Severe rhesus iso-immunization successfully treated with apheresis and azathioprine

Report of 2 cases

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Summary

Two patients are described in whom previous fetal loss had occurred due to rhesus (Rh) disease. In both patients apheresis was performed from a gestational age of 25 weeks in an attempt to remove excessive antibodies. In addition, production of new antibodies was suppressed by the administration of prednisone and azathioprine. A reduction in the antibody titres was accomplished although this was not reflected by a marked decrease in amniotic fluid bilirubin levels. The patients were delivered at gestational ages of 32 and 33 weeks since fetal lung maturity had then been demonstrated. Both babies were surprisingly little affected by the Rh disease and only one exchange transfusion was necessary for each. Neonatal follow-up for 2 years and 1 year respectively revealed no fetal abnormalities.

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Treatment of severe fetal haemolytic disease in early pregnancy is extremely difficult and results are unsatisfactory. Intra-uterine transfusion is an accepted method of therapy but the fetal survival rate is only 43 - 53%.[1] By excluding fetuses with hydrops or ascites and doing transfusion under direct ultrasound guidance, Frigoletto *et al.*[1] managed to improve the survival rate to 62%. Excellent results were also obtained by the Winnipeg group using intra-uterine transfusion under ultrasound guidance.[2]

It is, however, extremely difficult for obstetrics departments which do not encounter this problem frequently to obtain adequate experience in this technique. Successful ultrasound-guided intravenous fetal transfusion has been reported but it is still too early to comment about its place in the treatment of fetal haemolytic disease.

Plasmapheresis as a method of treatment has been reported in several studies.[3-6] In some studies replacement with fresh-frozen plasma was used. Although many studies report that plasmapheresis caused reduction in antibody titres, fetal outcome unfortunately did not similarly improve since fetal survival was only 73% when apheresis was initiated at 28 - 34 weeks.[7] Another way of treating auto-immune disease in pregnancy would be to suppress antibody production, as for patients after renal transplantation. However, as far as we are aware, immunosuppression for rhesus (Rh) disease has not yet been reported. In severely affected patients the combined use of apheresis to remove antibodies and immunosuppression to retard their production seems to be a possible way of treating this problem in early pregnancy. Two such cases are reported.

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Case reports

Case 1

A 26-year-old woman, para 3, gravida 6, had had an uneventful first pregnancy. Screening for antibodies was not done and she received no anti-D immunoglobulin although the baby was group A Rh-positive. Her second pregnancy ended in intra-uterine death at 20 weeks. During the third pregnancy rising anti-D antibody titres were discovered and it was necessary to deliver the baby at 35 weeks. Five exchange transfusions were performed in the early neonatal period, but the infant died on the 3rd day; the exact cause of death was uncertain. The fourth pregnancy terminated in a spontaneous abortion at 10 weeks. During the fifth pregnancy high antibody titres were found and the condition of the fetus was regularly assessed by amniocentesis and difference in optical density (Δ OD) measurements. Initial values fell just below the Whitfield's action line but at 33 weeks the Δ OD had crossed this line. As fetal lung maturity had been reached at this stage, the baby was delivered. Birth weight was 1 780 g, the blood group AB positive and the Coombs test positive. The cord bilirubin level was 141 mmol/l and the packed cell volume 23. After a total of 6 exchange transfusions the infant made an uneventful recovery and is presently in good health.

The patient's sixth pregnancy occurred approximately 2 years later. Amniocentesis performed at 25 weeks demonstrated an Δ OD in the upper zone of the Liley chart (Fig. 1). Since the patient had been informed about the possibility of apheresis during her previous pregnancy and again before she decided to have another baby, she knew very well what the implications were.

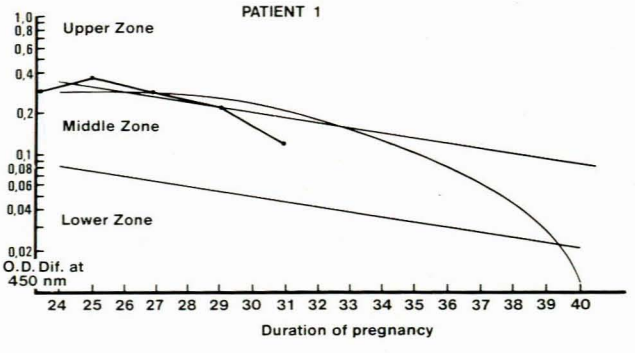

Fig. 1. Case 1 — improvement in amniotic fluid bilirubin levels is clear.

The patient was admitted to hospital and apheresis and replacement with 0,5 litre of group-specific plasma and 4% albumin was started 3 days after amniocentesis. Higher volumes of plasma replacement would have been desirable, but the patient showed adverse reactions to volumes greater than 0,5 litre. Initially 3 l/d were exchanged but since the desired effects were not obtained this was soon increased to 4 l/d. Antibody titres before and after apheresis are shown in Fig. 2.

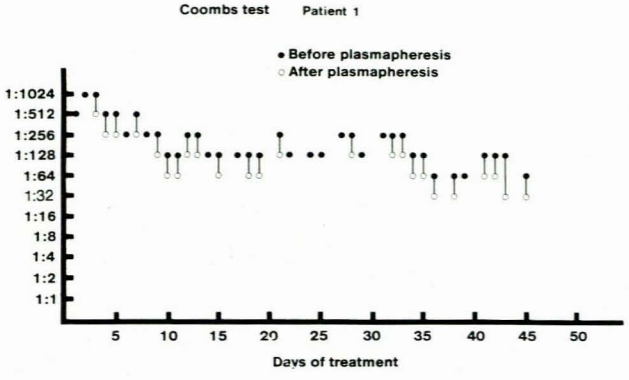

Fig. 2. Case 1 — gradual improvement in antibody titres.

Daily apheresis was performed for 8 days by when it was clear that no decline in antibody titre was being achieved. It was then decided to add prednisone 30 mg/d as a bolus immediately after each day's treatment and azathioprine 50 mg 3 times daily to the therapy. Again the possible dangers were carefully explained to the patient as well as the alternative of intra-uterine transfusion. Daily aphereses were continued for another week.

Antibody levels then gradually started to decline. A repeat amniocentesis at 27 weeks demonstrated that the Δ OD had declined from the previous value of 0,36 to 0,288 (Fig. 1). As the fetal condition seemed to have improved, and to relieve the patient from daily venepunctures, apheresis was skipped on every 3rd or 4th day. Antibody titres now remained constant. Amniocentesis at 29 weeks demonstrated a further decline in the Δ OD and a lecithin/sphingomyelin (L/S) ratio of 1,4. Azathioprine was now reduced to 50 mg twice daily.

The fetal condition was further assessed by daily fetal movement recordings and non-stress tests 3 times a week. On admission to hospital there were almost no fetal movements although the patient had felt strong and frequent movements earlier in the pregnancy.

The first few non-stress tests were non-reactive. However, soon after the beginning of apheresis fetal movements began to increase and the non-stress tests became reactive. All amniocenteses were done under direct ultrasound guidance. Serial biparietal diameters confirmed adequate growth and no signs of hydrops fetalis could be found at any stage.

Another amniocentesis was done at 31 weeks. A further decline in the Δ OD was noticed. Although the L/S ratio was 2, phosphatidylglycerol values were still negative. As the fetus did not seem to be in jeopardy and as the gestational age was only 31 weeks, it was decided to allow the pregnancy to continue. At 32 weeks the patient suddenly experienced severe nausea, nystagmus, headache and diplopia. Apheresis was discontinued. Apart from a low serum calcium level, all results of coagulation studies were within normal limits.

Since fetal lung maturity had been achieved it was decided not to continue with the apheresis and azathioprine. After a rest period of 24 hours a caesarean section was performed. Apgar scores of the female infant at 1 and 5 minutes were 8 and 9 respectively and the birth weight was 2020 g. Apart from a moderate splenomegaly, no signs of extramedullary erythropoeisis could be found. The cord haemoglobin level was 8,2 g/dl and the indirect serum bilirubin value 90 mg/dl. The Coombs test was positive and the blood group A Rh-positive. Phototherapy was commenced immediately after delivery and one exchange transfusion was performed.

The mother's postoperative course was uneventful. Opthalmic consultation suggested that a vascular lesion could have caused an isolated paralysis of the superior rectus muscle of her left eye. The nystagmus was probably caused by a thrombosis of the left labyrinthine artery. These problems very gradually improved after discharge from hospital. Follow-up of the baby at 3 months revealed no abnormalities.

Case 2

A 28-year-old woman, para 0, gravida 2, had had her first baby in 1982. Although it was known that she was Rh-negative and her husband Rh-positive, antibody levels were determined for the first time at a gestational age of 38 weeks. Because of a high antibody titre, an induction of labour was immediately performed but intra-uterine death occurred soon afterwards. Autopsy of the 3200 g fetus demonstrated extended extramedullary erythropoiesis. The second pregnancy occurred 1 year later. The Coombs antibody titre then was 1:156. Her genotype was c̄de/c̄de and that of her husband CDe/CDe. Amniocentesis was performed for the first time at a gestational age of 25 weeks. Amniotic fluid bilirubin levels fell on Whitfield's action line (Fig. 3). Ultrasound examination demonstrated minimal fetal ascites. Apheresis was immediately commenced and 2500 - 3000 ml plasma were exchanged six times weekly. Immunosuppression, consisting of azathioprine 100 mg and prednisone 20 mg daily, was started.

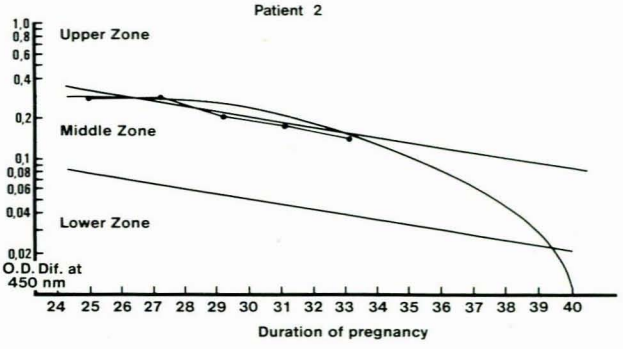

Fig. 3. Case 2 — gradual change in amniotic fluid bilirubin levels.

A second amniocentesis was performed 2 weeks later; bilirubin levels remained high. A small decline was noticed at the third amniocentesis (at 29 weeks). Maternal liver function tests were done every week and results remained within normal limits throughout. Coagulation studies and full blood counts were also done weekly. Fibrinogen levels after each apheresis were moderately depressed and fluctuated between 98 and 177 mg/dl. Haemoglobin levels declined from 11,8 to 9,9 g/dl. All the other aspects of the coagulation profile and full blood count remained within normal limits. The fetal condition was assessed by serial ultrasound examinations, fetal movement charts and non-stress tests. At no stage was there any indication of fetal jeopardy. Amniocentesis performed at 31 weeks demonstrated an L/S ratio of 1,9 but since phosphatidylglycerol was still not present and the condition of the fetus was satisfactory, it was decided to allow the pregnancy to continue for a further 2 weeks in spite of the high bilirubin levels.

By 33 weeks the patient had had 39 aphereses. Anti-D antibody titre declined from 1:256 initially to 1:64 immediately before delivery (Fig. 4). The titre of anti-C antibodies remained low throughout. Quantification of the anti-D antibodies demonstrated that the values declined from 52,3 IU to 3,3 IU (Fig. 5). By this time the L/S ratio was 2.

Since neonatal survival after 33 weeks was regarded as excellent, the patient was delivered by caesarean section after a 2-day rest period from apheresis had been allowed. A male infant weighing 2250 g was delivered in a satisfactory condition. The 1-, 5- and 10-minute Apgar scores were 9, 10 and 10 respectively. Neonatal examination demonstrated that the liver was 2 cm enlarged. The

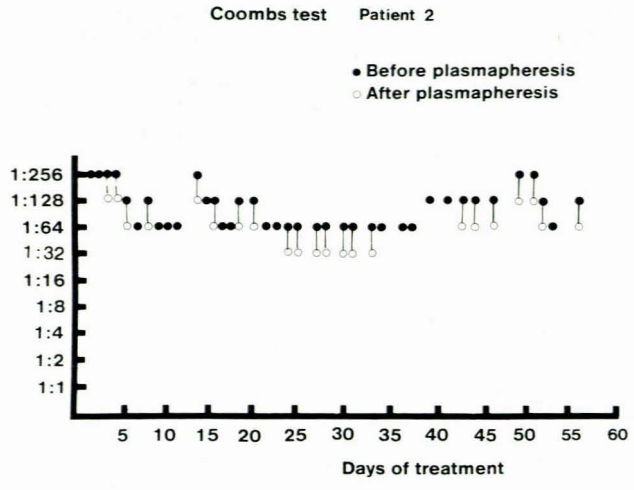

Fig. 4. Case 2 — improvement in antibody tires.

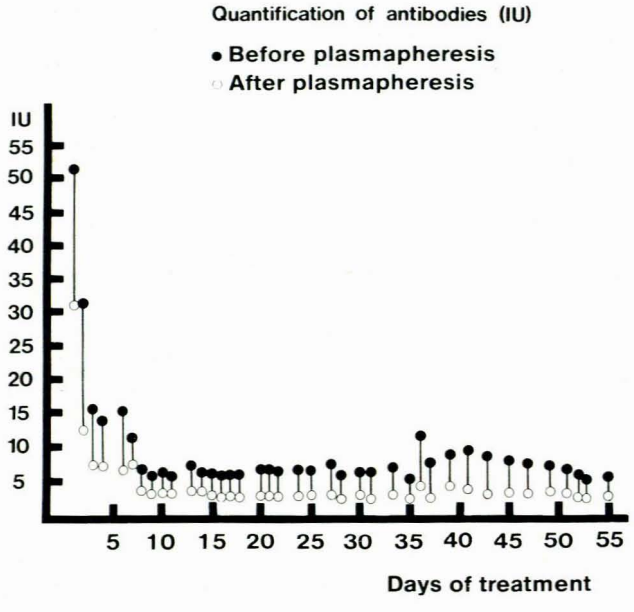

Fig. 5. Case 2 — quantification of antibodies demonstrates a sudden and persistent reduction.

spleen was not palpable. The cord bilirubin level was 50 μmol/l and the haemoglobin value 12,5 g/dl. The blood group of the baby was AB, CDe/c̄de. Both anti-C and anti-D antibodies were present. One exchange transfusion with 400 ml fresh blood was performed on the 1st day. The baby developed grade II hyaline membrane disease, which was successfully treated. Apart from phototherapy no further treatment was needed to control neonatal bilirubin levels. Neonatal examination 4 months after birth revealed no abnormalities.

Discussion

The three advantages of a bidirectional approach in the treatment of Rh disease in these patients were: (*i*) a decline in antibody titre towards the end of pregnancy; (*ii*) some decline in the amniotic fluid bilirubin levels as indicated by change in Δ OD; and (*iii*) in case 1 this baby was less affected than the previous one judging by the cord bilirubin and haemoglobin values and the number of exchange transfusions (it could have been expected that a subsequent Rh-positive baby would be more affected if the disease were allowed to follow a natural course).

It is also interesting to note that in both cases, in spite of the high amniotic fluid bilirubin levels, the babies were not severely affected at birth since both received only one exchange transfusion each. Possibly when apheresis is done amniotic fluid bilirubin levels do not accurately reflect the condition of the fetus. It is, however, necessary to note that it may occasionally happen in Rh disease that the latest pregnancy is affected less than the previous one.

Corticosteroids were given for their effects of decreased antibody production, impairment of the antibody red cell interaction and inhibition of macrophage binding of antibody-coated red cells. However, corticosteroids as such seem to be ineffective in the treatment of severe Rh iso-immunization and may falsely lower the Δ OD values of the amniotic fluid.[8]

Although we would generally be extremely careful not to prescribe immunosuppressive drugs unnecessarily during pregnancy, it seems that azathioprine is not associated with adverse fetal effects since it has been used several times during pregnancy in patients with renal transplants.[9] Apheresis in itself carries a risk for the mother.[10] Therapy should therefore not be instituted before careful explanation of complications such as haemorrhage and infection and unless a very clear indication for therapy exists. Since these are the only 2 case reports, definite conclusions regarding the efficacy of this treatment can certainly not be made. However, it is an exciting new approach in patients where intra-uterine transfusion is undesirable or where experience with this technique is insufficient.

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