Adolescent and Pediatric Primary Sclerosing Cholangitis

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Outline

Child and adolescent PSC vs Adult
- Variations in the disease
- Variations in the response
- Need for transplant
Definition

- Chronic liver disease involving the bile ducts
- Cause unknown
- Diffuse inflammation of biliary ducts = scarring
  - Narrowing
  - Obstruction
  - Dilation
- Frequently associated with inflammatory bowel disease
- Can lead to cirrhosis and portal hypertension
Clinical Presentation

- Elevated bilirubin or liver function enzymes
- Elevated GGT
- Most often asymptomatic
- May present with colitis and find liver disease also ~40% of time
- Fatigue, Jaundice, weight loss common
Diagnostic Criteria

- Cholangiogram abnormalities involving any part of the biliary tree (ERCP or MRCP)
- Biopsy proven bile duct scarring

Clinical and Laboratory findings
- Cholestasis (elevated bilirubin, LFTs, GGT)
- Alkaline phosphatase 2 to 3x normal
- IBD
- Autoantibodies
Prevalence of Autoantibodies

- Autoantibodies
  - P-ANCA 80%
  - AMA <2%
  - ANA 50-60%
  - SMA 35%
Primary Sclerosing Cholangitis

Comparison of ERCP and MRCP

Pruning
Primary Sclerosing Cholangitis

Classic Case of PSC

Multifocal stricture

Upstream dilation
Concentric Fibrosis in PSC

Bile duct

Concentric fibrosis
Relationship to Inflammatory Bowel Disease

- IBD in 60-80% of PSC patients
- Ulcerative colitis more common than Crohn’s disease (2:1)
- 4-5% of UC patients have PSC
PSC Associations

- Majority of adults with PSC have an associated non-liver disease
  - IBD
  - Diabetes Mellitus
  - Pancreatitis
  - Thyroid disease
  - Other autoimmune disease

- In children is mostly associated with IBD
# Primary Sclerosing Cholangitis

## Features Used in Prognostic Models

<table>
<thead>
<tr>
<th>Mayo Clinic (n=174)</th>
<th>King’s College (n=126)</th>
<th>Multicenter (n=426)</th>
<th>Swedish (n=305)</th>
<th>New Mayo Model (n=405)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Hepatomegaly</td>
<td>Bilirubin</td>
<td>Bilirubin</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Biopsy Stage</td>
<td>Biopsy Stage</td>
<td>Biopsy Stage</td>
<td>Biopsy Stage</td>
<td>Biopsy Stage AST</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Splenomegaly</td>
<td>Splenomegaly</td>
<td>Splenomegaly</td>
<td>Variceal Bleed</td>
</tr>
<tr>
<td>Inflammatory Bowel disease</td>
<td>Alkaline Phosphatase</td>
<td></td>
<td></td>
<td>Albumin</td>
</tr>
</tbody>
</table>
Disease Therapy

- Dilation of dominant strictures
- No proven medical therapy
  - Management of fat-soluble vitamin deficiencies = A, D, E, K
  - Screening for cancer
    - Lifetime risk for cholangiocarcinoma 7-15%
    - Incidence 0.5 to 1%
    - Smoking and IBD may increase risk
  - Screen for portal hypertension
  - Antibiotics for cholangitis
Primary Sclerosing Cholangitis

Medical Therapy Tested to Date

<table>
<thead>
<tr>
<th>Penicillamine</th>
<th>Colchicine</th>
<th>Mycophenolate Mofetil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>Methotrexate</td>
<td>Silymarin</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Budesonide</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Pirfenidone</td>
<td>Ursodeoxycholic acid</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Etanercept</td>
<td>(possible benefit)</td>
</tr>
</tbody>
</table>
Liver transplantation

- Survival
  - 1 year: 90-95%
  - 5 year: 85-88%

- Slight increase in problems with rejection and infection compared to other liver diseases

- PSC can reoccur post-transplant
Patterns of PSC in Children

- AIH/PSC overlap
  - “Autoimmune Sclerosing Cholangitis (ASC)”
- Small duct PSC
- Classic PSC
ASC

Strong autoimmune features
- Autoantibodies: ANA, SMA, IgG
- Sometimes looks like AIH but progresses to PSC
- 60% have perinuclear antineutrophil cytoplasmic antibodies (p-ANCA)

Bile duct damage – inflammation of bile ducts
Also inflammation attacking hepatocytes as well called “interface hepatitis”
Usually bile duct damage less advanced may not be evident on cholangiogram
ASC vs Classic PSC

- Younger age
- More females
- High ALT and IgG
- Less IBD
- If IBD present does not correlate with liver activity
- Good response to immunosuppression and Ursodiol
- Decreased need for OLT and less cancer than classic PSC in 8 year f/u

Floreani et al. Am J Gastroenterol 2005;100:1516-1522
Small duct PSC

- 5% of PSC
- Normal Cholangiogram but biopsy shows PSC
- Can progress to classic PSC
- +/- colitis
Small Duct PSC

- Findings of bile duct damage on liver biopsy
- No biliary abnormalities on MRCP or ERCP
# Reports on Pedi/Adol PSC

<table>
<thead>
<tr>
<th></th>
<th>Mount Sinai 2009</th>
<th>Mayo Clinic 2003</th>
<th>King’s College 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (M:F)</td>
<td>43 (3:2)</td>
<td>52 (2:1)</td>
<td>27 (1:1)</td>
</tr>
<tr>
<td>Age at dx</td>
<td>11</td>
<td>13.8</td>
<td>11.8</td>
</tr>
<tr>
<td>IBD</td>
<td>59%</td>
<td>81%</td>
<td>44%</td>
</tr>
<tr>
<td>Classic PSC</td>
<td>40%</td>
<td>56%</td>
<td>9/27</td>
</tr>
<tr>
<td>AIH/PSC</td>
<td>25%</td>
<td>35%</td>
<td>18/27</td>
</tr>
<tr>
<td>Small Duct PSC</td>
<td>34%</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>
## Reports on Pedi/Adol PSC

<table>
<thead>
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<th>Mount Sinai 2009</th>
<th>Mayo Clinic 2003</th>
<th>King’s College 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transplant</strong></td>
<td>9/43</td>
<td>11/52</td>
<td>4/27</td>
</tr>
<tr>
<td></td>
<td>(19% within 7 to</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 yrs of dx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reccurence</strong></td>
<td>1 patient 10 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>after OLT</td>
<td>3/11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>within 6 years of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>transplant</td>
<td></td>
</tr>
<tr>
<td><strong>Survival post-OLT</strong></td>
<td>89% at 10 years</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td><strong>Dilation of strictures</strong></td>
<td>6/43</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colectomy</strong></td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Child vs Adult PSC

<table>
<thead>
<tr>
<th></th>
<th>Child/Adolescent</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>F&gt;M</td>
<td>M&gt;F</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>0.23 per 100,000</td>
<td>1.11 per 100,000</td>
</tr>
<tr>
<td><strong>IBD at presentation</strong></td>
<td>40 to 60%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Overlap with AIH</strong></td>
<td>35%</td>
<td>7-10%</td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td>UDCA good</td>
<td>UDCA moderate</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression -good</td>
<td>Immunosuppression - rare</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Best for small duct dx</td>
<td>Depends on stage at presentation</td>
</tr>
<tr>
<td></td>
<td>Depends on stage at presentation</td>
<td></td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
<td>50% transplanted 12 yrs from time of diagnosis</td>
<td>50% transplanted 12 yrs from time of diagnosis</td>
</tr>
<tr>
<td><strong>Recurrence after OLT</strong></td>
<td>27%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Recurrence after Transplant

- Report from the most experienced Living related Donor program
- All PSC patients transplanted over 10 years, 30 total, 10 excluded
- 11/20 had recurrence from 26-71 months post trplnt
  - Risk factors were related donor, early CMV infection and age

<table>
<thead>
<tr>
<th>Donor</th>
<th>Number pt (% of pt)</th>
<th>Relapse %</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-related</td>
<td>5 (25)</td>
<td>20%</td>
<td>1</td>
</tr>
<tr>
<td>Parents</td>
<td>10(50)</td>
<td>80%</td>
<td>17</td>
</tr>
<tr>
<td>Son</td>
<td>2(10)</td>
<td>50%</td>
<td>11</td>
</tr>
<tr>
<td>Sibling</td>
<td>3(15)</td>
<td>33%</td>
<td>3</td>
</tr>
</tbody>
</table>
Consequences of Liver Disease

Hepatocyte damage

Bile duct damage

Poor function
Liver Scarring
Cirrhosis
Portal Hypertension
Consequences of Liver Disease

Poor function

- Jaundice
- Fatigue
- Poor weight gain and muscle mass
- Weak bones
- Deficiencies in Fat-soluble vitamins
- Itching
Monitoring of Liver Disease

- Nutrition
- Bone health
- Medications for itching
Monitoring of Liver Disease

- **Monitor for portal hypertension**
  - Endoscopies
  - Banding varices
  - Beta-blockers to prevent bleeding
  - Shunts to prevent bleeding

- **Monitor for cancer**
  - Check serum markers
  - Radiologic studies
Different Care for PSC in Children - Not Small Adults?

- Vigilant for bile duct involvement in IBD
  - If elevated LFTS or GGT
  - Need liver biopsy and MRCP

- Vigilant for bile duct involvement in Autoimmune hepatitis

- Vigilant for IBD in PSC
  - Need endoscopy and colonoscopy for screening
Different Care for PSC in Children?

- If Autoimmune features (ASC) present will use immunosuppression
- All get Ursodiol
- Screen for IBD regardless of symptoms
- Focus on nutrition and growth
- Focus on bone health
- Less focus on cancer
Conclusion

- Speak to your Doctor about what you read
- Very little data in children – not “small adults”
- Controversies in care are not black and white – wide spectrum of disease
Conclusion

Research leads to improvements in therapy for liver disease each year – especially in children

The future is bright

Keep looking ahead……

Thank you for coming