Neonatal Liver Disease

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Outline

• Embryology
• Etiologies of neonatal liver disease
• Approach to neonate/infant with liver disease
• Liver is derived from **endoderm**.
• It forms from a diverticulum (bud) which branches out from the primitive gut.
• The pancreas develops dorsally, while the liver bud develops ventrally.
Development of the Liver, Gall Bladder and Pancreas

- pharynx
- esophagus
- stomach
- liver
- gall bladder
- ventral pancreas
- yolk stalk

- liver
- ventral pancreas
- gall bladder
- dorsal pancreas
- common bile duct
- ventral pancreas
• The liver metabolizes nutrients absorbed from the gut: first organ to receive intake.

• It removes toxic compounds which are absorbed by modifying them so they are soluble.
• At birth the hepatocyte is already specialized with two surfaces:

  – Sinusoidal side: receives and absorbs a mixture of oxygenated blood and nutrients from the portal vein;

  – Canalicular side: delivers bile and other products of conjugation and metabolism (especially drugs) to the canalicular network which joins up to the bile ductules.
Neonatal liver diseases
Neonatal liver disease

- The estimated incidence of neonatal liver disease is as high as 1 in 2,500 live births.
Presentation

- Jaundice / Cholestasis
- ALT/AST rise
- Coagulopathy
Risk factors

- Prematurity
- NPO
- Prolong TPN
- Intestinal injury
- Sepsis and inflammation
- Hypoxia
- Hepatotoxic medications
Neonatal Hepatitis

• Nonspecific collective term for intrahepatic cholestasis due to all various etiologies in an infant or neonate.

• Idiopathic neonatal hepatitis
Differential Dx of neonatal cholestasis in 1970

- Idiopathic neonatal hepatitis: 65%
- Biliary atresia: 25%
- Miscellaneous: 7%
- Viral (TORCH): 3%
Differential Dx of neonatal cholestasis in 2004

- idiopathic NH: 10%
- Biliary atresia: 20%
- PFIC, Alagille: 20%
- Metabolic: 25%
- A-1-AT deficiency: 25%
- Viral: 5%
• Cholestasis: physiological reduction in canalicular bile formation or flow.

• Can be caused by defects in
  – Intrahepatic production.
  – Transmembrane transport of bile.
  – Mechanical obstruction to bile flow.
• Cholestasis: is primarily manifested as conjugated hyperbilirubinemia.

• Conjugated hyperbilirubinemia in a neonate is defined as:
  – Serum conjugated bilirubin concentration greater than 17.1 micromol/L if the total serum bilirubin is 85.5 micromol/L
  – Or greater than 20 percent of the total serum bilirubin if the total serum bilirubin is 85.5 micromol/L.
Etiologies

• Obstructive cholestasis:
  
  – Biliary atresia:
    
    • Occurs in 1 in 10,000 to 20,000 infants
    
    • Obliteration or discontinuity of the extrahepatic biliary system, resulting in obstruction to bile flow
    
    • Cause is unknown
    
    • Important to diagnose BA early as ideal time for successful Kasai is 45-60 days
• **Alagille syndrome:**
  
  – dominantly inherited disorder of variable expressivity. The gene has been identified as the Jagged1 (JAG1)
    
    • congenital cardiac defects (PPS)
    • posterior embryotoxon in the eye
    • dysmorphic features
    • butterfly vertebrae.
  
  – Liver biopsy will show bile duct paucity
  
  – liver transplant for hepatic decompensation, bone fractures, pruritus, and xanthomas
• Choledochal Cyst
  – Can be diagnosed with ultrasound
• Inspissated bile
• Cystic fibrosis
• Neonatal sclerosing cholangitis
• Congenital hepatic fibrosis/Caroli’s disease
Non obstructive

- Idiopathic neonatal giant cell hepatitis
  - Histologic appearance of widespread giant cell transformation
  - Non-specific and may be associated with infectious, metabolic, and syndromic disorders
  - Needs close follow up and may self resolve

- Infection
  - Sepsis
  - Cytomegalovirus, HIV, Toxoplamosis, Syphilis
• Genetic/metabolic disorders
  – α1-antitrypsin deficiency (A1AT)
  – Tyrosinemia
  – Galactosemia
  – Hypothyroidism
  – Progressive familial intrahepatic cholestasis (PFIC)
  – Cystic fibrosis
  – Panhypopituitarism

• Toxic/secondary
  – Parenteral nutrition-associated cholestasis
PFIC

• Three conditions comprise the currently known group of biliary transport defects

  – **PFIC I**: Mutations in the FIC1 gene (ATP8B1)
    • FIC1 mediates the flipping of aminophospholipids from outer to inner hemi-leaflet of the canalicular membrane
    • FIC1 is located on other tissues including the pancreas and intestine leading to other extrahepatic signs and symptoms
- PFIC II have defects in the canalicular bile salt export pump (BSEP) caused by mutation in ABCC11

- BSEP is responsible for transporting bile acids from inside the hepatocyte into the bile canaliculus
– **PFIC III** caused by mutations in ABCB4
  
  • Encodes multidrug resistance-associated protein 3 (MDR3) and mediates the flopping of aminophospholipids from inner to outer hemi-leaflet of the canalicular lipid bi-layer

• Liver disease in PFIC results from the effects of hepatocellular accumulation of bile acids
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<th>PFIC2</th>
<th>PFIC3</th>
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<td>Low</td>
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<td>Bile</td>
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<td>FIC1</td>
<td>BSEP</td>
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<td>Bile salt pump</td>
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<td>(membrane flippase)</td>
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<td>Cell localization</td>
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<td>Cyclalicular membrane</td>
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<td>membrane</td>
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<tr>
<td>Clinical course</td>
<td>Neonatal onset, variable progression</td>
<td>Neonatal onset, rapid progression</td>
<td>Neonatal or later onset with</td>
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<td></td>
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<td>cholestasis, variable progression</td>
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<td>Pruritus</td>
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<td>Histology</td>
<td>Pseudoacinar pattern of hepatocytes,</td>
<td>Giant cell transformation of hepatocytes,</td>
<td>Portal fibrosis, bile ductular</td>
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<td></td>
<td>canalicular cholestasis, coarsely granular</td>
<td>amorphous or dense bile in bile canaliculi</td>
<td>proliferation</td>
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<td>bile in bile canaliculi on electron</td>
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Pathophysiology

- Cholesterol
- Cholic acid
- Chenodeoxy cholic acid

Bile acid synthetic dis

Bile acids

PFIC type 1

Bile acids

BSEP

MDR 3

PFIC type 2

PFIC type 3

Phospholipids

Intrahepatic Bile ductule

Cholangiocyte

Water

HCO 3

Cl

CFTR

CF
TPN Cholestasis

• occurring in almost 50% of infants whose birthweights are less than 1,000 g.

• onset often seen after 2 weeks of receiving TPN

• pathogenesis of TPN-associated cholestasis is multifactorial.
• TPN-associated cholestasis has the potential to lead to progressive liver disease and cirrhosis.
TPN-associated cholestasis:

- Precise etiology remains unknown

- Risk factors are well-characterized:
  - Prematurity
  - Lack of enteral feeds
  - Intestinal surgery
  - Repeated bouts of sepsis
  - Lipid loads
Treatment: Cycling parenteral nutrition

- **Proposed benefits:**
  - Theoretical decreased risk of cholestatic liver disease
    - 2-6 hour cycle off PN promotes GI hormones
    - Improved quality of life at home

- **Caution:**
  - No prospective, randomized controlled trials confirming the hepatoprotective effect of PN cycling
  - Monitor for hypoglycemia during cycles off PN in patients with end-stage liver disease
Treatment: Ethanol locks to central lines

- Bactericidal and fungicidal via denaturing of cell membranes
- Benefits include ease of acquisition, low cost, and low likelihood of promoting antibiotic resistance
- Potential adverse effects include CNS depression, arrhythmias, local venous irritation, and flushing
- Effective alone or in combination with other agents for eradication of various microorganisms
Novel Lipid emulsion
SMOF

- S: Soybean oil
- M: MCT oil
- O: Olive oil
- F: Fish oil
• SMOFlipid 20% was safe/well tolerated
• Decreased plasma bilirubin in SMOFlipid20% cohort vs. IL cohort
• Increased ω3 FA and α-tocopherol status in SMOFlipid20% cohort vs. IL cohort without changing lipid peroxidation.
Acute neonatal liver failure

- Galactosemia
- Tyrosinemia
- Neonatal haemochromatosis
- Haemophagocytic lymphohistiocytosis and congenital leukaemia
- Septicemia and shock
- Giant cell hepatitis with hemolytic anemia
- HHV-6, Hepatitis B, Adenovirus, Parvovirus
- Mitochondrial hepatopathy
- Vascular malformations and congenital heart disease
- Maternal overdose (paracetamol)
- Hypocortisolism
APPROACH TO INFANT WITH LIVER DISEASE
History

- **H/o Neonatal infection**
  - UTI, sepsis and viral infection
- **Feeding history and history of weight gain**
  - metabolic disease can cause anorexia, FTT, and jaundice
- **Bowel history**
  - Vomiting - metabolic disease, pyloric stenosis, bowel obstruction
  - Delayed stooling—CF, hypothyroidism
  - Diarrhea—infection, metabolic disease, PFIC1, CF
  - Clay colored stool—biliary obstruction
• Dark urine color

• Source of nutrition
  – Composition of formula:
    • Galactose containing $\rightarrow$ galactosemia
    • Fructose or sucrose containing $\rightarrow$ hereditary fructose intolerance
• Lethargy
  – Hypothyroidism, panhypopituitarism, sepsis, or infection
• Excessive bleeding
  – coagulopathy, vitamin K deficiency
• Similar problem with parents or among siblings
  – A1AT deficiency, Alagille syndrome, cystic fibrosis, PFIC
• Consanguinity
  – Risk for autosomal recessive inheritance
• Maternal infection that can affect baby
  – TORCH infections, occasionally HBV
• Cholestasis of pregnancy
  – May be seen in PFIC
• Past ABO or Rh disease, or Rh negative
Physical examination

• Global assessment of general health and nutrition status
  – Dysmorphic findings (Alagille’s)
• HEENT
  – Slit-lamp findings (Alagille’s, cataracts)
• Chest/heart
  – Murmur or evidence of congenital heart disease (biliary atresia, Alagille’s)
• Abdomen
  – Liver and spleen size and consistency
  – Distention, Ascites, Abdominal wall vasculature
• **Skin**
  – Jaundice, bruising, petechiae, rashes
• **Neurologic**
  – General assessment of vigor, tone, and symmetry
• **Diaper**
  – Dark urine (conjugated hyperbilirubinemia)
  – Pale or clay colored stool (cholestasis, rule out obstruction)
Investigations

- Total and direct bilirubin
- LFT, GGT
- Synthetic function
  - PT/PTT, glucose, albumin
- CBC
- Urine and blood culture
- Viral serologies
  - TORCH infections, HBsAg, CMV, HIV if indicated
- UA
- Urine reducing substances
- Thyroid function studies
- Alpha-1-antitrypsin
- Sweat chloride or mutation analysis for CF gene
- Follow-up newborn screen
Radiological investigations

• Ultrasound with dopplers
  – Choledochal cyst
  – Portal vein thrombosis
  – For Biliary Atresia
    • Triangular cord sign (TC) - obliterated fibrous ductal remnant in the porta hepatis
    • May demonstrate absence of the gallbladder and no dilatation of the biliary tree
• HIDA scan
  – Consider biliary atresia if good hepatic uptake with no evidence of excretion into the bowel at 24 hours
  – Not specific for biliary atresia
  – Pretreatment with phenobarbital (5 mg/kg/day for 5 days) to increase biliary secretion may help minimize false positives
• Refer to Hepatology

• May need:
  – Liver biopsy
    • For BA → portal tract fibrosis, edema, ductular proliferation, and cholestasis with the appearance of bile plugs
  – Intra-op cholangiogram
  – Further work up for cholestasis including directed genetic testing
**General Principles in management of childhood cholestasis**

- Should aim for a caloric intake of 125 – 150% of the recommended dietary allowance based on ideal body weight.

- Supplement fat soluble vitamins:
  - Vit A : 5000 – 25000 IU/ day.
  - Vit D3 : 1200 – 4000 IU/day.
  - Vit E : 15 – 5 mg PO every other day.
  - If oral form is not available give Vit K injection every 2 – 3 weeks at a dose 2 – 5 mg IV/IM.
• Management of Pruritus
  – Ursodeoxy cholic acid 20 mg / kg / day BID
  – Antihistamines
    • Hydroxyzine 2 – 5mg / kg / day.
    • Diphenhydramine 5 – 10 mg / kg / day.
  – Phenobarbitone 5 mg / kg / day BID.
  – Rifampicin 10 mg / kg / day.
  – Cholestyramine 250 – 500 mg / kg / day.
Summary

• It is essential to detect liver disease in an infant through a careful history, physical examination, and fractionation of the serum bilirubin

• Many intrahepatic disorders, such as congenital infection and inborn errors of metabolism can lead to cholestasis

• Early recognition and diagnostic evaluation of the cholestatic infant is needed to manage the complications