Don’t be Mellow When an Infant is Yellow: Deciphering Cholestasis

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Learning Objectives

• Discuss at least three functions of the liver
• Identify the most common diagnoses for cholestasis in the newborn
• Describe the long-term treatment for an infant with a cholestatic liver disease including pharmacological therapies

What percentage of all term and late preterm newborns develop jaundice?

A. 10%
B. 25%
C. 50%
D. 80%

Liver Physiology

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Liver Physiology

• Distribution/metabolism of all nutrients
• Bile production
• Detoxification
• Assists immune system
• Supports normal blood circulation

Disclosures

Role: Research Coordinator

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• Our patients and families
What is Bilirubin?
- Degradation of hemoglobin
- Heme → biliverdin heme oxygenase
- Biliverdin reduced to unconjugated bilirubin and bound to albumin and circulated to liver
- In liver, unconjugated bilirubin is conjugated with glucuronic acid → excreted into small intestine
- Bilirubin
  - Gets unconjugated and reabsorbed into portal circulation OR
  - Modified by GI flora/intestinal enzymes into bilirubin pigments → stool

Types of Hyperbilirubinemia
- Indirect/unconjugated hyperbilirubinemia
  - Physiologic
  - Breast Milk
  - Hemolytic anemias
- Direct/conjugated hyperbilirubinemia
  - Cholestasis

Physiologic Jaundice
- Unconjugated hyperbilirubinemia – non-pathologic
- When does it occur?
  - After 1st postnatal day
- How long does it last?
  - Up to 1 week

Breast Milk Jaundice
- Unconjugated hyperbilirubinemia – non-pathologic
- Early-onset
  - When does it occur?
  - How long can it last?
- Late-onset
  - When does it occur?
  - How long can it last?

Hemolytic Anemias
- ABO
- Rh
- G6PD

Risk Factors for Severe Hyperbilirubinemia
- Cephalohematoma
- East Asian
- Exclusively breastfed
- Isoimmune/hemolytic disease
- Jaundice
- Lower gestational age
- Predischarge Tbili high-risk or high-intermediate-risk zone

Maisels et al., 2009. Pediatrics
Laboratory Definition

- INDIRECT + DIRECT \( \equiv \) TBILI
- UNCONJUGATED + CONJUGATED \( \equiv \) TBILI
- FRACTIONATION OF BILIRUBIN =

What physical exam finding(s) aid(s) the NP in identifying jaundice in the infant?

A. Skin color
B. Sclera color
C. Oral mucosa
D. Combination of above

At what age should the NP fractionate the bilirubin in a full-term, well-appearing jaundiced neonate?

A. 1 week
B. 2 weeks
C. 3 weeks
D. 4 weeks
E. 5 weeks

If a full-term, well-appearing jaundiced neonate is exclusively breast-fed, at what age should the NP fractionate the bilirubin?

A. 1 week
B. 2 weeks
C. 3 weeks
D. 4 weeks
E. 5 weeks

In which race is there a higher incidence of G6PD, putting them at risk for severe hyperbilirubinemia and kernicterus?

A. Asians
B. Blacks
C. Caucasians
D. Native Americans, Eskimos
E. Pacific Islanders
Differential Diagnosis of Hyperbilirubinemia

- Infection
- Metabolic disorders
- Toxins
- Genetic disorders
- Obstruction
- Prematurity
- Shock
- ECMO

From Fawaz et al., 2016; Suchy et al., 2001

Approach to Hyperbilirubinemia

- Detailed H & P
  - Pregnancy history
  - Family history
  - Neonatal course
  - Extrahepatic anomalies
  - Stool color
- Laboratory testing
  - Fractionated bilirubin
  - Alk phos; GGT
  - Liver function tests
  - CBC
  - Bacterial cultures

From Suchy et al., 2001

Defining Cholestasis

- "reduced bile formation or flow resulting in the retention of biliary substances within the liver normally excreted into bile and destined for elimination into the intestinal lumen."
- "...conjugated (or direct) hyperbilirubinemia is a practical clinical marker and surrogate of cholestasis."

From Fawaz et al., Journal of Pediatric Gastroenterology and Nutrition. 2016

How many term neonates develop cholestasis?

A. 1 in 500 – 1,000
B. 1 in 1,500
C. 1 in 2,500 – 5,000
D. 1 in 6,000 – 8,000

Most Common Causes of Persistent Cholestasis

- TPN-cholestasis
- Idiopathic neonatal hepatitis (INH)
- Alpha-1-antitrypsin deficiency (A1AT)
- Bile acid synthesis defects
- Progressive familial intrahepatic cholestasis (PFIC)
- Alagille syndrome (AGS)
- Biliary atresia (BA)

Of these diseases, which one needs to be identified as early as possible?

A. Alagille syndrome
B. Idiopathic neonatal hepatitis
C. Biliary atresia
D. Alpha-1-antitrypsin deficiency
E. Progressive familial intrahepatic cholestasis
Biliary Atresia

- Progressive oblitative idiopathic cholangiopathy
  - Uniformly lethal if untreated
  - F>M
  - Incidence

- Etiology
  - Ductal plate remodeling?
  - Genetics?
  - Viral infections?
  - Immunological?

Diagnosing Biliary Atresia

- History and physical exam
  - Detailed history
  - Physical exam
    - Facial features
    - Skin
    - HEENT
    - Cardiac
    - Abdomen
    - Nutritional status
    - Neuro

- Diagnostic studies
  - Routine laboratory tests
  - Ultrasound
  - HIDA scan
  - Liver biopsy
  - Intraoperative cholangiogram (IOC)

Is This Stool Acholic?

A. Yes
B. No
C. Unsure

Ultrasound Findings

- Absent or small gallbladder
- Triangular cord sign
- Cyst at porta hepatis
- Increased echogenicity
- Nondilated intrahepatic ducts and nonvisualized CBD

HIDA Scan

Does this HIDA scan show tracer excretion into the intestines?

A. Yes
B. No
C. Unsure
Liver Biopsy

Portal inflammation
Bile plugs
Ductular proliferation

Intraoperative Cholangiogram

Kasai Procedure

Timing of Diagnosis/Treatment is KEY

<table>
<thead>
<tr>
<th>Age at operation (days)</th>
<th># Cases</th>
<th>10 yr. survival # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–50</td>
<td>63</td>
<td>36 (57%)</td>
</tr>
<tr>
<td>61–70</td>
<td>49</td>
<td>20 (41%)</td>
</tr>
<tr>
<td>71–90</td>
<td>61</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>78</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>251</td>
<td>84 (33%)</td>
</tr>
</tbody>
</table>


Post-Kasai Outcomes

- Survival with native liver (SNL)
  - USA
  - England/Wales
  - France
  - Netherlands

CHILDReN Outcomes (U.S.A)

At CHLA over 50% of pts with bilirubin <2 within 3 months remain transplant-free at 3 yr.

Superina et al, Ann Surg 2011
**Post-Operative Management**

- Antibiotics
- Analgesics
- Oral bile acid therapy
- Steroids
- Vitamin supplements
- Bilirubin/LFTs
- Family education for discharge

**Are steroids beneficial in improving outcomes post-Kasai for all patients with BA?**

A. Yes  
B. No  
C. Unsure

**Hospital Discharge – Now What??**

CHOLANGITIS  
TRANSPLANT?  
WHO ELSE HAS THIS?  
NORMALCY  
FUTURE?

**Chronic Disease and the Family**

- Emotional pain/disappointment
- Blame
- Decreased self-worth
- Fear/apprehension
- Grief, “chronic sorrow”

**Primary Care Management**

- Regular f/u with pediatric hepatologist/GI
- Post-operative check
- VACCINES
- Growth and nutrition
- OTC medications
- Re-enforcement of signs/symptoms to watch for
- Open communication

**Fat Soluble Vitamins**

- **Vitamin A**  
  – Integral for vision, immune function, and growth
- **Vitamin D**  
  – Integral for bone health, immune function, growth, and prevention of chronic disease
- **Vitamin E**  
  – Powerful antioxidant; prevents damage to cells
- **Vitamin K**  
  – Component of many proteins in body including those involved in clotting and bone formation
What percentage of pediatric liver transplants are for biliary atresia?

A. 10%
B. 20%
C. 30%
D. 40%
E. 50%

Liver Transplant

- Biliary atresia
- Inherited syndromes
- Alpha-antitrypsin
- Viral ("TORCH")
- "Nonrenal hepatitis"
- Metabolic
- Other

Where Do We Go From Here?

- Determine etiology
- Screening
- Education

Screening for BA - Taiwan

Screening for BA – PoopMD app

http://www.hopkinsmedicine.org/news/media/releases/free_poop_app_newly_equipped_to_evaluate_potential_as_health_intervention

Screening in the US?
Resources

- http://childrennetwork.org
- www.transplantliving.org
- www.alagille.org
- www.alpha1.org
- www.classkids.org
- www.rarediseases.info.nih.gov
- www.raredisease.org
- www.pfic.org
- www.childliverdisease.org
- www.niddk.nih.gov
- PoopMD+ at iTunes store (Apple) and Google Play (Android) (free)

References

References
