PSC in Children and Adolescents: Similarities and Differences with PSC in Adults

Michael Narkewicz MD
Professor of Pediatrics Hewit-Andrews Chair in Pediatric Liver Disease
Medical Director Pediatric Liver Center

Children’s Hospital Colorado
Goals

• Describe the epidemiology of PSC in Children and Adolescents (Pediatrics)

• Describe key features and how they differ from PSC in Adults

• Describe outcome features
Key Concepts Pediatric PSC

• Incidence is $1/5^{th}$ that of Adults

• Accounts for 2-3% of liver transplants in children (<18 years of age)

• Unlike adults there are many disorders that can mimic “Primary” Sclerosing Cholangitis which are called Secondary SC
Key Concepts

• AST and ALT (liver enzymes) generally higher in PSC in Pediatrics than in Adults

• PSC in Pediatrics is a much more immunologic / inflammatory disease than in adults
  - Treatment with medications to suppress inflammation / immune response more commonly used in Pediatrics
Key Concepts

• Autoimmune hepatitis (AIH) in Pediatrics often can have bile duct inflammation and injury

• In England
  - All children with AIH have testing for bile duct involvement and colitis
  - ~40 have bile duct involvement (autoimmune sclerosing cholangitis: ASC)
Key Concepts

• The bile ducts inside the liver are more commonly affected than outside the liver
  ▪ Dominant Strictures are less common

• Cancer of the bile ducts is VERY RARE in PSC in Pediatrics
PSC Incidence Pediatrics

- Incidence: Number of new diagnosed cases in a defined period of time
  - Utah incidence per 100,000 children in 25 years
    - PSC: 0.2
    - ASC: 0.1
    - AIH: 0.4

Hepatology 58:1392, 2013
PSC Prevalence

• Prevalence: Measure that tells us the risk of developing a disease (higher than incidence): Measures all cases

• Utah: Prevalence / 100,000 Pediatric Patients for 25 years
  - PSC: 1.5
  - ASC: 0.6
  - AIH: 3.0

Hepatology 58:1392, 2013
### Average Age at Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Avg Age (yrs)</th>
<th>% Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC</td>
<td>13</td>
<td>76</td>
</tr>
<tr>
<td>ASC</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>AIH</td>
<td>10</td>
<td>34</td>
</tr>
</tbody>
</table>

- Like adults, most are males
- Mayo: 2/3s male, 1/3 female
- Male/Female about the same for ASC

- 80% with PSC have IBD

Progression of Liver Disease

- Development of complications in 5 years
  - PSC 37%
  - ASC 25%
  - AIH 15%

- 5 year survival with native liver (no transplant)
  - PSC: 78%
  - ASC: 90%
  - AIH: 87%

Net 85% 5 year survival with native liver

Hepatology 58:1392, 2013
IBD and PSC: Similar to Adults

- My child has IBD, what is their risk of developing PSC?

- 1.5% of 1009 children with UC had PSC (JPGN 51:140, 2010)

- 9.5% (Utah) – 35% (Houston) of pediatric patients with UC had PSC

- 0.6% of pediatric patients with Crohn disease developed PSC

- Most diagnosed with PSC after IBD diagnosis

Pediatric PSC Treatment Differences with Adult PSC

- Autoimmune involvement, some have a good response to immunosuppression (ASC)
- Histologic changes of SC with no associated radiologic changes (small duct SC) Thus stents less useful
- Ursodeoxycholic acid: no controlled study of ursodeoxycholic acid in children: still used and guidelines do not give direction
Bile duct involvement common in AIH in children

- 55 patients with AIH
- ERCP/MRCP and sigmoidoscopy
- 23 ERCP/MRCP abnormalities 40% ASC
- Autoimmune Sclerosing Cholangitis:
  - More IBD 44% vs 18%
  - More ANCA positive 74% vs 36%
  - More cholangitis on biopsy: 35% vs 12%

Hepatology. 2001;33:544
Liver biopsy
ERCP in AIH

A Normal

B Abnormal

Hepatology. 2001;33:544
Pediatric AIH/PSC

- Pediatric patients with AIH
- Large percentage have ERCP/MRCP abnormalities
- UK recommends ERCP/MRCP on all patients with AIH
- Alternative approach: ERCP/MRCP if signs of biliary involvement
- Overlap of inflammation between liver cell injury and bile duct injury is more common in children
Cholangiocarcinoma

- “Rare” in Pediatric PSC
- 6.9% prevalence in Utah study (2 cases)
- Other rare case reports in the literature
- All in the older adolescent population

- Need a good partnership with adult PSC team to help sort this out
IgG4 Sclerosing Cholangitis

- IgG4-related sclerosing disease
- Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) RARE
- Characterized by sclerosing inflammation with abundant IgG4-positive plasma cells
- Most cases associated with pancreatitis
- IgG4/IgG1 cells elevated in Autoimmune PSC
- Elevated IgG4 cells (>10/HPF) present in ampulla and bile duct biopsy in 52%

Liver Transplant

• ~500 liver transplants per year in pediatrics
• ~2.6% of pediatric transplants due to PSC (10-20 per year)
• Excellent 1 year (98.7%) and 5 year (86.6%) patient survival rates
• About 10% have recurrent bile duct injury/PSC
Summary

• Compared to PSC in Adults, Pediatric PSC has
  • More immune / inflammation
  • May respond better to immunosuppression
  • Involves the small bile ducts more than the large bile ducts
  • May have a better outcome overall and a better transplant survival
QUESTIONS?
Model for Intestinal Inflammation Promoting Autoimmune Disease

Intestinal Inflammation

1. Bacterial Overgrowth/Pathogenic Species
2. Activation of Innate Immune System
3. Inflammation and Lesions
4. Absorption of LPS, bacteria
5. Activation of Kupffer Cells (KC) & Stellate Cells (SC)
6. Development of autoantibodies

Liver Injury
Bile duct injury
Pancreatic injury

Lipid mediators
IgG4

Chemokines
Cytokines

Inflammation → Fibrosis → Cirrhosis

Intestinal Inflammation

1. Bacterial Overgrowth/Pathogenic Species
2. Activation of Innate Immune System
3. Inflammation and Lesions

6. Immune mediated targeted injury to Biliary and Pancreatic ductal epithelium