Case report

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

Z. Felc

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 paternal- ly 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. Agar 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 ccedDee; 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. Rilirubin 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]. Kozłowski 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

<table>
<thead>
<tr>
<th>Age</th>
<th>Hour</th>
<th>Bilirubin µmol/L</th>
<th>Haematocrit %</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-8</td>
<td>1</td>
<td>154</td>
<td>48</td>
<td>Admission to the neonatal department, LKH Salzburg</td>
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<tr>
<td>9-16</td>
<td>1</td>
<td>286</td>
<td>/</td>
<td>Double phototherapy, Octagam, Luminal</td>
</tr>
<tr>
<td>17-24</td>
<td>1</td>
<td>255</td>
<td>43</td>
<td>Double phototherapy</td>
</tr>
<tr>
<td>25-32</td>
<td>2</td>
<td>292</td>
<td>44</td>
<td>Double phototherapy, Luminal</td>
</tr>
<tr>
<td>33-40</td>
<td>2</td>
<td>308</td>
<td>/</td>
<td>Double phototherapy, Octagam</td>
</tr>
<tr>
<td>41-48</td>
<td>2</td>
<td>318</td>
<td>/</td>
<td>Double phototherapy, Luminal</td>
</tr>
<tr>
<td>49-56</td>
<td>3</td>
<td>359</td>
<td>36</td>
<td>Double phototherapy, Luminal</td>
</tr>
<tr>
<td>57-64</td>
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<td>263</td>
<td>38</td>
<td>Double phototherapy, exchange transfusion, Luminal</td>
</tr>
<tr>
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<td>241</td>
<td>44</td>
<td>Double phototherapy, Octagam, Luminal</td>
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<tr>
<td>73-80</td>
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<td>289</td>
<td>48</td>
<td>Double phototherapy</td>
</tr>
<tr>
<td>81-88</td>
<td>4</td>
<td>248</td>
<td>/</td>
<td>Phototherapy</td>
</tr>
<tr>
<td>89-96</td>
<td>4</td>
<td>227</td>
<td>/</td>
<td>Phototherapy</td>
</tr>
<tr>
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<td>183</td>
<td>48</td>
<td>Phototherapy</td>
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<tr>
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<td>6</td>
<td>161</td>
<td>45</td>
<td>Phototherapy</td>
</tr>
<tr>
<td>145-168</td>
<td>7</td>
<td>135</td>
<td>/</td>
<td>Phototherapy</td>
</tr>
<tr>
<td>169-192</td>
<td>8</td>
<td>111</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>&gt;192</td>
<td>9</td>
<td>101</td>
<td>45</td>
<td>Discharge home in good condition</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>15</td>
<td>44</td>
<td>First follow-up examination, the girl in good condition</td>
</tr>
</tbody>
</table>

/ = no measurement.
// = no treatment.

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

المجلة الصحية لشرق المتوسط، منظمة الصحة العالمية، المجلد السابع، العدد 6، 2001
associated with severe anaemia and jaundice [1,8].

The highest bilirubin levels recorded were 572, 559 and 520 μmol/L in new-
borns with maternal anti-c antagonism [9,10]. In the present case study, up-to-
date management and effective treatment prevented such high bilirubin levels. Biliru-
bin 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 dis-
ease 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, in-
travenous immunoglobulin) and to prevent anaemia (exchange transfusion, intrave-
nous 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 ex-
change transfusion may be reduced or eliminated [1]. Double or triple lights are
usually used (BillBlanket or BillBed below, one or two lights above) as was done in this
case. Exchange transfusion removes bilirubin, removes haemolytic antibodies and
correction anaemia [1–3]. In this case, ex-
change 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 lev-
els 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 deliv-
ery [1]. However, the administration of
phenobarbitone makes the infant sluggish
and may induce other enzymes not benefi-
cial to the preterm neonate, and therefore
routine use of phenobarbitone is not rec-
ommended [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 in-
travenous immunoglobulin were adminis-
tered.

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 pre-
vented in a manner similar to that with anti-
D. In practice, it would be very costly and
time-consuming to Rh phenotype all wom-
en in pregnancy and to produce sufficient
quantities of anti-c from male “volunteers”
by injection of incompatible blood to pro-
duce the appropriate immunoglobulin.
Therefore, the best choice is that women
of reproductive age receive primary pre-
vention 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 new-
born and of managing neonatal jaundice, it
is now a very rare condition in industrial-
ized 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-E antibodies.

References


