Non-conjugated hyperbilirubinemia – Dr. Haidar

Crigler-Najjar Syndrome (type I and type II)

- It is a serious permanent deficiency of glucuronyl transferase enzyme that result in severe indirect hyperbilirubinemia. It is inherited as autosomal dominant condition.
- **Clinical Features:** Severe non-conjugated hyperbilirubinemia develops in homozygous infants during the first 3 days of life, and without treatment, serum concentration of 25-35 mg/dL are reached during the 1st month of life.
- Kernicterus an almost universal complication of this disorder, is usually first noted in the early neonatal period, but some treated infants have survival childhood without clinical sequelae. Usually the patient has pale yellow stool. Any case of persistent unconjugated hyperbilirubinemia at levels above 20 mg/dL after 1st week of life in the absence of hemolysis should suggest this syndrome.
- **Diagnosis:** in addition to high level of unconjugated hyperbilirubinemia, the definitive diagnosis is made by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by a closed biopsy.
- **Treatment:** serum bilirubin concentration should be kept below 20 mg/dL for at least 2-4 wk of life either by repeated exchange transfusion or phototherapy or may be by phenobarbital therapy.
- Gilbert syndrome is less severe (jaundice during stress).

Breast Milk Jaundice

- It is estimated in 2% of breast milk infants after the 7 days of life, with maximal concentration as high as 10-30 mg/dL reached during the 2nd -3rd wk. If breast milk is continued, the hyperbilirubinemia gradually decreases and may then persist for 3-10 wk at lower levels. If nursing discontinued, the serum bilirubin level falls rapidly, usually reaching normal levels within a few days. Cessation of breast feeding for 1-2 days and substitution of formula for breast milk result in rapid decline in serum bilirubin, after which nursing can be resumed without return of the hyperbilirubinemia to its previously high levels. If indicated, phototherapy may be of benefit.
- These infants have no other sign of illness; but one case of kernicterus has been reported (due to unknown reason)
- The cause of breast milk jaundice is unknown, but in some women their breast milk contains a glucuronidase that may be responsible for the jaundice.
- The condition is diagnosed by exclusion of other causes of jaundice.

Hemolytic disease of the newborn (erythroblastosis fetalis)

- It is caused by trans-placental passage of maternal Ab active against RBC Ag of the infant and is characterized by an increased rate of RBC destruction. It is considered as an important cause of anemia and jaundice in newborn infants despite the development of preventing maternal iso-immunization by Rh Ag. Although more than 60 different RBC Ag capable of eliciting an Ab, significant disease is associated primarily with the D Ag of the Rh group and with incompatibility of ABO factors.
- Hemolytic disease of the newborn caused by Rh incompatibility:
  - The Rh antigenic determinants are genetically transmitted from each parent and determine the Rh type and direct the production of number of blood group factors (C, c, D, d, E, and e). Each factor can elicit a specific antibody response under suitable conditions. 90% are due to D Ag and remainder to C or d Ag.
**Pathogenesis**

- Isoimmune hemolytic disease from D Ag is approximately three times more frequent in white persons than blacks. When Rh-positive blood is infused into Rh-negative women through error or when small quantities (usually more than 1 ml) of Rh-positive fetal blood containing D Ag inherited from an Rh-positive father enters the maternal circulation during pregnancy, with spontaneous or induced abortion, or at delivery, antibody formation against D antigen may be induced in the unsensitized Rh-negative recipient mother. Once sensitization has taken place, considerably smaller doses of antigen can stimulate an increase Ab titer. Initially, a rise in IgM antibody occurs, which is later replaced by IgG antibody; the latter readily crosses the placenta & causes hemolytic manifestations.
- Hemolytic disease rarely occurs during a first pregnancy because transfusions of Rh positive fetal blood into an Rh-negative mother tend to occur near the time of delivery, too late for the mother to become sensitized and transmit antibody to her infant before delivery, so the first baby may not be affected. The severity of Rh illness tends to worsen with successive pregnancies. When the mother and fetus are also incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh positive cells from her circulation by her pre-existing anti A or anti B, which are IgM antibodies and do not cross the placenta.

**Clinical Features**

- The severity of the disease may range from only laboratory evidence of mild hemolysis (15% of cases) to severe anemia with compensatory hyperplasia of erythropoietic tissue leading to massive enlargement of the liver and spleen. Profound anemia may occur and result in pallor, sign of cardiac decompensation (cardiomegaly, respiratory distress, massive anasarca and circulatory collapse). This clinical picture of excessive abnormal fluid in two or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid) termed hydrops fetalis, frequently result in death in utero or shortly after birth. The severity of hydrops related to the level of anemia and the degree of reduction in serum albumin (oncotic pressure), which is due in part to hepatic dysfunction.
- Petechiae, purpura and thrombocytopenia may also present in some cases as a result of decreased platelet production or the presence of D.I.C.
- Jaundice may be absent at birth because of placental clearance of lipid soluble unconjugated bilirubin, but in severe cases, bilirubin pigments stain amniotic fluid, cord and vernix caseosa yellow. Jaundice is generally evident on the first day of life.
- The risk of bilirubin encephalopathy developing from hemolytic disease is greater than from comparable non-hemolytic hyperbilirubinemia.

**Laboratory data**

- Usually there is Rh –ve mother and Rh +ve baby, the direct Coombs test is usually positive, and anemia is generally present. The blood smear typically shows polychromasia and a marked increase in nucleated RBCs. The reticulocyte count is increased. The white cell count is usually normal but may be elevated, thrombocytopenia may develop in severe cases. Cord bilirubin is generally between 3-5 mg/dL, and indirect bilirubin rises rapidly to high levels in the first 6 hr of life.

**Antenatal Diagnosis**

- In Rh –ve women, a history of previous transfusions, abortions, or pregnancy should suggest the possibility of sensitization.
- Blood types should be tested for potential incompatibility, and the maternal titer of IgG Ab to D Ag should be assayed at 12-16, 28-32 and 36 wk.
- Fetal Rh status may be determined by isolating fetal cells or fetal DNA (plasma) from the maternal circulation or by aminocentesis and polymerase chain reaction.
- The presence of measurable antibody titer at the beginning of the pregnancy, a rapid rise in titer, or a titer of 1:64 or greater suggests significant hemolytic disease.
- The severity of fetal disease should be monitored by aminocentesis, percutaneous umbilical blood cord sampling (PUBS), and ultrasonography.
- If the fetal disease is present it can be treated by intrauterine exchange transfusion.
**Postnatal Diagnosis**

- After birth of any infant to an Rh-ve women, blood from the umbilical cord or from the infant should be examined for ABO blood group, Rh type, Hct and hemoglobin and reaction of the direct Coombs test. In addition to that base line of serum bilirubin should be tested.

**ABO Incompatibility**

- Isoimmune hemolytic anemia may result when ABO incompatibility occurs between the mother and the newborn infant. This disorder is most commonly with the type A or B infants born to type O mothers.
- The risk factors for ABO incompatibility are present in 12-15% of pregnancies, but evidence of fetal sensitization (positive direct Coombs test) occurs in only 3-4%. Symptomatic ABO hemolytic disease occurs in < 1% of all newborn infants but accounts approximately two thirds of observed cases of hemolytic disease in the newborn.
- Although Ab against A and B factors occurs without previous sensitization (natural Ab) they are ordinary present in the IgM fraction of gamma globulin, which does not cross the placenta. However, univalent, incomplete (albumin active) Ab to A Ag may be present in the IgG fraction, which cross the placenta, so ABO isoimmune hemolytic disease may be found in first born infants.
- **Clinical Features:** most cases are mild, with jaundice being the only clinical manifestation, no other clinical findings like pallor or organomegally. Jaundice usually appears during the first 24 hr, rarely it will be in severe form.

**Diagnosis**

- Presumptive diagnosis is based on the presence of ABO incompatibility, a weakly or to moderately positive direct Coombs test result, and spherocytes in the blood smear, which may at time suggest the presence of hereditary spherocytosis.
- Hyperbilirubinemia is often the only lab. abnormal test.
- The Hb level is usually normal but may be as low as 10-12 gm/dL. Reticulocytes may be increased to 10-15 % with extensive polychromasia and increase numbers of nucleated RBCs.
- In 10-20 % of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL
- The severity of ABO incompatibility decrease with subsequent pregnancies (the reverse of Rh incompatibility hemolytic disease).