BILIARY ATRESIA : *THE PATHOGENESIS*

Surgico-pediatric conference
25 July 06

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

Barbara AH,et al. Biliary atresia. Gastroenterol Clin N Am 2003;32:891–911.

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

Barbara AH,et al. Biliary atresia. Gastroenterol Clin N Am 2003;32:891–911.
Claus P. Pathogenesis and treatment opportunities for biliary atresia. Clin Liver Dis 2006; 10: 73– 88.
Jorge AB.The next challenge in pediatric cholestasis: deciphering the pathogenesis of biliary atresia. J Pediatr Gastroenterol Nutr 2006;43:S23-9.

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

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

Jorge AB.The next challenge in pediatric cholestasis: deciphering the pathogenesis of biliary atresia. J Pediatr Gastroenterol Nutr 2006;43:S23-9.

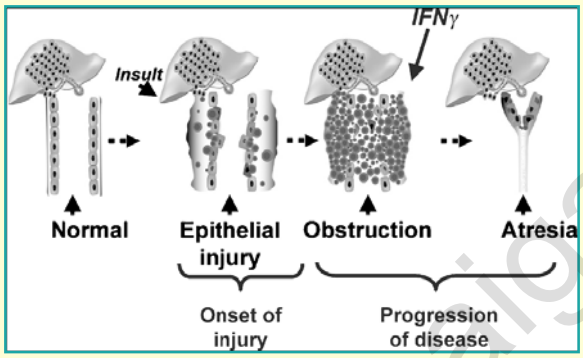
- **Proinflammatory genes (Th 1)**
  - IFN-γ
  - Osteopontin
- **Apoptosis genes**
  - Complement cascade
- **Regulator genes and imprinted genes**

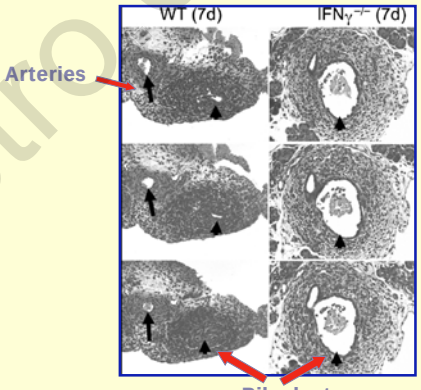
IFN-γ

- 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





IFN-γ

- 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.

Peter FW,et al. Expression of osteopontin correlates with portal biliary proliferation and fibrosis in biliary atresia. Pediatr Res 2005;57:837-44.

Apoptosis genes

- Overexpression of C3a receptor-1, C1qα 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 5 imprinted genes in perinatal form
  - IGF2
  - PEG3
  - PEG10
  - MEG3
  - IPW