Haemolytic Jaundice

Rhesus disease

ABO incompatibility

G6PD deficiency

Rhesus isoimmunisation

Introduction

Rh-negative mothers who have become sensitised to the D-antigen in an Rh-positive fetus develop anti-D antibodies which can cross the placenta and attack the blood of Rh-positive fetuses in subsequent pregnancies. This leads to the condition usually referred to as Rhesus Isoimmunisation\(^1,2\), but also referred to as Haemolytic Disease of the Newborn and Erythroblastosis fetalis. This condition primarily involves haemolysis of red blood cells before and after birth. In severe cases fetal anaemia develops, causing congestive cardiac failure ("hydrops fetalis"). The other consequence of haemolysis is release of haemoglobin which is rapidly converted to unconjugated bilirubin (SBR). The fetus is protected because of placental removal of bilirubin, but following birth the rapidly rising SBR places the baby at risk of kernicterus.

Incidence and risk factors:

The incidence of Rhesus isoimmunisation has dramatically declined since the implementation of prophylaxis (treatment of Rh-negative mothers with anti-D antibody following birth of an Rh-positive baby, or in association with miscarriages, termination, ectopic pregnancies and other invasive procedures). Once very common, we now treat about only 5 cases/year. Factors which increase the risk of kernicterus for a given SBR level include:

- prematurity
- acidosis
- hypoalbuminaemia
- rapidly rising SBR

Consequences of disease

1. **Kernicterus** (bilirubin encephalopathy)
   - *Early:* This clinical syndrome includes hypertonia progressing to ophistotonia, seizures, and often death. At autopsy, such babies display evidence of bilirubin staining of the basal gangia.
   - *Late:* Survivors may go on to develop sensorineural hearing impairment and cerebral palsy, often with ataxia and chorioathetosis.

2. **Anaemia**
   - Haemolytic antibody will cause ongoing RBC haemolysis until it has dissipated (usually at about 3 months). This is most pronounced in babies who did not require an exchange transfusion. Repeated top-up transfusions may be needed

It is widely accepted that brain injury is caused by "free bilirubin", which results when albumin binding sites are exceeded.\(^3\) This process is exacerbated by acidosis, which favours dissociation and precipitation of bilirubin into lipid-rich tissues such as cell membranes and brain.

Investigations

\(^1\) Haemolytic Jaundice, \(^2\) Rhesus disease, \(^3\) ABO incompatibility
1. Fetus already known to be affected
   - Cord Blood - SBR, FBC, Group, DCT
   - Cross-match
   - Repeat SBR Q 6 hr initially
   - Repeat FBC daily

2. Post-natal diagnosis (rare these days)
   - Baby: SBR, Group & DCT, FBC; Mother: Group & antibodies
   - Continue as above

### Positive Coombs Tests without maternal sensitization

Occasionally the situation arises where rhesus-negative mothers who receive anti-D immunoglobulin prophylaxis close to the baby’s birth, have a baby with a positive Coombs test, with antibodies identified as anti-D. These cases have only been seen in the last couple of years since propylactic anti-D has been routinely given. This is passively transferred antibody, and may be associated with significant jaundice. However, no such cases at RPA have led to the need for exchange transfusion.

### Treatment

#### Modalities

1. **Phototherapy**: Details of the procedure are provided in the Nursing Manual. 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. Double or triple lights are usually employed (biliblanket below, one or two light from above).

2. **Intravenous immunoglobulin combined with phototherapy**. Compared with phototherapy alone, this has been shown in randomised, controlled trials to significantly reduce the maximum serum bilirubin and the need for exchange transfusion in babies with isoimmune haemolytic jaundice. Other outcomes that were significantly reduced were duration of phototherapy and length of hospitalisation.

   However, such was the problem with small numbers and weak design, that the authors of this Cochrane Review did not recommend the routine use of this treatment, and suggested that the results of further RTCs of higher quality be awaited. They suggested that in circumstances where there was a strong need to avoid transfusion, that it may be justified.

3. **Exchange transfusion**: Details for setting up and performing the procedure are given in the Medical Procedures and Nursing Manual. Exchange transfusion removes bilirubin, removes hemolytic antibody, and corrects anaemia. Due to fetal transfusion, sick hydropic babies are uncommon these days. However, early exchange transfusion for jaundice and/or later top-up transfusion for anaemia are still often needed in these infants.

### Treat:

- Cord Hb <12 mg/dl and/or cord SBR >80: Exchange Tx
- Cord Hb >11 mg/dl: Phototherapy (multilamp)
- Exchange Tx if rate of rise of SBR is such that SBR is likely to reach 300 micromol/L (ie aim to keep below 340)
- Continue phototherapy until SBR falls below 240, and watch for rebound.
- Continue to monitor Hb until about 3 months of age.

**NOTE:** Babies who received *intrauterine transfusions* are born with most of their RBC’s being Rh-negative, and these babies occasionally do not require exchanging on the basis of their SBR level. Such babies will have had no anti-D antibody removed, and often have ongoing haemolysis over the next 2-3
Other causes of haemolytic jaundice

Other haemolytic antibodies

Antibodies similar to anti-D but much less common may cause a similar clinical picture to rhesus isoimmunisation. These include anti-C, anti-Kell, anti-Duffy, etc. They are usually managed along similar lines to rhesus disease.

ABO incompatibility

ABO incompatibility is most often seen in the setting of mother being group O and the baby being groups A or B. It is milder than Rhesus disease, and rarely affects the fetus. They typically have jaundice that becomes apparent on day 1 or 2, but which responds well to phototherapy. Exchange transfusion for ABO incompatibility in the otherwise well, term infant is rarely required.

Diagnosis is straightforward when the blood groups are appropriate and the Direct Coombs Test is positive. It can be difficult when the evidence points towards ABO, but the Direct Coombs Test is negative. In this case the diagnosis is likely if the mother’s plasma contains anti-A or anti-B IgG antibody, and the same antibody is detectable on the baby’s RBC’s. This assumes other etiologies have been excluded.

Glucose-6-phosphate dehydrogenase deficiency

G6PD is a cytoplasmic enzyme that catalyses the first step in the hexose monophosphate pathway producing NADPH, and is responsible for the generation and maintenance of reduced glutathione. This protects the red blood cell membrane from the deleterious effects of oxidation.

The G6PD gene lies on the X chromosome, and over 300 mutants have been described. The normal variety is GdB, and the severe form, first described in the Mediterranean region and later in SE Asia, is called GdMed. This has nearly zero activity in all cells. Because of the high gene frequency in some regions, homozygous affected females are not uncommon.

G6PD deficiency is associated with severe, rapidly rising jaundice, following one of a number of documented triggers. The most important in our experience are firstly naphthalene (“moth balls”), and secondly fava beans (“broad beans”). Other triggers include infection and drugs. For a full list, see triggers. Early, aggressive phototherapy is warranted, but exchange transfusion is still often required.

Summary

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<tr>
<th>Key Points</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Commence aggressive phototherapy on admission</td>
<td>![4 stars]</td>
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<tr>
<td>IVIG and phototherapy combined reduces the maximum SBR and the need for exchange transfusion</td>
<td>![5 stars]</td>
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<td>Kernicterus can be prevented in Rhesus disease if total SBR is kept below 340umol/L</td>
<td>![1 star]</td>
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<td>Late anaemia is a common complication due to ongoing haemolysis</td>
<td>![2 stars]</td>
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References


Last Reviewed: May, 2003