below the phototherapy treatment level after 24 hours. Serial haemoglobin, reticulocyte count and serum bilirubin levels are highlighted in *Table 3*.

During follow up in the paediatric clinic at 4 weeks, the infant was noted to be very pale with a heart rate of 160/min at resting state. For technical reasons no blood sample could be obtained from 3–6 weeks of age, at which the haemoglobin level was 33 g/litre, serum bilirubin level was elevated at 167 µmol/litre and the reticulocyte level had reduced to $6x10^9$/litre, all suggesting continuing haemolysis together with myelosuppression. After an urgent blood transfusion the haemoglobin level rose to 76 g/litre and she was discharged home the next day.

The infant was closely monitored with weekly blood investigations; the haemoglobin levels gradually stabilized without the need for any further blood transfusions. The reticulocyte response remained inappropriately low in relation to the degree of anaemia until the postnatal age of 10 weeks. Routine blood tests were stopped after 20 weeks when the haemoglobin level was 108 g/litre. At the last clinic follow up the infant was reported to be thriving well and developing normally. The serial haematological findings are shown in *Figure 1*.

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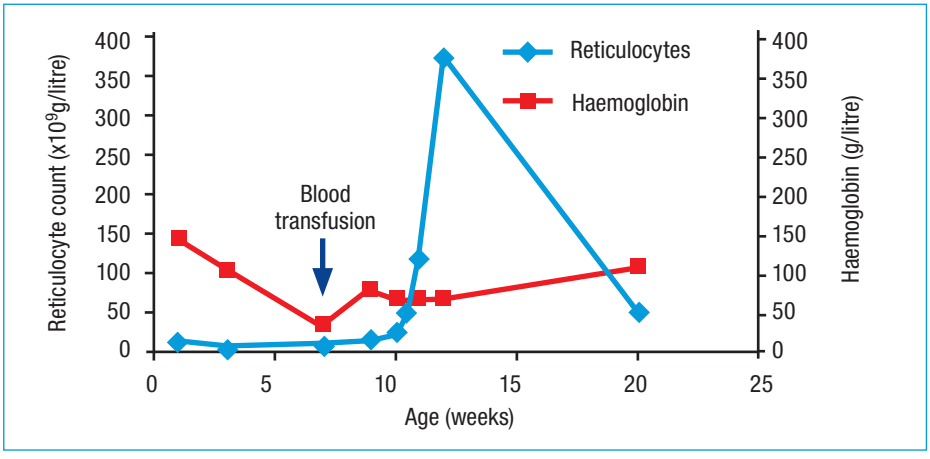
Table 3. Postnatal haemoglobin, reticulocyte and serum bilirubin levels

Age (weeks)	Reticulocyte count (x10^{9}g/litre)	Haemoglobin (g/litre)	Bilirubin (µmol/litre)
Birth		143	73
1	12	142	178
3	3	103	243
6	9	33	167
7	14	76	39
8	20	68	45
9	49	64	47
10	116	64	120
12	376	67	116
18	49	108	7

Figure 1. Postnatal serial haematological findings.



but the precise underlying pathological mechanisms remain unclear. Besides ongoing haemolysis, bone marrow suppression from intrauterine transfusion and erythropoietin deficiency have been considered as causative mechanisms.

Early neonatal anaemia as a result of severe haemolysis is well described and clinicians should remain highly vigilant for this in patients with Rh incompatibility (Louis et al, 2010; Roda et al, 2012). Treatment with prophylactic immunoglobulin therapy in early onset Rh incompatibility has been reported and is practiced in some centres.

Rh haemolytic disease can be complicated in some cases by prolonged postnatal anaemia with an extended need for monitoring with full blood count, combined with postnatal packed red blood cell transfusion if judged necessary. Late onset Rh incompatibility can present with features of poor feeding, lethargy, pallor, apnoeas, and seizures which can mimic sepsis-like episodes and are sometimes treated as such (Mitchell and James, 1999). It is vital that a full blood count is performed early in such cases and blood transfusion started without delay.

This infant had erythroid hypoplasia most likely secondary to bone marrow suppression following intrauterine transfusion. Transient erythropoietin deficiency was probably present. The concept of the regulation of erythropoiesis is based on the theory that erythropoietin stimulates red blood cell production through its effects on the erythropoietin sensitive stem cell, on DNA synthesis in the erythroblast, and on the release of reticulocytes (Palis and Segel, 1998). Erythropoiesis markedly decreases during the first week of extrauterine life.

Conclusions

Clinicians should remain alert to the fact that where intrauterine transfusion has been performed, the infant should be monitored closely for haemoglobin level and reticulocyte count postnatally until such time that both become stable. This may be necessary for several months even if normal haemoglobin levels were present initially at birth and at the time of discharge from hospital. BJHM

LEARNING POINTS

- Rhesus disease can cause significant anaemia at any time from the second trimester to several months after delivery, but the pathophysiological mechanisms vary.
- Early anaemia from rhesus disease is the result of haemolysis.
- Anaemia from rhesus disease in the first few weeks of postnatal life may be from continuing haemolysis, and haemoglobin levels should be monitored carefully.
- When intrauterine transfusion is needed for rhesus disease there may be prolonged suppression of erythropoiesis.
- Intrauterine transfusion for rhesus disease may cause severe prolonged anaemia as a result of suppression of erythropoiesis, even if there is little active haemolysis.
- In cases of intrauterine transfusion for rhesus disease, haemoglobin and reticulocyte count should be monitored closely until levels are stable.

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