Biliary Atresia

Progressive, idiopathic, necroinflammatory process initially involving a segment or all of the extrahepatic biliary tree.

As the disease progresses, the extrahepatic bile duct lumen is obliterated and bile flow is obstructed, resulting in cholestasis and chronic liver damage.

Clinical phenotypes

1. Fetal/Embryogenic form
   - ~ 20%
   - Associated with syndrome: Polysplenia syndrome
   - Present earlier and more severe

2. Perinatal/Postnatal form
   - ~ 80%
   - Isolated biliary atresia
   - No non-hepatic anomalies
   - Jaundice at 2-6 weeks of age

Defect in morphogenesis of biliary tract

Coexistence of non-hepatic embryologic abnormalities in embryonic form.

Abnormal remodeling of ductal plate in fetus
- compensatory bile duct proliferation
- increased bile flow in postnatal life
- bile leak & inflammation

Pathogenesis

1. Defect in morphogenesis of the biliary tract
2. Defect in fetal/prenatal circulation
3. Environmental toxin exposure
4. Viral infection
5. Immunologic/inflammatory dysregulation
6. Genetic

Defect in morphogenesis of biliary tract

Inv mouse (deletion or a recessive insertional mutation of Inversin gene): model of biliary obstruction and situs inversus.

Relationship to choledochal cysts: Antenatal detection of prestenotic cystic dilatation of the common bile duct has been reported.
Defect in fetal/prenatal circulation
- Bile ducts receive blood supply exclusively from the hepatic arterial circulation → interruptions of this flow account for bile duct damage.
- Intrauterine devascularization results in abnormal extrahepatic bile ducts.
- Frequent association in BA between abnormalities of portal vein and hepatic artery.

Environmental toxin exposure
- Time-space clustering
- The disease appears to be acquired postnatally most frequently.
- Drugs or toxins.

Viral infection
- Seasonal variation (predominating in winter)
- CMV, reovirus, rotavirus, and other viruses detected in infants with biliary atresia.
- Reovirus type 3 and rotavirus type C
- Hepatotropic viruses A, B, C and rubella have not been implicated in BA.
- Biliary obstruction in newborn mice infected with rotavirus.

Immunologic/inflammatory dysregulation
- T-cell-mediated inflammation. (Th1)
- Increased expression of intercellular adhesion molecules (ICAM-1).
- Abnormal expression of antigens in bile duct epithelium.
- ↑ frequency of HLA-B12, B8 or DR3 alleles in those without other anomalies.
- A potential role for Kupffer cells in promoting inflammation and fibrosis.

Genetic
- BA is not thought to be a heritable disorder.
- Jagged 1 gene is responsible for bile duct paucity in Alagille syndrome.
- Jagged 1 gene is involved at different stages of biliary development.
- Increased frequency of Jagged 1 mutations in cases of BA.

The next challenge in pathogenesis of Biliary Atresia: Biliary transcriptome

• Proinflammatory genes (Th 1)
  • IFN-γ
  • Osteopontin

• Apoptosis genes
  • Complement cascade

• Regulator genes and imprinted genes

IFN-γ

- Murine model of rotavirus-induced biliary atresia
  - RRV challenge
  - Jaundice, lymphocytic infiltrates at portal triads
  - Bile duct proliferation
  - Extrahepatic bile ducts obstruction by inflammatory cells
  - Duct stenosis
  - ↑ CD3/CD4+ and CD3/CD8+ lymphocytes in liver
  - Hepatic overexpression of murine IFN-γ and IL-12 genes

The loss of IFN-γ did not prevent the onset of inflammation, but significantly reduced the degree of inflammation.

IFN-γ plays a critical role in the inflammatory obstruction of extrahepatic bile ducts in an experimental model of biliary atresia.

Osteopontin

- Osteopontin (OPN)
  • Th1 cytokine
  • Implicated in several fibro-inflammatory and autoimmune diseases.

- Hepatic OPN expression is markedly increased in biliary atresia.

- Associated with proliferation of biliary structures and fibrosis.

Apoptosis genes
- Overexpression of C3a receptor-1, C1qa and C1qβ (activation of the complement cascade)
- Increased expression of genes that either trigger or drive apoptosis.
- No previous reports of an association between complement system and pathogenesis of biliary atresia in humans.

Regulator genes and imprinted genes
- Regulatory genes were predominantly in embryonic form (45% of genes)
  - SMARCA-1
  - RYBP
  - HDAC3
- Overexpression of 5 imprinted genes in perinatal form
  - IGF2
  - PEG3
  - PEG10
  - MEG3
  - IPW

Thank You