### Congenital and Pediatric Liver Diseases

Nitika Arora Gupta, MD, DCH, DNB, MRCPCH (UK)
Associate Professor
Department of Pediatrics
Division of Gastroenterology, Hepatology & Nutrition
Emory University School of Medicine
Nitika.gupta@emory.edu

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### What is Cholestasis?

- Process that results in a decrease in bile flow/formation
- Presence of bile pigment in hepatocytes and BD
- Accumulation of substances in the blood and extra hepatic tissues which are normally excreted in the bile duct (bilirubin, bile salts and cholesterol)
- Cholestasis ≠ Jaundice
- Jaundice is a convenient clinical marker for cholestasis and can be caused by the failure to excrete bilirubin in bile

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### Neonatal Cholestasis

- Neonatal liver is sensitive to injury and has limited response
- Immaturity of the hepatic excretory function
- Susceptibility to sepsis
- Physiologic hypercholeremia
  - levels of bile salts in blood of infants similar to pathologic states in adults

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### Personal/Professional Financial Relationships with Industry in the past year

<table>
<thead>
<tr>
<th>Financial Relationship</th>
<th>Company Name</th>
<th>Role</th>
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<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>None</td>
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<td>Board of Directors or officer</td>
<td>None</td>
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<td>Royalties from Emory or from external entity</td>
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<tr>
<td>Industry funds to Emory for my research</td>
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<tr>
<td>Other</td>
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</table>
Neonatal Cholestasis

- Disorders accounting for > 95% of diagnoses
  - Biliary Atresia
  - Neonatal Hepatitis
  - Progressive Familial Intrahepatic Cholestasis
  - Alpha 1 Antitrypsin Deficiency
  - Choledochal cyst
  - Drug related, Total Parenteral Nutrition-associated
  - Paucity of bile ducts (syndromic and non syndromic): Alagille’s syndrome

Biliary Atresia

- Progressive destruction of intra and extra hepatic bile ducts
- Can be classified according to the extent of extrahepatic biliary damage
- Classification does not generally correlate with clinical outcome
Biliary Atresia

• Clinical features
  – Full term
  – Jaundice present at birth
  – Hepatosplenomegaly
  – Dark urine
  – Acholic stool
  – Elevated direct bilirubin (>2 or > 20% of total), GGT (> 100 IU/L)
  – Normal Albumin and Prothrombin time early in course
  – Untreated, death by 2 years of age

Biliary Atresia

• Etiology is unknown
• May be the final clinical phenotype of several biliary injuries
  – Two major classifications
    • Fetal/embryonal
    • Acquired

Ultrasound

Liver Biopsy

- Liver biopsy
  - Reliable
  - A single biopsy may be limited by the dynamics of the disease

HIDA scan

- Excretion into bowel and bladder
- No excretion
- Choledochal cyst

Intra-operotive cholangiogram

- Normal
- Biliary Atresia

Stool color

1. 3
2. 2
3. 1
**Biliary Atresia: Screening**

- Early identification important to outcome
- Screening
  - Bile acids in dried blood spots (US)
  - Conjugated bilirubin between 6-10 days of age (UK)
  - Stool color charts (Taiwan)
    - sensitivity and specificity for the detection of biliary atresia are 97.1% and 99.9%, respectively
  - Stool color chart (Swiss)

**Biliary Atresia**

Kasai Operation- hepatoportoenterostomy

**Management**

- Surgery: Kasai portoenterostomy
- Fat soluble multivitamins: ADEK
- Ursodeoxycholic acid
- Nutrition, nutrition, nutrition: MCT
- Prophylactic antibiotics
- Therapy for pruritus: Rifampin, cholestyramine
- Management of complications: PHT, LT

**Choledochal cyst**

- Congenital abnormality of the bile duct
- Can present with acholic stools
- LFTs might or might not be elevated
- Diagnosis: Ultrasound, MRI
- Management: Resection portoenterostomy
- Outcome: generally good, long term risk of cholangiocarcinoma
Choledochal cysts

Makin and Davenport. Archives of Dis in Childhood 2012

Jaundice in the newborn

• Anatomic
  – Choledochal cysts
• Infections
• Metabolic
• Familial
• TPN Cholestasis
• Miscellaneous

TPN cholestasis

Precise etiology unknown, likely multifactorial
Risk factors are well-characterized:

• Prematurity
• Absence of enteral feeds
• Bowel surgery
• Repeated episodes of sepsis
• Lipids

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An Analysis of Factors Contributing to the Development of Total Parenteral Nutrition-induced Cholestasis

Parenteral nutrition and neonatal cholestasis

Parenteral nutrition and neonatal cholestasis

Parenteral nutrition and neonatal cholestasis
What causes liver injury?

The precise etiology probably multifactorial, with risk factors including prematurity, history of bowel resection and/or lack of enteral feeds, catheter infections and/or sepsis, and lack of or presence of specific components in the parenteral nutrition itself.

Animal models suggest that there is a developmental component to bile acid transporter gene expression; these factors indicate that the expression of critical hepatic protective genes might be involved in susceptibility to PNAC.

Animal models of parenteral nutrition administration suggest that parenteral nutrition itself and/or particular components of the nutrition might affect key hepatic bile acid transporters, apoptotic signaling, and other detoxification and proliferation/ductopenia at the gene level, thereby promoting cholestasis.

Outcomes of TPN cholestasis

High Rates of Mortality and Morbidity Occur in Infants With Parenteral Nutrition–Associated Cholestasis

Thomas C. Wilke, MD; Beth A. Garcia, MD; Stefania P. Rogers, MD; Jill N. Hershberger, MD; Bruce D. Israe, PNP; and Steven A. Myers, MD

Diagnosis/outcomes of TPN cholestasis

Cholestasis, bile pigment

Steatosis, fibrosis, bile duct proliferation/ductopenia
Outcome of TPN cholestasis

The improvement in liver function usually begins only after full enteral nutrition is tolerated and PN is withdrawn.

Management of TPN cholestasis

- Enteral feeds
- UDCA: Levine et al 1999
- Vitamin supplementation
- Management of complications: PHT, LT

Neonatal Hepatitis

- Infections
  - CMV, EBV, HSV, TORCH
  - Parvovirus B19
  - Listeria, syphilis
  - Gm pos and Gm neg: Ecoli, Staph
  - Enterovirus /adenovirus
  - HIV
  - Paramyxoviruses
  - Hepatitis viruses

CMV hepatitis

- 5-10% develop clinical symptoms
- Low birth weight, microcephaly, cerebral calcifications, chorioretinitis, low platelets, purpura, deafness
- Hepatosplenomegaly
- Liver bx: Giant cell transformation, intranuclear inclusion bodies
- Usually mild, self resolving
**Metabolic liver disease**

- Urea cycle defects
- Disorders of lipid metabolism: Niemann Pick disease, Cholesterol ester defect
- Disorders of AA metabolism: Tyrosinemia
- Disorders of carbohydrate metabolism: Galactosemia, fructosemia, GSD Type 4
- Mitochondrial defects

**Endocrine**
- Hypothyroidism
- Pan hypopituitarism
- Down’s syndrome

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**Familial Neonatal Cholestasis**

- Familial
  - PFIC
  - Alagille’s syndrome
  - Cystic fibrosis
  - BA synthetic defects

**Progressive familial intrahepatic cholestasis**

- Autosomal recessive familial cholestasis
- Recurrent, benign; progressive cholestasis, pruritus
- Type 1 and 2: Low GGT; Type 3: Normal to high GGT
- Diagnosis: gene mutation testing(ATP8B1, ABCB11, ABCB4) and biopsy
- Management: UDCA, rifampin, cholestyramine, biliary diversion, OLT
Cystic Fibrosis

- Abnormal chloride transport caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) located on chromosome 7
  - Abnormally tenacious mucus and secretions in the:
    - Lungs
    - Intestine
    - Pancreas
    - Hepatobiliary system

Alagille’s syndrome

- AD disorder associated with liver, heart, skeletal and eye abnormalities
- 1 in 100,000
- Jaundice, poor growth, pruritus, mild developmental delay
- At least 3 of the following: Cholestasis, butterfly vertebrae, posterior embryotoxon, peripheral pulmonic stenosis
- Diagnosis: Clinical, biopsy, JAG 1 mutation
- Management: nutrition, pruritus, complications, OLT

Alpha1-antitrypsin deficiency

- 1 in 600 to 1 in 2000 live births, AR
- Defective secretion of α1-antitrypsin from the liver
- Mutant α1-antitrypsin Z (misfolded) protein is trapped in the ER of the hepatocyte
- Causes liver injury in 10% to 20% of affected individuals
- Destructive lung disease/emphysema in adulthood
- Diagnosis: Phenotype, biopsy (PAS+)
- Management: nutrition, complications, OLT
Summary

• Injury to the liver is common in the neonatal period
• Critical to exclude biliary atresia vs neonatal cholestasis
• Common disorders: Infections, TPN, hypoxia, metabolic, familial disorders
• Detailed history and systematic work up is important
• Medical and nutritional management
• Timing of orthotopic liver transplantation

Thank you!