California Association
for
Medical Laboratory Technology

HEMOLYTIC DISEASE OF THE NEWBORN

Course # DL-995

by

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HEMOLYTIC DISEASE OF THE NEWBORN

OBJECTIVES:
1. Summarize the history of Rh-Hemolytic Disease of the Newborn (HDN)
2. Outline the model of Rh-HDN
3. Explain the cause of ABO-HDN and contrast to Rh-HDN
4. State the racial differences in incidence of the Rh negative gene
5. Discuss the conditions that affect the sensitization of the mother to the Rh antigen.
6. Discuss the symptoms of HDN
7. Outline the treatment options for the fetus and newborn with HDN
8. List the tests for HDN done on the mother, fetus, and newborn

INTRODUCTION:
In the past Hemolytic Disease of the Newborn (HDN) was a major cause of death and disability in Caucasian fetuses and newborn infants. The condition occurs when an infant has a RBC antigen, inherited from the father, that the mother lacks, and she produces IgG antibodies to this antigen. These antibodies in the mother cross the placenta and cause destruction of red blood cells in the fetus. The infant develops anemia in utero that may lead to hydrops fetalis (severe edema) and other problems. After birth the infant may develop jaundice due to accumulation of bilirubin from continued hemolysis of RBCs.

Formerly the most common cause of HDN was Rh (D) incompatibility. It wasn’t until this blood group antigen was identified in 1940, and then associated with HDN in 1941, that the pathogenesis was described. By the late1960s this led to the use of therapeutic antibodies to prevent sensitization of the Rh-negative mother by the infant’s RBCs. Now all Rh-negative mothers at risk of becoming sensitized are given anti-Rh (D) antibodies during pregnancy and at the time of delivery.

At present the most common cause of HDN is ABO incompatibility, with Rh (D) next. Other blood groups are less frequent causes of HDN.

Laboratory testing plays a crucial role in the identification of at-risk pregnancies, the prophylaxis of HDN, the diagnosis of the disease, and the identification of the antibody causing the problem.

CASE STUDY:
A 23-year-old indigent Caucasian mother (grvida 2, para 1) delivered an infant at a local county hospital. Her first infant was delivered at home by a midwife. The mother had not received prenatal care during either pregnancy. The present baby developed jaundice about four hours after birth. Physical examination of the infant also showed hepatomegaly and splenomegaly. Laboratory results on the infant’s cord blood showed: Group O, Rh positive. The cells were direct antiglobulin test (DAT) positive. The mother was Group A, Rh negative. The infant’s hemoglobin was 8.5 g/dl and the serum total bilirubin was 10.6 mg/dl. A blood smear showed numerous nucleated RBCs (200 nRBC/100WBC) and marked polychromatophilia. The findings are consistent with HDN.
Questions to consider:
1. What is the most probable type of HDN?
2. What laboratory tests should be done next?
3. Is the mother a candidate for Rh immune globulin (RhIg)?
4. What conditions in the infant need treatment? Why?

HISTORY:

Historians have postulated that in the early 1500s the pregnancies of Katherine of Aragon, the first wife of Henry VIII, were consistent with Rh-HDN. She had five babies who were either stillborn or died early in the newborn period.

The first description of hemolytic disease of the newborn is thought to have been in 1609 by a French midwife who assisted in the delivery of twin boys. She described that one infant was swollen (edema) and died soon after birth and the other developed severe jaundice and died in a few days. In 1641 Plater gave a definitive description of hydrops fetalis.

Over the years the disease has been known by various names—describing the clinical symptoms: hydrops fetalis, referring to the edema; erythroblastosis fetalis, referring to the nucleated red cells found in peripheral blood; and icterus gravis neonatorum, referring to the jaundice.

• In 1892 Ballantyne described the criteria for diagnosis. He mentioned edema, anemia, enlargement of the spleen and liver, and enlargement of the placenta.
• In 1912 Diamond, Blackfan, and Baty made the association that hydrops fetalis, icterus gravis neonatorum, and anicteric anemia of the newborn were all the same disease.
• In 1938 Hellman and Hertig first recognized the familial incidence of the disease.
• In 1940 approximately 10% of pregnancies were affected by hemolytic disease of the newborn.
• In 1939 to 1941 the cause of hemolytic disease of the newborn began to emerge. In 1939 Levine and Stetson found the antibody causing the disease, and they postulated maternal sensitization. In 1940 Landsteiner and Weiner discovered the Rh factor. And, finally in 1941 Levine and Stetson put it all together. They described an antibody that reacted with Landsteiner and Weiner’s factor, and they proposed that maternal sensitization was caused by an antigen that crossed the placental barrier.
• Before 1940, 45% of Rh sensitized pregnancies resulted in death of the fetus. In 1946 Diamond, et al., developed a method of exchange transfusion for affected infants, and infant mortality was dramatically reduced.
• In 1950, it became known that hyperbilirubinemia causes kernicterus, bilirubin deposits in the basal ganglia and other areas of the brain. This is a potentially fatal condition that leaves permanent neurological damage in the infants that survive. This led to use of exchange transfusions on infants with hyperbilirubinemia. The level of bilirubin that produces kernicterus is approximately 20 mg/dl, so it became accepted practice to perform these transfusions to reduce the level of bilirubin when it approached this level. (In
utero excess bilirubin produced by hemolysis of RBCs is taken up by the placenta and degraded by the mother’s system. After birth the neonate’s immature liver is unable to metabolize the increased amount of bilirubin and it accumulates in the blood.)

- In 1954 it was recommended that hemolytic disease babies be delivered early. By removing the baby from the hostile environment and performing exchange transfusions, many babies were saved; however, there was still a 22% mortality even with these procedures.
- In 1956 it was recognized that analysis of the bilirubin content in amniotic fluid was a good indicator of the severity of the infant’s morbidity. At this point, amniocentesis became the accepted procedure for monitoring sensitized pregnancies.
- In 1963 the first intrauterine transfusion was performed. Intrauterine transfusions always use Group O Rh-negative leukocyte-poor cell mass that has been irradiated to prevent graft vs. host reaction in the infant.
- In 1960 an American group (Gorman, Freda, and Pollack) and a British group (Finn and Clark) proposed that passive immunity given the mother might prevent active immunization. They noticed that when the mother and the baby were ABO incompatible, the mother’s anti-A or anti-B antibodies usually destroyed the fetal cells that entered her system before they were able to sensitize her. They postulated that this mechanism might work with Rh antibodies and RhoGam© was developed.
- In 1966 the two groups from the United Kingdom and the United States demonstrated that anti-Rho (anti-D) immunoglobulin gamma (IgG) prophylaxis soon after delivery prevents sensitization in Rh-negative women.
- 1968: Rh immune globulin was approved and given routinely to qualified (unsensitized) Rh-negative mothers.
- In 1971 the World Health Organization recommended the procedure and gave the recommended dosage of anti-Rh immunoglobulin.
- In 1998 the recommendation was reinforced by the American Association of Blood Banks and the American College of Obstetrics and Gynecologists with inclusion of prophylaxis at 28 weeks’ gestation.
- Routine use of Rh IgG prophylaxis resulted in a significant decline in the incidence of Rh alloimmunization, and Rh-HDN has become infrequent. Before prophylaxis there were 20,000 cases/year of Rh-HDN in the U.S.; after prophylaxis there are fewer than 4,000 cases/year.

MODEL OF HEMOLYTIC DISEASE OF THE NEWBORN
- Infant has a RBC antigen that the mother lacks
- The mother is exposed to the antigen, or has pre-formed antibodies
- The mother forms IgG antibodies to the antigen
- The antibody crosses the placenta and causes destruction of the infant’s RBCs
RH SYSTEM NOMENCLATURE
Below is a review of the Fisher/Race and Weiner nomenclature of the most common antigens and phenotypes:

<table>
<thead>
<tr>
<th>Fisher-Race</th>
<th>Weiner</th>
<th>Rh designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCe</td>
<td>R1</td>
<td>Rh positive</td>
</tr>
<tr>
<td>DeE</td>
<td>R2</td>
<td>Rh positive</td>
</tr>
<tr>
<td>(d)ce*</td>
<td>r</td>
<td>Rh negative</td>
</tr>
<tr>
<td>Dce</td>
<td>Ro</td>
<td>Rh positive</td>
</tr>
</tbody>
</table>

*there is no d antigen; (d) or d indicates the lack of D antigen

CONDITIONS AFFECTING SENSITIZATION OF THE MOTHER
The overall probability of a mother who lacks Rho (D) antigen possessed by her child being sensitized is about 10%. This probability depends on the amount of fetal-to-maternal bleed: 0.1 ml results in 1 in 6 sensitized; 0.4 ml results in about 60% sensitized.

If the mother and infant are ABO compatible (both are the same ABO group or baby is Group O, or mother is Group AB), the probability of sensitization is greatly increased. If the mother and infant are ABO incompatible, (the baby is Group A or B and the mother is the opposite group or is Group O), the infant’s cells that enter the maternal circulation are usually destroyed by the mother’s anti-A or anti-B alloantibodies before the cells can sensitize the mother.

The frequency of exposure, the inherent ability of the mother to make antibodies, and the heterozygosity of the father are all factors in determining the probability of sensitization. If the father is heterozygous for D, the infant has 50% chance of being Rh negative.

With the exception of ABO hemolytic disease of the newborn, which can occur in the first pregnancy from IgG forms of the anti-A or anti-B alloagglutinins, most other forms of HDN occur in the second or subsequent pregnancies. This is because the major fetal to maternal bleed most commonly occurs with the trauma of delivery. Sensitization of the mother is uncommon during pregnancy, especially infrequent during the first 28 weeks (40 weeks is the usual gestation time) because not enough of the infant’s RBC cross the placenta. However other conditions, such as abortion, amniocentesis, ectopic pregnancy, abdominal trauma, and chorionic villus sampling (removal of a small amount of placental tissue) may increase the risk of sensitization.

Now HDN is most commonly caused by ABO alloagglutinins. This most frequently occurs when the mother is group O and the fetus is Group A or Group B. The mother’s plasma contains anti-A, anti-B, and anti-A,B, which in Group O people tend to be of the IgG class and can therefore cross the placenta and hemolyze fetal RBCs. (IgM antibodies do not cross the placenta.) ABO-HDN is usually mild, and may require only minimal treatment. This is because the somatic cells also have the ABO antigens, and the maternal antibody can be mopped up by these cells—leaving the RBCs to bear a small part of the total antibody. (See Table I)

Rh-HDN, on the other hand, is primarily a disease of red cell destruction because the Rh antigens occur only on the RBC membrane. Rh-HDN is a much more severe disease.
Other antibodies besides ABO and Rho (D) have been associated with HDN. These include RBC antigens in the following systems: Kell, Kidd, Duffy, other Rh (c, e, C, E), and Ss. Of these, anti-Kell and anti-c are more common. Antibodies in Lewis, P1, and M/N systems are usually IgM and do not cross the placenta. HLA (Human leukocyte antigen) antibodies that cause thrombocytopenia of the newborn can also occur. Thrombocytopenia of the newborn is a relatively rare disease, but the platelets and WBCs can migrate extravascularly from the infant into the mother’s immune system and sensitize her during the first pregnancy. When thrombocytopenia occurs in the newborn, the best treatment is to prepare a platelet concentrate from the mother, and transfuse it to the infant. This platelet concentrate will be compatible with the mother’s antibodies.

### TABLE I
DIFFERENCES BETWEEN RH AND ABO HEMOLYTIC DISEASE OF THE NEWBORN

<table>
<thead>
<tr>
<th>Findings</th>
<th>Hemolytic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFANT</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Findings</td>
<td></td>
</tr>
<tr>
<td>Enlargement of liver and spleen</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Early jaundice</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Laboratory Findings</td>
<td></td>
</tr>
<tr>
<td>Early inc. bilirubin</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Low</td>
</tr>
<tr>
<td>Anemia</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Direct antiglobulin</td>
<td>Positive</td>
</tr>
<tr>
<td>Spherocytes</td>
<td>Absent</td>
</tr>
<tr>
<td>Reticulocytosis</td>
<td>Marked</td>
</tr>
<tr>
<td>Nucleated RBC</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Polychromatophilia</td>
<td>Contains anti-Rh antibody</td>
</tr>
<tr>
<td>Eluate of RBCs</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Indirect antiglobulin with cord serum</td>
<td>Positive with Rh+ cells</td>
</tr>
<tr>
<td><strong>MOTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Findings</td>
<td></td>
</tr>
<tr>
<td>Immunization</td>
<td>Transfusion, previous pregnancy</td>
</tr>
<tr>
<td>Occurrence in 1st preg.</td>
<td>Unusual unless previously transfused with Rh+ blood</td>
</tr>
<tr>
<td>Laboratory Findings</td>
<td></td>
</tr>
<tr>
<td>Indirect antiglobulin with mother’s serum</td>
<td>Positive with Rh+ cells</td>
</tr>
</tbody>
</table>
RACIAL DISTRIBUTION OF RH NEGATIVE GENE

- Caucasians are at highest risk for Rh-HDN since 15% are Rh negative. (The highest incidence of Rh negative is in the Basques of Northern Spain—close to 30%).
- African Americans—5-9% Rh negative
- Asians—1% Rh negative.

CLINICAL SYMPTOMS OF HDN

**Fetus:**
Other than the obvious RBC destruction, HDN causes a variety of problems in the affected fetus. Severe anemia in the fetus results in edema, fetal ascites, jaundice, enlarged umbilical vein, enlarged placenta, and enlarged spleen and liver. The most severe manifestation of these symptoms is called hydrops fetalis. All the symptoms are related to the hemolysis of the fetal RBCs. The enlargement of the spleen and liver, due to extramedullary production of RBCs, causes accumulation of fluid in the fetal trunk. The spleen is also enlarged by its removal of the damaged RBC. The lysis of RBC leads to a buildup of bilirubin. Usually this excess bilirubin is transported across the placenta and removed by the mother’s liver, but edema of the placenta may hinder this. Bilirubin can be measured by OD450 analysis of the amniotic fluid. The overall symptoms may be mild to severe. Intrauterine death is usually due to very severe anemia and hydrops fetalis. Anemia in the fetus may be gauged by ultrasound measurement of the blood velocity in the middle cerebral artery—the faster the flow, the greater the anemia.

**Newborn:**
The signs of hemolytic disease in the newborn vary from mild to severe. The typical findings are pallor, jaundice, enlarged liver and spleen, and hydrops in severe cases. Hydrops usually does not occur until the hemoglobin drops below 4 g/dl. The jaundice develops in the first 24 hours as the hemolysis exceeds the capacity of the infant’s liver to process bilirubin. Clinically significant jaundice occurs in up to 20% of ABO-incompatible infants.

TREATMENT

**Fetus:** If monitoring the fetus by untrasonography, amniocentesis, and cordocentesis indicates active hemolysis and anemia, a blood transfusion may be done **in utero**.

**Newborn:** Blood transfusions may be needed to correct the anemia. If the bilirubin rises to a critical level, phototherapy (placing the infant under ultraviolet light) is used. If phototherapy doesn’t bring it down sufficiently, exchange transfusions may be used.

LABORATORY TESTING

**Pregnant women:** ABO and Rh testing and an antibody screen are ordered the first time a pregnant woman sees a physician. The father may also be tested at this time. If he is heterozygous for the D antigen, the possibility of the infant being D positive is 50%. If the patient is Rh negative and the antibody screen is negative, the antibody screen is repeated at 26-28 weeks (the end of the second trimester). The antibody screen is done at this time to detect whether immunity to D antigen has developed. The risk of the mother becoming sensitized before 28 weeks is very small, about 2 in 1000 Rh-negative
pregnancies. At this time the unsensitized Rh-negative woman is given Rh immune globulin to prevent sensitization during the third trimester.

If the initial antibody screen is positive, the antibody is identified and a titer is done. The titer is repeated at 18-20 weeks. Antibody identification is necessary to determine if the antibody is likely to cause HDN. IgG anti-D, other Rh, Kell, Duffy, Kidd, and S are likely to cause HDN. IgM antibodies (anti-Lewis, -P1, -M, -I) do not cross the placenta.

Antibody titer is done to help the obstetrician determine the severity of HDN and the need for fetal monitoring (ultrasound, amniocentesis, cordocentesis). Amniocentesis and cordocentesis may cause more fetal RBC to enter the mother’s circulation, so these procedures are not done until the antibody level reaches a critical point. This is either a rising titer or a titer of 16. (This critical level may vary from one institution to another; usually between 8 and 32.) If the antibody is anti-D, the use of R2R2 (cDE/cDE) cells is recommended for titrations because they have a uniform expression of D antigen.

Amniotic fluid is tested at OD450 to determine the level of bilirubin. The normal level is .02 or less; up to .09 indicates no or mild HDN. Ultrasound measurement of the rate of blood flow in the middle cerebral artery blood velocity can estimate fetal anemia.

Results of these tests help determine whether an intrauterine transfusion is necessary. If intrauterine transfusion is done, the transfused blood should be Group O, Rh negative, irradiated, cytomegalovirus negative, leukocyte reduced, and fresh.

**After Delivery:**

**Mother:**

- ABO and Rh (should agree with the prenatal results)
- Antibody screen and identification of any antibody present.
- Tests to determine amount of fetal-maternal hemorrhage: If an unsensitized Rh negative mother with an Rh positive fetus has a larger than expected bleed of fetal blood, an increased amount of Rh immune globulin is necessary to prevent sensitization. The screening test for the amount of fetal to maternal hemorrhage is the rosette test. In this test the mother’s red cells are incubated with anti-D reagent. The anti-D attaches to the Rh positive infant’s cells. Then indicator D cells are added. They react with the antibody molecules bound to the surface of the infant’s D positive cells and form rosettes. If, on examination at 100x, the number of rosettes exceeds the maximum for a negative test (about 6 rosettes per 5 fields, depending on the method), a quantitative test, such as the Kleihauer-Betke acid elution procedure should be done. The results indicate if more than the usual amount (300 _g) of Rh immune globulin should be given to the mother.

**Newborn:**

- Cord blood: Perform ABO (forward grouping only) and Rh
- If HDN is suspected, do direct antiglobulin (DAT) test.
  
  Note: if the infant’s cells are heavily coated with maternal antibody, there may be a reaction in the Rh control as well as the Rh test. It may not be
possible to get a proper Rh type, or even ABO without first performing heat elution of the antibody.

- If the DAT is positive, or if the DAT is negative but the infant shows symptoms, elute the antibody from the cord blood cells and run a panel to determine the identity of the antibody. Compare to the mother’s antibody.
- If the mother has anti-A, anti-B or anti-A,B, and the infant is Group A or B, test the eluate against screening cells, A1 and B cells. In ABO-HDN the cord cells may be DAT negative but the cord serum may have anti-A, anti-B or anti-A,B. Test the serum against A1, B, and O red cells by indirect antiglobulin method.

INTERPRETATION OF THE CASE STUDY:
1. What is the most probable type of HDN?
   The Rh positive infant and the Rh negative mother indicate the most probable antibody is anti-D. This is also more likely since the baby and mother are ABO compatible (infant is Group O, mother is Group A).
2. What laboratory tests should be done next?
   DAT test on cord blood. Elution of antibodies and identification of the antibody. Screen the mother for unexpected antibodies and identification of any antibody present. Hemoglobin and bilirubin on the infant for anemia and critical bilirubin level.
3. Is the mother a candidate for RhIg?
   If she has an anti-Rho antibody she is not a candidate for RhIg. Once a mother is sensitized, administration of RhIg will not help.
4. The anemia may be treated with transfusion. The blood should be compatible with the mother’s antibodies. The infant may not be able to replace hemoglobin adequately at this time. The baby’s red cells may still be destroyed by the mother’s antibodies. The bilirubin level is above normal. The infant should be put under ultraviolet light to break down the bilirubin. Determination of bilirubin levels should be continued to make sure a harmful level is not reached. If the level approaches 20mg%, exchange transfusion should be performed.

REFERENCES
REVIEW QUESTIONS
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Choose the one best answer

1. Which of the following scenarios could produce an ABO-HDN infant?
   a. mother AB, infant A
   b. mother O, infant B
   c. mother A, infant O
   d. father O, mother A

2. Which of the following could produce an Rh-HDN infant?
   a. mother R1r, infant rr
   b. mother R2R2, infant R2r
   c. mother rr, infant R1r
   d. father rr, mother R2r

3. The first known description of hemolytic disease of the newborn was by
   a. Plater
   b. Diamond, Blackfan, and Baty
   c. Katherine of Aragon
   d. a French midwife

4. The highest incidence of the Rh negative gene is in
   a. Basques
   b. Blacks
   c. American Caucasians
   d. Asians

5. Hyperbilirubinemia associated with HDN is not usually found in the fetus because
   a. the fetal liver breaks it down
   b. bilirubin is not produced in the fetus
   c. it is removed by the mother’s system
   d. it is removed by ultraviolet radiation

6. Which of the following is not a finding in HDN?
   a. mild to severe anemia
   b. bilirubinemia
   c. enlarged spleen
   d. reduced erythroblasts

7. Which of the following is a difference between ABO-HDN and Rh-HDN?
   a. presence of anemia
   b. presence of spherocytes
   c. presence of hyperbilirubinemia
   d. increase in erythroblasts
8. Who of the following is not eligible to receive Rh immune globulin?
   a. Rh negative woman with Rh positive infant
   b. woman who has an abortion at 2 months pregnancy
   c. pregnant woman who has amniocentesis
   d. postpartum woman with anti-Rh antibodies.

9. Which laboratory test is not done on a newborn with suspected HDN?
   a. direct antiglobulin test (DAT)
   b. ABO, forward and back grouping
   c. Rh typing
   d. elution of antibody from DAT positive cells

10. A pregnant woman has a positive antibody screen at her first visit to an obstetrician. Which of the following antibodies might cause HDN in the infant?
    a. anti-Kell
    b. anti-M
    c. anti-P₁
    d. anti-Lewis
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1. a b c d
2. a b c d
3. a b c d
4. a b c d
5. a b c d

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   (strongly agree) 5 4 3 2 1 (strongly disagree)

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