Jaundice and hemolytic disease of the newborn infant

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Brief Introduction

• Jaundice, from old French *Jaundice*, a word rooted in the Latin *galbinus*, meaning greenish yellow, from *galbus*.

• Generally, Juandice is the visible manifestation in skin and sclera of elevated serum concentration of *bilirubin* levels exceed 2.0mg/dl(34µmol/L).

• Neonates, however, may not appear jaundiced until the serum bilirubin concentration exceeds 5.0 to 7.0mg/dl(119µmol/L).

• Jaundice as refer to *physiological state* appears often in normal neonates by 60%~70%, that is induced and determined by its metabolism during the early period of newborn infants.

• But in some circumstances such as sepsis, severe acidosis, hemolysis, hypoalbuminemia et. that could lead to pathological hyperbilirubinemia, the serum bilirubin (*unconjugated*) will come across brain blood barrier and damage to CNS—*Bilirubin encephalopathy*.
Features of metabolism of Bilirubin in newborn infants

RE. system
Catabolism of Effete RBC
Ineffective Erythropoiesis-Bone Marrow Tissue Heme-Heme Protein
Liver

Heme oxygenase

Biliverdin

Biliverdin Reductase

Bilirubin+Serum Albumin

Acceptor Proteins Y,Z

Glucuronyl Transferase

Bilirubin Glucuronide

β-Glucuronidase

Fecal Bilirubin, Stercobilinogen

S.E.R. OF LIVER

Liver

75%Heme

25% Heme

β-Glucuronidase

Fecal Bilirubin, Stercobilinogen

Features of metabolism of Bilirubin in newborn infants

Early Peak

Ineffective Erythropoiesis-Bone Marrow Tissue Heme-Heme Protein

Liver
Characteristics of Bilirubin metabolism in Neonate

Over product in bilirubin---8.8mg/kg/day, but 3.8mg in adult
- Red Blood Cells life span 90 days;
- Shunt bilirubin---from bone marrow(ineffect erythropoiesis), liver (heme proteins, heme tissue)

Transport of bilirubin
- pH intensively relative to the binding of albumin to bilirubin (pH > 7.4);
- Relative lower concentration of serum albumin

Immaturity in Metabolism in Liver
- Acceptor proteins Y, Z in lower level;
- Lower activity of Uridine diphosphoglucuronyl transferase (UDPG-T)

Enterohepatic circulation
- Relative intestinal sterile;
- High activity of β-glucuronase
Typing the Neonatal Jaundice into Physiological and Pathological states

- **Physiological**
  1. Visible at 2~3 day of birth and most apparent at 4~6 day after birth;
  2. Absent after 2 and 3~4 weeks of birth for full-term and preterm infants respectively;
  3. Total Serum Bilirubin <12 mg/dl (205 µmol/L), <15 mg/dl (257 µmol/L)
  4. No disorders were found

- **Pathological**
  - Clinical jaundice in first 24 hours of life;
  - Total serum bilirubin >12~15 mg/dl (205~257 µmol/L) or increase by 5 mg/dl (85 µmol/L) a day;
  - Direct serum bilirubin >1.5~2.0 mg (26~34 µmol/L)
  - Prolonged jaundice
  - Reocurrence of jaundice
Unconjugated Hyperbilirubinemia Related to Pathological State

Excessive production of bilirubin (hemolyis)
- Blood group incompatibility (Rh, ABO, Minor blood group)
- Red blood cell enzyme abnormalities
- Glucose-6-phosphate dehydrogenase
- Pyruvate kinase
- Sepsis
- Red blood cell membrane defects
- Extravascular blood
- Polycythemia

Impaired conjugation or excretion
- Hormonal deficiency (hypothyroidism, hypopituitarism)

Disorders of bilirubin metabolism
- Criglers-Najjar syndromes Type I, II
- Gilbert disease
- Lucey-driscoll syndrome

Enhanced enterohepatic circulation
- Intestinal obstruction, pyloric stenosis
- Ileus, meconium plugs, cystic fibrosis
Conjugated Hyperbilirubinemia Related to Patological State

- **Obstruction to biliary flow (biliary atresis)**
- **Hepatic cell injury**
  - Infection (bacterial, viral, Parasitic, TORCH)
  - Toxic
    - Bacterial sepsis
    - Intravenous alimentation
    - Drugs
- **Metabolic errors**
  - Galactosemia
  - Fructosemia
  - Alpha-antitrypsin deficiency
  - Cystic fibrosis
  - Rotor syndrome Dubin-johnson syndrome
- **Immunological neonatal lupus erythematosus**
- **Chromosomal disorders**
- **Chronic bilirubin overload**
  - Erthroblastosis fetalis
  - Red cell enzyme deficience
  - Spherocytosis, elliptocytosis, pyknocytosis
  - Congenital erythropoietic porphyria
Hemolytic Disease of the Newborn

- HDN referred as isoimmunized hemolytic disorder due to incompatibility blood groups between mother and fetus
- Extravascular hemolysis occurred in RES (reticular endothelial system) --- Pathogenesis

Excessive production of bilirubin
Anemia
Hypoprotienemia
Heart failure
Extramedullar erythropoiesis
Hepatosplenomegaly
Bilirubin encephalopathy
Clinical and Laboratory Features of Immune hemolysis Due to Rh Disease and ABO incompatibility

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Rh Disease</th>
<th>ABO incompatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Pallor</td>
<td>Marked</td>
<td>Minimal</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Marked</td>
<td>Minimal to Moderate</td>
</tr>
<tr>
<td>Hydrops</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>Marked</td>
<td>Rare</td>
</tr>
<tr>
<td>Risk to BE</td>
<td>higher risk</td>
<td>little</td>
</tr>
</tbody>
</table>

**Laboratory Features**

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Rh(-)</th>
<th>O</th>
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</thead>
<tbody>
<tr>
<td>Mathor</td>
<td>Rh(+)</td>
<td>A/B, AB</td>
</tr>
<tr>
<td>Infant</td>
<td>Marked</td>
<td>Minimal</td>
</tr>
<tr>
<td>Anemia</td>
<td>Positive</td>
<td>Frequently negative</td>
</tr>
<tr>
<td>Direct Combs`test</td>
<td>Positive</td>
<td>Usually positive</td>
</tr>
<tr>
<td>Indirect Combs`test</td>
<td>Positive</td>
<td>Variable</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Marked</td>
<td>Spherocytes</td>
</tr>
<tr>
<td>RBC morphology</td>
<td>Nucleated RBCs</td>
<td></td>
</tr>
</tbody>
</table>
Kernicterus (KI) is the German term for intense jaundice of the basal ganglia of the brain, and is found in some infants dying with hyperbilirubinemia.

Johannes Orth (1847 in Nassau, Germany)
Autopsy: more intense yellow coloring of the basal ganglia, the wall of the third ventricle, the hippocampus, and the central parts of the cerebellum, where particularly the granular layer was found to be intensely stained.
Microscopic: basal ganglia noted that the neurons were stained, the glial elements were spare.

Christian Schmorl (1861 in Mugeln, Germany)
Two distinct staining patterns, one of diffuse yellow staining, the other of more intense staining of the basal ganglia, as well as the nuclei of the medulla and cerebellum. It was for this pattern that Schmorl coined the term KI, which has subsequently been used to denote both the neuropathological finding as well as the clinical correlate in survivors, consisting of choreoathetosis, deafness, gaze paresis, and occasional mental retardation. Schmorl, further described changes in these neurons suggesting that they were in the process of dying.
Bilirubin Encephalopathy
胆红素脑病
Clinical Manifestations of Bilirubin Encephalopathy

Classic symptoms and signs mainly occurred in the neonates with hemolytic disorders. Certainly preterm infants take much more risk at BE, but we find it difficult to give their early diagnosis.

- Step 1 Usually at 2~7 day of life with sever hyperbilirubinemia, lethargy, poor feeding, weak swallowing, Moro reflex and hypotonia;

- Step 2 12-24 hours after Step 1, irritability, staring, hypertonia, opisthotonos or seizure, vomiting, frequent apnea, high-pitch crying, the severe ones of them mostly died at this period;

- Step 3 one week later from step 2, the survivors will recover partly, but they often show high-frequency hearing loss, mental retardation, cerebral palsy (due to involved extrapyramid) with choreoathetosis, ataxia one month later.
How to give the diagnosis of isoimmunized hemolysis?

• **History for the mother in risk:** stillbirth, abortion, her baby with severe jaundice in neonatal period or bilirubin encephalopathy;

• **Early progressive hyperbilirubinemia and anemia**;

• **Laboratory findings indicate hemolysis**:  
  • Fetal-maternal blood groups incompatibility;  
  • Decreased Hb, Reticulocytosis, Increased Nucleated RBC;  
  • Direct Combs`test/Indirect Combs`test positive (Antibody releasing test for ABO incompatibility)
Diagnosis for Bilirubin Encephalopathy

Bilirubin encephalopathy often called as Kernicterus, kern-, meaning nuclear and icterus, meaning jaundice

- History of hyperbilirubinemia and relative high-risk factor: preterm, sepsis, acidosis (metabolic acidosis), hypoxemia, hypoalbuminemia;
- Clinical manifestations;
- Brain stem auditory evoked potential show weak or absent response to high auditory threshold and prolonged latency;
- MRI shows hyperintensity on T2WI at globus pallidus (characteristic)
Bilirubin Encephalopathy MRI
Bilirubin Encephalopathy MRI
**Therapy for HDN and Unconjugated hyperbilirubinemia**

- **Antepartum:** monitoring the titer of antibody (Rh)
  - If >1:64, early labor;
  - Severe one: plasma exchange transfusion;
  - Transfusion of packed RBC;
  - In utero exchange transfusion

- **Prevention of kernicterus**
  1. **Phototherapy:** lipid soluble bilirubin water soluble (photoisozimer, or structural isozimer)
     - wave length 427-475nm
     - intensity 160~320 W
     - distance 20~25cm
     - Be aware of dehydration and cover eyes and reproductive organs
  2. **Exchange Transfusion:** In Rh disease selected blood group compatible with infant`s and Rh(-); ABO: O packed RBC, AB /O plasma; Exchanged volume 150~180ml/kg.
Therapy for HDN and Unconjugated hyperbilirubinemia

Indications:
- Rh disease
- Diagnosed one with Hb<12mg/L, edema, HF and hepatosplenomegaly;
- Progressive increasing Total Bil >12µmol/L/hour, or >342 µmol/L;
- Preterm, or one with severe hemolysis in last gestation, particular in hypoxia, acidosis, sepsis and hypoglycemia.

Drugs:
- Correct acidosis, Albumin, Phenobarbital

Others: Prevention of hypoxia, hypoglycemia, hypothermia, dehydration, VitaminK3, SMZ