CASE REPORT

Bilateral cystic encephalomalacia following multiple intrauterine transfusions for anti-Kell isoimmunisation

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SUMMARY

Fetal and neonatal haemolytic diseases result from maternal allo-immunisation to fetal antigens. Maternal antibodies cross the placenta causing red cell haemolysis, resulting in fetal anaemia and, in severe cases, hydrops and perinatal death. Intravascular intrauterine blood transfusion (IUT) has markedly reduced perinatal mortality and is now a standard procedure. IUT is considered to be a safe procedure with fetal loss rate reported to be less than 5% and no reported increase in the rate of neurodevelopmental impairment. In this report, we are presenting a case of bilateral cystic encephalomalacia following fetal anaemia secondary to anti-Kell iso-immunisation treated with multiple IUTs. Such a significant adverse outcome following IUT for anti-Kell iso-immunisation has not been reported in the literature. This case highlights the need for appropriate parental counselling and routine postnatal head ultrasound in all babies delivered following multiple IUTs.

BACKGROUND

Fetal and neonatal haemolytic disease results from maternal immunoglobulin G (IgG) crossing the placenta to the fetal circulation and causing destruction of the fetal red cells.¹

The Kell blood-group system is one of the major antigenic systems in human red cells.² Since the introduction of effective prophylaxis against allo-immunisation to the D antigen of the Rh blood-group system, anti-Kell antibodies have accounted for 10% of the cases of antibody-mediated severe fetal anaemia.²

Intrauterine blood transfusion (IUT) is an effective method in the management of neonatal allo-immune anaemia.¹ The incidence of neurodevelopmental impairment in children treated with intrauterine transfusion is low.¹

Many studies have looked at the long-term outcome after treatment of fetal anaemia by intrauterine transfusion to identify the risk factors associated with poor neurological outcome.^{1–5}

CASE PRESENTATION

A 33⁺ weeks male infant was born by an elective C/S due to fetal anaemia. At 17 weeks gestation, the mother was found to have a high level of anti-Kell antibodies reaching a maximum titre of 1:1000 by 32⁺ weeks. Fetal haemoglobin gradually dropped to 6.7 g/dL and the baby received his first intrauterine transfusion at 21 weeks gestation. A further four transfusions were performed before birth, the last one around 10 days prior to delivery.

The lowest fetal haemoglobin (Hb) level recorded was 5.6 g/dL at 29 weeks gestation.

The baby was born in good health and did not require resuscitation. In view of moderate respiratory distress, he was started on continuous positive airway pressure, which was gradually weaned over the first 2 days of life. The baby's initial Hb was 10.9 g/dL. His serum bilirubin level was 88 µg/dL at birth with a negative direct antiglobulin test. He was started on triple phototherapy and was given one dose of intravenous immunoglobulin in view of the need for multiple intrauterine transfusions. The serum bilirubin was well controlled with phototherapy reaching a maximum of 147 µg/dL on day 3 of life.

INVESTIGATIONS

Cranial ultrasound scan (USS) was performed on day 1 as a baseline, although there was no clear indication for this. USS showed bilateral cystic changes. A brain MRI was therefore carried out at 4 days of age, which showed extensive bilateral cystic encephalomalacia. Neuroradiology opinion was sought from a tertiary neuroradiologist. The scan was reported to show marked atrophy with cystic infarctions with atrophied basal ganglia and thalami (figure 1A,B). It was felt that these lesions were possibly related to the fetal anaemia and intrauterine transfusions.

OUTCOME AND FOLLOW-UP

The parents were counselled about the imaging results and guarded prognosis was given with regard to neurodevelopmental outcome. The baby was discharged from the neonatal unit at 2 weeks of age. Outpatient follow-up at 11 months of age revealed upper motor neuron signs and the baby was diagnosed with quadriplegic cerebral palsy with microcephaly.

DISCUSSION

Untreated fetal anaemia can lead to hydrops fetalis and perinatal death. IUT was first performed by Liley using the intraperitoneal technique and has been a major advance in treatment of fetal anaemia with a perinatal survival rate now exceeding 95%.¹

Different studies have looked at the long-term neurodevelopmental outcome after IUT in fetal anaemia/hydrops. The largest was the *LOTUS study 2012*.¹ It evaluated the outcome of 1284 IUTs on 451 fetuses. Neurological follow-up was completed on 291 children between the ages of 2 and 17 years (median age 8.2 years). The incidence of severe neurodevelopmental outcome was in line with the

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Figure 1 (A) MRI performed on day 4 at 34⁺¹ weeks postmenstrual age. T1-weighted image in axial plane showing bilateral established infarction of both hemispheres, more severe on the right. This is mainly but not exclusively in the territory of the middle cerebral arteries. The ventricles are mildly dilated posteriorly and there is marked widening of the extracerebral space. There is some high signal intensity on T1 at the edge of the infarct consistent with calcification (long arrow). Cortical folding in the left sylvian fissure appears abnormal, suggestive of developing polymicrogyria (short arrow). (B) T2-weighted image in coronal plane showing bilateral established infarction of both hemispheres with marked widening of the extracerebral space.

Dutch normative population (2.3%). Fetal hydrops was the only risk factor independently associated with neurodevelopmental impairment (OR 11.2; 95% CI 1.7 to 92.7).

In a smaller retrospective cohort study by Weisz *et al.*³ 54 fetuses were treated with 154 IUTs. Long-term follow-up was carried out on 40 children at a median age of 5 years. The study compared the neurological outcome of babies with severe anaemia to those with mild to moderate anaemia and found no difference in short-term or long-term neurological outcome. The author therefore concluded that despite severe fetal haemolytic disease, normal developmental outcome can be expected for children treated with IUTs.

An earlier study by Grab *et al.*⁴ confirmed a similar outcome. In this study, the neurological outcome after 136 IUTs performed on 43 fetuses was assessed. Eleven of the 43 fetuses had

some degree of hydrops and the lowest pretransfusion Hb was 1.5 g/dL. The study reported no observed moderate or severe neurological disabilities in any of the survivors even when hydrops or extremely low haemoglobin was present.

Leijser *et al.*⁵ studied the cranial ultrasound findings in neonates treated with IUT for fetal anaemia. Ultrasound images of 127 neonates treated with IUT for fetal anaemia were retrospectively studied. Fifty-seven per cent of the neonates had ≥ 1 abnormality on their ultrasound. Examples of these abnormalities include change in ventricular size and/or shape, intraventricular haemorrhage (IVH), periventricular echodensities and echodensities in the basal ganglia and thalami. Neurological follow-up was carried out at 1.9–2.2 years. Neurological outcome was adverse in five infants. Presence of brain USS abnormalities was not significantly related to any of the perinatal parameters or to neurological outcome.

On literature review, most of the studies confirmed that IUT is considered to be a safe procedure to treat fetal anaemia. *None of the studies showed an increased incidence of long term disability or higher incidence of cerebral palsy.* We have not come across any report of such a significant adverse outcome following a non-hydrotic intrauterine course requiring IUT. Our case did not have any of the risk factors mentioned in the above studies that might increase the incidence of long-term neurodisability. The baby was not hydrotic at any stage during pregnancy. His lowest Hb was 5.6 g/dL (much higher than the figures quoted in the other studies). All IUT procedures went smoothly and he was born in good general health at 33⁺⁴ weeks gestation.

The reason for the poor outcome of our case is not clear. The two potential documented causes are fetal anaemia or multiple IUTs. As discussed earlier, the lowest Hb in our case was much better than the reported figures and the baby had no signs of hydrops at any stage. Multiple IUTs could potentially have accounted for the poor outcome. This may be related to the changes in cerebral haemodynamics augmented by transient hypervolaemia and/or hyperviscosity. This is in keeping with the study by Leijser *et al.* Other potential causes such as twin-to-twin transfusion or intrauterine infections were not pertinent in our case.

Learning points

- Non-invasive investigation such as cranial ultrasound should be performed in all babies who have received intrauterine transfusion.
- Ultrasound findings can be used to assess the need for further MRI studies.
- This approach will help foster larger studies with neuroimaging outcome for babies who have received intrauterine transfusion during fetal life. This will have implications while counselling parents who are due to start treatment with intrauterine blood transfusion (IUT) and on improving surveillance for neonates delivered following IUT.

Contributors The case was selected by RG. Most of the writing was done by HE with some contribution from MN. RG reviewed the final work. MR provided the report for the MRI.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Verduin EP, Lindenburg IT, Smits-Wintjens VE, *et al.* Long-term follow up after intra-uterine transfusion S; the LOTUS study. *Am J Obstet Gynecol* 2012;141:e1–8.
- 2 Vaughan JJ, Manning M, Warwick RM, *et al.* Inhibition of erythroid progenitor cells by anti-Kell antibodies in fetal alloimmune anemia. *N Engl J Med* 1998;338:798–803.
- 3 Weisz B, Rosenbaum O, Chayen B, *et al.* Outcome of severely anaemic fetuses treated by intrauterine transfusions. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F201–4.
- 4 Grab D, Paulus WE, Bommer A, *et al.* Treatment of fetal erythroblastosis by intravascular transfusions: outcome at 6 years. *Obstet Gynecol* 1999;93:165–8.
- 5 Leijser LM, Vos N, Walther FJ, *et al.* Brain ultrasound findings in neonates treated with intrauterine transfusion for fetal anaemia. *Early Hum Dev* 2012;88:717–24.

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