Neonatal Jaundice and Cholestasis

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Bilirubin metabolism

• Heme is catalyzed by heme-oxygenase in the presence of P-450
• Bilirubin is conjugated to 2 molecules of glucuronide which come from UDPG dehydrogenase
• Conjugated bilirubin is then excreted into the bile and then into the intestines where it is transformed into urobilinogen by bacteria

Neonatal jaundice

• Direct vs. indirect
  – Direct bilirubin = conjugated bilirubin
  – Direct >1.5 mg% or greater than 15% of total bilirubin is abnormal (indicates direct or conjugated hyperbilirubinemia)
  – Conjugated bilirubin is water-soluble but unconjugated bilirubin is more lipid soluble
Unconjugated Hyperbilirubinemia

Neonatal unconjugated hyperbilirubinemia

- Physiologic jaundice
  - Delayed conjugation and increased turnover of heme, as well as immature secretory system within the liver and an immature excretory system outside the liver
  - Bilirubin peaks at 6-12 mg/dl by day 4-6. Usually jaundice appears by day 2-3. Max usually about 15 mg/dl.
  - Urine is pale and stools normal color

Causes for exaggerated physiologic jaundice

- Prematurity
- Medications
- Bruising
- Inadequate oral intake
- Delayed stooling
- Breast feeding
Question 1
- Breast fed 40 day old baby with total bilirubin 6.2/direct bili 0.5, sudden rise to 15 with normal direct bili. What is not a possible cause for the increase in indirect bilirubin?
  A. breast milk jaundice
  B. sepsis
  C. biliary atresia
  D. fasting

Neonatal unconjugated hyperbilirubinemia
- Red flags in “physiologic jaundice”
  - jaundice in first 36 hr. of life
  - total hyperbilirubinemia >12 mg/dl
  - persistent hyperbilirubinemia after 8 days age
  - elevated conjugated hyperbilirubinemia (>1.5 mg/dl)
Neonatal unconjugated hyperbilirubinemia

- Breast milk jaundice
  - Jaundice becomes apparent after 5-6 days of life or
  - Physiologic jaundice deepens
  - Rarely exceeds 20 mg/dl, max
  - Can last 6-8 weeks
  - Decreases significantly after holding breast feeding for 2-3 days.

Breast milk jaundice pathophysiology

- An unusual metabolite of progesterone, a substance in the breast milk that inhibits uridine diphosphoglucuronic acid (UDPGA) glucuronyl transferase
- Increased concentrations of nonesterified free fatty acids that inhibit hepatic glucuronyl transferase
- Increased enterohepatic circulation of bilirubin
- Defects in uridine diphosphate-glucuronyl transferase (UGT1A1) activity in infants who are homozygous or heterozygous for variant Gilbert syndrome promoter polymorphism

Neonatal unconjugated hyperbilirubinemia

- Breast milk jaundice treatment
  - Continued breast feeding increasing frequency
  - Cessation of breast feeding for 24-48 hrs (rarely indicated)
  - Phototherapy as indicated
Early feeding in the neonatal period does all of the following except:

A. Slows down intestinal motility

B. Promotes the development of a normal bacterial flora

C. Improves the evacuation of meconium

D. Increases the amount of uridine diphosphoglucuronic acid

Neonatal unconjugated hyperbilirubinemia

- Hemolytic anemia
  - Production of heme activates heme-oxygenase leading to increased bilirubin. Low neonatal levels of UDPG dehydrogenase causes slower conjugation.
  - 1st 36 hrs.
  - Normal colored urine and stool
  - Signs of hydrops fetalis or hepatosplenomegaly
  - Peripheral smear shows numerous erythroblasts
Neonatal unconjugated hyperbilirubinemia

- Causes of hemolytic anemia
  - blood group incompatibilities
  - hereditary hemolytic syndromes
  - neonatal infections of bacterial or viral origin

Neonatal unconjugated hyperbilirubinemia

- Crigler-Najjar syndrome
  - Types I and II; absence of UDP-glucuronyl transferase.
  - Presents soon after birth with jaundice, light urine and grayish stools. Kernicterus frequently occurs
  - Type II patients can respond to phenobarbital.

Question 3

- 10 week old brought into office by mother, you note that baby appears jaundice. At 3 weeks of age had a TB 8.2, DB 0.3 mg/dL. Baby is otherwise well, light colored urine and green stool. Is this still within the realm of “okay” for breast fed babies?

  A. Yes     B. No
Question 3

- 10 week old brought into office by mother, you note that baby appears jaundice. At 3 weeks of age had a TB 8.2, DB 0.3 mg/dL. Baby is otherwise well, light colored urine and green stool. Is this still within the realm of “okay” for breast fed babies?

A. Yes    B. No

Unconjugated hyperbilirubinemia

- Gilbert’s syndrome
  - often exaggerated elevation of bilirubin under times of stress such as fasting, intercurrent illness, or times of significant stress
  - Deficiency of UDP-glucuronyl transferase
  - Males:females 2:1 to 7:1
  - Autosomal dominant with incomplete penetrance

Other causes neonatal unconjugated hyperbilirubinemia

- Pyloric stenosis
- Hypothyroidism
- Stress
  - fasting
  - hypoxia
  - hypoglycemia
Cholestasis

Neonatal cholestasis - definition

- Physiologic
  - decrease in bile flow
- Pathologic
  - histologic presence of bile pigment in hepatocytes and bile ducts
- Clinical
  - accumulation of bile substance in extrahepatic tissues

Neonatal cholestasis - clinical manifestations

- Conjugated bilirubin >1.5 mg/dl or over 15% or total bilirubin concentration
- Neonate may not appear jaundiced till bilirubin >5.0 mg/dl, in older children may be noticeable over 2.0-3.0 mg/dl.
- most present within 1st month of life
- consider in any patient jaundiced greater than 2-3 weeks of age
Neonatal Cholestasis - Diagnostic Evaluation

History & Physical
- Family hx, pregnancy, neonatal course, extrahepatic anomalies, stool color

Fractionated bilirubin
- TB, DB

Liver injury tests
- ALT, AST, Alk phos, GGTP

Liver function tests
- PT, PTT, factors, albumin, glucose, (NH₄), (cholesterol)

Hematology
- CBC, platelets

Bacterial infection
- Urine, blood, as indicated

Paracentesis
- If ascites present

Neonatal cholestasis - diagnostic evaluation (cont’d)

- Ultrasound
- Serum α-1-antitrypsin [and phenotype]
- Infectious serologies (HbsAg, TORCH)
- Ohio Newborn Metabolic screen: amino acids, organic acids, CF, thyroid
  - Total of 32 disorders screened

Neonatal cholestasis - diagnostic evaluation (cont’d)

- HIDA (hepatic function and excretion)
- Liver biopsy: routine histology, immunohistochemistry, EM, viral cultures
- Exploratory laparotomy & intraoperative cholangiogram
Biliary Atresia

Intrahepatic Vs. Extrahepatic biliary atresia (EHBA)

<table>
<thead>
<tr>
<th></th>
<th>Intrahepatic</th>
<th>EHBA</th>
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<tbody>
<tr>
<td>Male gender</td>
<td>66%</td>
<td>45%</td>
</tr>
<tr>
<td>Low birth wt.</td>
<td>2680g</td>
<td>3230g</td>
</tr>
<tr>
<td>Onset jaundice</td>
<td>23 days</td>
<td>11 days</td>
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<tr>
<td>Onset acholic stools</td>
<td>30 days</td>
<td>16 days</td>
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<tr>
<td>Hepatomegaly</td>
<td>53%</td>
<td>87%</td>
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30 day old FT infant with total bilirubin of 6.2 and direct of 3.2 mg/dl, enlarged hard spleen and liver. What is likely diagnosis?

A. Crigler-Najjar type II
B. Physiologic jaundice
C. Biliary atresia
D. Gilbert’s syndrome
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B. Physiologic jaundice  
C. Biliary atresia  
D. Gilbert’s syndrome

Biliary Atresia (EHBA)

• Progressive, sclerosing, inflammatory process that can affect any portion of extrahepatic biliary tract  
• Leads to segmental or complete ductular obliteration; progressive/rapid development of endstage liver disease due to persistent intrahepatic inflammation

Clinical forms of EHBA

- Perinatal form
  - 65-90% of cases
  - Obliteration of fully formed bile ducts
  - Late onset
  - Initially jaundiced free
  - Bile duct remnants present
  - Occasional association with other anomalies

- Embryonic form
  - 10-35% of cases
  - Early onset
  - Jaundiced at birth
  - Minimal bile duct remnants
  - Often associated with other anomalies
Congenital anomalies associated with EHBA

- Single (59%) vs. combination (29%)
- Polysplenia or asplenia
- Cardiovascular defects
- Abdominal situs inversus
- Intestinal malrotation
- Portal vein anomalies
- Hepatic artery anomalies

Carmi, 1993

EHBA outcome

- Timing
  - Surgery center

McKiernan, 2000

EBHA outcome dependent on timing

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<th>Age at Referral</th>
<th>% success</th>
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<td>&lt; 8 weeks</td>
<td>86%</td>
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<tr>
<td>&gt; 8 weeks</td>
<td>36%</td>
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Alagille, 1979
EHBA outcome

- Timing
- **Surgery center**
  - definite improved outcome (w/o transplant) in centers where surgery is done frequently

Pathology of EHBA

Post EHBA repair

- Nutrition may need to be met by increased caloric intake
- Psychological development may be impaired due to nutritional deficiencies and due to parental anxieties
- Immunizations should not be delayed and they should receive both Hepatitis A and B vaccines sooner than later
Vitamin supplementation

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<tr>
<th>Deficiency</th>
<th>Treatment</th>
<th>Toxicity</th>
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<tr>
<td>A Corneal damage</td>
<td>5k – 25k units/day</td>
<td>Hepatotoxicity; dermatitis; pseudotumor cerebri,</td>
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<td></td>
<td></td>
<td>Hypercalcemia; lethargy, arrhythmia, nephrocalcinosis</td>
</tr>
<tr>
<td>D Rickets, hypocalcemia</td>
<td>Vit D. 800-5K units/day; 25OH-Vit D₃ 3-5 μg/kg/d</td>
<td>None known due to E (PEG hyperosmolarity if renal failure present)</td>
</tr>
<tr>
<td>E Peripheral neuropathy; retinopathy, ataxia; ophthalmoplegia</td>
<td>TPGS 15-25 IU/kg/d or α-tocopherol 25-200 IU/kg/d</td>
<td>None known due to E (PEG hyperosmolarity if renal failure present)</td>
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<td>K Coagulopathy</td>
<td>2.5 mg BIW – 5 mg qd</td>
<td>Clotting diathesis?</td>
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Extrahepatic cholestasis

- EHBA
- Choledochal cyst
- Choledocholithiasis
- Spontaneous CBD perforation

Choledochal cyst-MRCP
Idiopathic Neonatal Hepatitis (INH)

- Sporadic vs. Familial
- Cholestasis is in central zones within hepatocytes and canaliculi and rarely in bile ducts
- Prominent giant cell transformation
- Prominent extramedullary hematopoiesis
- No fat present on biopsy

Prognosis of Idiopathic Neonatal Hepatitis

- Sporadic INH
  - 74% recover
  - 7% chronic liver disease
  - 19% death
- Familial form
  - 22% recover
  - 16% chronic liver disease
  - 63% death

TPN-associated Cholestasis

- Mostly in critically ill premature pts who are not receiving enteral nutrition
- Risk factors:
  - Increasing prematurity
  - Longer duration of exclusive TPN
  - Severe gastrointestinal disease
    - NEC, gastrochisis or intestinal atresia, short gut
  - Hypoxia or hyperperfusion
  - Other medications, sepsis, or localized infections
Clinical features TPN-assoc Cholestasis

- Conjugated hyperbilirubinemia
- Hepatomegaly
- Acholic stools
- Elevated AST/ALT/alkaline phosphatase/GGT
- Contracted GB on U/S
- Liver biopsy

TPN-associated Complications

- Biliary sludge
- Cholelithiasis
- Acalculous cholecystitis

Question 5

- 6 week old brought into the office by the parents due to worsening jaundice. Taking a hypoallergenic formula (USA), and is maybe a little fussier. Family history remarkable for prolonged jaundice in some cousins, hypertension, and emphysema. Differential includes all but which one?

A. Galactosemia  
B. Sepsis  
C. Alpha-1-antitrypsin deficiency  
D. Biliary atresia
**Question 5**

- 6 week old brought into the office by the parents due to worsening jaundice. Taking a hypoallergenic formula (USA), and is maybe a little fussier. Family history remarkable for prolonged jaundice in some cousins, hypertension, and emphysema. Differential includes all but which one?

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<td>D. Biliary atresia</td>
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**Neonatal α-1-antitrypsin deficiency**

- Liver disease primarily associated with PiZZ, rare association with PiZ null and PiZS
- Only 15% of PiZZ develop liver disease in 1st 20 years of life
- If present in neonatal period, 50% develop micronodular cirrhosis

**Intrahepatic causes of neonatal cholestasis**

- Giant cell hepatitis
- Paucity of intrahepatic bile ducts
  - Syndromic (Alagille’s)
  - Nonsyndromic
- Progressive familial intrahepatic cholestasis
  - FIC1 deficiency
  - BSEP deficiency
  - MDR3 deficiency
  - 3βHSD deficiency
Bile Duct Paucity defects

Alagille’s syndrome
(arteriohepatic dysplasia)

- Associated abnormalities
  - Eye: posterior embryotoxon
  - Heart: pulmonic stenosis, Tetralogy of Fallot, ...
  - Skeletal: butterfly vertebrae, foreshortened fingers, stunted growth
  - Renal: interstitial nephritis, glomerular disease
  - Facial: prominent forehead, hypertelorism, flattened malar eminence, pointed chin
  - Other: mental retardation

Prognosis of Alagille’s syndrome

- Mortality 17-28% due to either liver disease or cardiac disease
- Liver disease present in 95% in 1st yr. life
- Survival post transplant 75%
- Inheritance autosomal dominant with incomplete penetrance
Non-syndromic bile duct paucity

- Causes
  - Prematurity
  - Infection: CMV, rubella, syphilis, hepatitis B
  - Metabolic: alpha-1-antitrypsin, CF, Zellweger syndrome, Byler syndrome, Ivemark syndrome, prune belly syndrome, hypopituitarism
  - Genetic: Trisomy 18 & 21, partial trisomy 11, monosomy X
  - Severe idiopathic neonatal hepatitis
  - Isolated/idiopathic

Progressive familial intrahepatic cholestasis

- Clinically: pruritus, steatorrhea, poor growth, progression to cirrhosis
  - Low or normal serum GGT (PFIC-1 and –2)
  - High GGT (PFIC-3)
- Diagnosis
  - GGT, cholesterol, sweat chloride may be elevated, liver biopsy shows little inflammation, canalicular bile plugs with characteristic granular appearance on EM, small duct paucity possible

Drug induced liver disease

- Prolonged chloral hydrate (conjugated hyperbilirubinemia)
- Drugs through maternal breast milk (eg carbamazepine)
- Furosemide (cholelithiasis)
- Antibiotics such as ceftriaxone (cholelithiasis)
Vascular causes of cholestasis

- Budd-chiari syndrome (rare)
  - Hepatomegaly, splenomegaly or ascites, jaundice in infants
- Veno-occlusive disease
- Severe congestive heart failure
- Neonatal asphyxia
- Neoplasia

Metabolic disorders associated with neonatal cholestasis

- Lipid disorders
  - Gaucher’s disease
  - Niemann-Pick disease
  - Wolman’s disease
- Amino Acid disorders
  - Tyrosinemia
- Carbohydrate disorder
  - Galactosemia
  - Fructosemia
  - Glycogen storage disease, Type IV

Miscellaneous metabolic defects causing neonatal cholestasis

- Cystic fibrosis
- Neonatal iron storage disease
- Copper overload
- Indian childhood cirrhosis
- Zellweger syndrome
- Hypopituitarism
- Hypothyroidism
Infectious causes of neonatal cholestasis

• Viral
  – CMV
  – Hepatitis A and B
  – Herpes simplex
  – Rubella
  – Reovirus
  – ECHO
  – Coxsackie
  – Varicella

• Bacterial
  – Mycobacterium
  – Toxoplasmosis