Case report

Haemolytic disease of the newborn caused by rhesus isoimmunization (anti-c)

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Introduction

Haemolytic disease of the newborn is a condition in which the lifespan of an infant's red cells is shortened by the action of specific antibodies derived from the mother [*1*]. Anti-c is an important rhesus (Rh) antibody that causes haemolytic disease of the newborn with anaemia and high bilirubin levels, which can cause bilirubin encephalopathy (kernicterus) [*1*]. The immune antibodies in the maternal plasma are small molecule immunoglobulins of the IgG subclass and therefore, unlike the naturally occurring large molecule antibodies of the ABO blood group system (IgM), are able to cross the placenta. Haemolytic disease of the newborn can theoretically occur in any situation where the mother lacks a paternally derived antigen that her baby carries on its red cells [2].

Case report

The girl A-L, the third child of unrelated Austrian parents, was born by induced vaginal delivery at 38 weeks gestation in the Department of Gynaecology and Obstetrics in LKH, Salzburg on 3 July 2000. Apgar scores at 1 and 5 minutes were 9 and 10 respectively, birth weight was 3610 g (72th centile). The delivery was induced because the anti-c titre in maternal serum had increased from 1:256 to 1:512.

Family history revealed that the brother of A-L was born at 40 weeks gestation, birth weight 4180 g (> 90th centile) as a healthy neonate at KH Hallein in 1992. Immediately after this first delivery the mother of A-L was transfused two times. The sister of A-L was born at 40 weeks gestation, birth weight 3920 g (90th centile) at KH Hallein on 22 August 1995. On day 1 she was noted to be markedly jaundiced, serum bilirubin was 359 mmol/L and packed volume (haematocrit) was 37%. On day 2 she was urgently admitted to the neonatal department of LKH Salzburg where it was realized that the jaundice was caused by anti-c antibodies (blood group of mother: A, Rhesus factor: positive CCDdee; indirect Coomb test: positive 1:256; Rhesus factor of father: negative ccddee; blood group of the neonate: A, Rhesus factor: negative Ccddee; direct Coomb test: positive ++++). She required phototherapy from days 2 to 4, high-dose intravenous immunoglobulin and 40 mL of concentrat-

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ed erythrocytes. After discharge home 9 days after birth, she needed treatment with erythropoetin to prevent late anaemia due to ongoing haemolysis. At the moment she is a healthy and normally developed girl. The mother was informed that any future pregnancy would be risky, and serial estimations of serum antibodies from the 10th to 12th week of gestation at 2–4 week intervals should be carried out, serial ultrasound should be performed and delivery should be planned at an institution with facilities for exchange transfusion.

A-L became jaundiced 6 hours after birth and was admitted to the neonatal department, LKH Salzburg, for further management. The initial examination revealed jaundice with mild oedema. The bilirubin level was estimated frequently. Eight hours after birth, a blood sample demonstrated a bilirubin level of 154 µmol/L, haematocrit of 48%, and the blood group A, Rhesus factor positive (CcDdee) and direct Coombs test positive (++++). A full infection screen was undertaken and *Escherichia coli* was isolated from the meconium; other tests remained negative.

She was subjected immediately to double phototherapy (BiliBed below, one light above) for a further 4 days. In addition, she received oral phenobarbitone for a further 3 days. She received high doses of intravenous immunoglobulin Octagam (Table 1).

On day 3, the bilirubin was 359 µmol/L and the haematocrit 36% (Figure 1). An urgent exchange transfusion with 252 mL of packed cell volume of O Rh (D) positive washed concentrated red blood cells in the haematocrit region of 50%–55% together with 88 mL of platelets was performed. Exchange transfusion was carried out over 4 hours. Bilirubin level was reduced to 248 µmol/L. Immediately after exchange transfusion she received a third high dose of intravenous immunoglobulin Octagam. She remained under phototherapy for a further 3 days with a progressive decline in the bilirubin level and rise in haematocrit value. The final diagnosis was haemolytic disease of the newborn, Rh isoimmunization (anti-c). She was discharged home 9 days after birth; bilirubin was then 161 µmol/L and the haematocrit 45%. The first follow-up examination was done at the neonatal department of LKH Salzburg 8 days after discharge; bilirubin was 15 µmol/L and the haematocrit 44%.

Discussion

Within the rhesus blood group system the most immunogenic antigens after D are c and E [2–5]. These antibodies are found most usually in women who are Rh (D) positive and lack the c and E antigens, for example those women who have the genotype CDe/Cde like the mother of A-L. Although the molecular genetic basis of the Rh C, Rh c, Rh E and Rh e antigens has recently been clarified [5], little is known about the defects responsible for the lack of C/c and E/e antigen expression in the gene complex defined as –D [6,7]. The management of haemolytic disease of the newborn due to alloimmunization by c antigen is the same as that for Rh (D) and there is, as yet, no way of preventing these conditions [8–10]. Some cases of haemolytic disease of the newborn due to anti-c are as severe as anti-D haemolytic disease of the newborn and may end in hydrops fetalis [8,9]. Kozlowski et al. established that when the anti-c level in the mother is below 75 IU/mL, the fetus is unlikely to be seriously affected and invasive obstetric intervention is unnecessary [5]. Clinical manifestations of haemolytic disease of the newborn range from asymptomatic mild anaemia to hydrops fetalis or stillbirth asso-

Table 1 **Serum bilirubin concentration, haematocrit values and treatment related to postnatal age**

Age		Bilirubin	Haematocrit	Treatment
Hour	Day	µmol/L	%	
0–8	1	154	48	Admission to the neonatal department, LKH Salzburg
9–16	1	286	/	Double phototherapy, Octagam, Luminal
17–24	1	255	43	Double phototherapy
25–32	2	282	44	Double phototherapy, Luminal
33–40	2	308	/	Double phototherapy, Octagam
41–48	2	318	/	Double phototherapy, Luminal
49–56	3	359	36	Double phototherapy, Luminal
57–64	3	263	38	Double phototherapy, exchange transfusion, Luminal
65–72	3	241	44	Double phototherapy, Octagam, Luminal
73–80	4	289	48	Double phototherapy
81–88	4	248	/	Phototherapy
89–96	4	227	/	Phototherapy
97–120	5	183	48	Phototherapy
121–144	6	161	45	Phototherapy
145–168	7	135	/	Phototherapy
169–192	8	111	/	//
>192	9	101	45	Discharge home in good condition
	17	15	44	First follow-up examination, the girl in good condition

/ = no measurement.
// = no treatment.

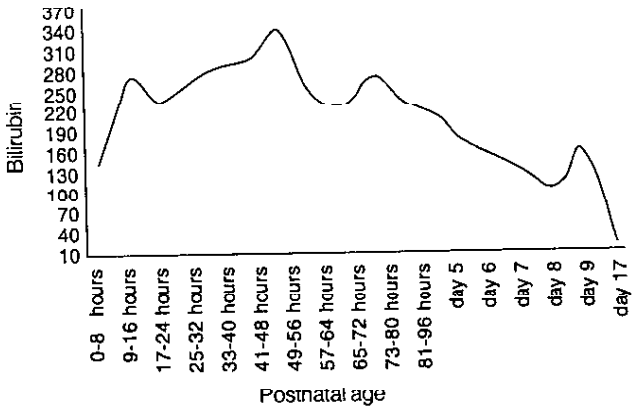

Figure 1 **Serum bilirubin values in µmol/L in relation to postnatal age**

ciated with severe anaemia and jaundice [*1,8*].

The highest bilirubin levels recorded were 572, 559 and 520 µmol/L in newborns with maternal anti-c antagonism [*9,10*]. In the present case study, up-to-date management and effective treatment prevented such high bilirubin levels. Bilirubin neurotoxicity is now a very rare condition in industrialized countries due to effective methods of preventing and treating haemolytic disease of the newborn, and of managing neonatal jaundice. Bilirubin estimations in newborns with haemolytic disease of the newborn should be made frequently in order to institute appropriate treatment before brain injury occurs. With A-L, bilirubin estimations were made often enough to select appropriate therapy. Appropriate therapy was directed to reduce hyperbilirubinaemia (phototherapy, exchange transfusion, enzyme induction, intravenous immunoglobulin) and to prevent anaemia (exchange transfusion, intravenous immunoglobulin, transfusion with red blood cells). Phototherapy is normally started as soon as the baby reaches the nursery, in the hope that the need for exchange transfusion may be reduced or eliminated [*1*]. Double or triple lights are usually used (BiliBlanket or BiliBed below, one or two lights above) as was done in this case. Exchange transfusion removes bilirubin, removes haemolytic antibodies and corrects anaemia [*1–3*]. In this case, exchange transfusion reduced bilirubin level to 248 µmol/L and increased haematocrit to 48%.

Phenobarbitone, 30 mg administered to the mother 3 times daily for 48–72 hours prior to delivery, reduces peak bilirubin levels in the affected neonate. Since there is a latent period of 2–3 days before adequate enzyme induction occurs, treatment is more successful if administered to the mother than if given to the baby after delivery [*1*]. However, the administration of phenobarbitone makes the infant sluggish and may induce other enzymes not beneficial to the preterm neonate, and therefore routine use of phenobarbitone is not recommended [*11*]. With A-L, minimal doses of phenobarbitone were administered for 72 hours to reduce peak bilirubin levels.

High dose intravenous immunoglobulin reduces jaundice in haemolytic disease of the newborn by inhibiting haemolysis [*4,12*]. In this case, three high doses of intravenous immunoglobulin were administered.

Theoretically, alloimmunization by transfusion can occur [*1,10*]. Immediately after the first delivery, the mother of A-L was transfused two times. Theoretically, alloimmunization to other red-cell antigens by transfusion or pregnancy could be prevented in a manner similar to that with anti-D. In practice, it would be very costly and time-consuming to Rh phenotype all women in pregnancy and to produce sufficient quantities of anti-c from male "volunteers" by injection of incompatible blood to produce the appropriate immunoglobulin. Therefore, the best choice is that women of reproductive age receive primary prevention against the development of irregular anti-erythrocyte antibodies by application of a selective blood transfusion policy, bearing in mind the frequency of occurrence of the antigens c, E and K [*10*].

Bilirubin neurotoxicity used to be one of the common causes of cerebral palsy but because of effective methods of preventing and treating haemolytic disease of the newborn and of managing neonatal jaundice, it is now a very rare condition in industrialized countries [*1,8*].

In conclusion, it can be speculated that high-dose intravenous immunoglobulin combined with phenobarbitone, double phototherapy and exchange transfusion may be a potential regimen for the treatment of haemolytic disease of the newborn caused by anti-c antibodies.

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