Primary sclerosing cholangitis: the pediatric perspective.

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Objectives
• To review current nomenclature and diagnostic challenges
• To review pathogenic mechanisms
• To discuss treatment options for PSC and outcomes in children.

Primary sclerosing cholangitis (PSC) is a chronic fibro-inflammatory disorder of the biliary tree that affects children and adults, in whom it gives rise to characteristic cholangiographic and histopathological appearances.

Diagnosis
Children with PSC typically present to pediatric gastroenterologists with no or few symptoms, which if present may include lethargy, itch or jaundice. They may have been found to have hepatosplenomegaly on physical examination. Bloodwork results may have demonstrated elevated aminotransferases, gamma-glutamyl transferase (GGT) and/or alkaline phosphatase (1-4). Abdominal ultrasound scan may have shown heterogeneous liver parenchyma, thickened common bile duct wall, dilated intra- or extra-hepatic bile ducts, and/or perihilar lymphadenopathy.

The pediatric gastroenterologist must first determine whether this clinical presentation is due to PSC. Diagnostic criteria for PSC in children have not been validated. The Studies of PSC (“STOPSC”) multicentre research consortium proposed diagnostic criteria that require the presence of two of the following three conditions:
• Elevated GGT or alkaline phosphatase,
• Intrahepatic and/or extrahepatic bile duct irregularities consistent with PSC (MRC, ERCP, PTC or intra-operative cholangiogram),
• Liver biopsy abnormalities consistent with chronic biliary injury.

In addition, there should be no evidence of a secondary cause of sclerosing cholangitis. Numerous causes of secondary sclerosing cholangitis have been reported and should be considered and excluded in all patients as appropriate for their clinical circumstances (Table 1) (5). Distinct from these causes of secondary sclerosing cholangitis, PSC is known to be associated with various co-morbidities, most notably inflammatory bowel disease.
Many centres now view magnetic resonance cholangiography (MRC) as the preferred imaging technique for the diagnosis of PSC, following advances in the quality of images obtained and the relative lack of safety concerns when compared to endoscopic retrograde cholangiography (ERC). ERC maintains a role primarily for management of obstructing biliary strictures. Clinicians must carefully consider the risks and benefits of ERC when used solely for confirmation of small intrahepatic duct disease that may be beyond the resolution of MRC.

Liver biopsy frequently provides important additional information in the diagnostic process for PSC in children, including

• Demonstration of features consistent with PSC
• Demonstration of features of autoimmune hepatitis to enable a diagnosis of autoimmune sclerosing cholangitis (ASC) to be reached,
• Staging the severity of disease,
• Finding or excluding features of other liver diseases.

The diagnosis of ASC also requires knowledge of total immunoglobulin G level, and the presence of anti-nuclear and/or anti-smooth muscle autoantibodies. Many centres will also evaluate anti-neutrophil cytoplasmic antibodies. Anti-liver kidney microsomal antibody is very unlikely to be found in children with ASC, although its assessment is included by some clinicians to ensure completeness.

Children presenting with possible PSC will also require testing to rule out other liver diseases as appropriate for their clinical circumstances.

**Categories of sclerosing cholangitis**

Children who fulfill diagnostic criteria for sclerosing cholangitis may be classified as having:

**Primary sclerosing cholangitis.** Absence of evidence of a secondary cause, although often in the setting of associated conditions including inflammatory bowel disease and autoimmune diseases.

**Secondary sclerosing cholangitis.** Features of sclerosing cholangitis identified to be secondary to another disease process (Table 1).

**Small duct PSC.** Clinical, bloodwork and liver biopsy findings consistent with PSC, but with normal cholangiography.

**Autoimmune sclerosing cholangitis.** Also known as “PSC with autoimmune hepatitis overlap”, ASC is diagnosed when features of PSC are found in a patient with positive anti-nuclear and/or anti-smooth muscle antibodies (rarely anti-liver kidney microsomal antibody), elevated IgG and liver biopsy abnormalities that include features of autoimmune hepatitis (especially lympho-plasmacytic infiltrate with interface hepatitis) as well as those of PSC.

**Neonatal PSC.** Usually presenting with cholestasis in the newborn period, cholangiographic imaging shows changes consistent with PSC.
Pathogenic mechanisms of PSC
Recent reviews of this area are available (6, 7). A proposed model suggests that an initial insult to cholangiocytes may be caused by infection or the effects of microbial products, autoimmunity, toxins, dietary exposures, or other unknown factors. In the genetically susceptible host, this initial insult generates inflammation and chronic damage to bile ducts with their subsequent progressive, immune-mediated destruction. This ultimately results in cholestasis and cirrhosis. Evidence for genetic susceptibility suggests a complex genetic disease, and has focused on the MHC complex. A recent genome wide association study confirmed that HLA associations and a subset of genes involved in bile homeostasis and inflammation constituted key components of the “genetic architecture” of PSC (8).

Table 1. Examples of conditions associated with sclerosing cholangitis (5)

<table>
<thead>
<tr>
<th>Conditions associated with primary sclerosing cholangitis</th>
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<tbody>
<tr>
<td>Inflammatory bowel disease</td>
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<td>Autoimmune &amp; connective tissue disorders</td>
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<tr>
<th>Causes of secondary sclerosing cholangitis</th>
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<tr>
<td>Abnormalities of immune function</td>
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<tr>
<td>e.g. Immunodeficiency, liver transplant rejection, GVHD</td>
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<td>Infiltrative disorders</td>
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<td>e.g. Langerhans cell histiocytosis, lymphoma</td>
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<td>Recurrent cholangitis ± choledolithiasis</td>
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<td>Pancreatitis</td>
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<td>Ischemic bile duct damage</td>
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<tr>
<td>Others</td>
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<tr>
<td>e.g. Cystic fibrosis, portal biliopathy, Caroli disease, Kabuki syndrome</td>
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Treatment of PSC
Early studies showed that ursodeoxycholic acid (UDCA) effectively reduces the degree of elevation of liver enzyme values including GGT and transaminases (9). This evidence led to widespread use of UDCA in adults and children with PSC.

More recently, two studies in adults with PSC have explored the effectiveness of UDCA in improving long-term outcomes including mortality rate and the likelihood of liver
transplantation. A European multicentre study showed a non-significant trend towards better outcomes with UDCA treatment at 20 mg/kg/day, but was underpowered after a failure to recruit the target number of patients (10). A subsequent study in the USA using high dose UDCA (30 mg/kg/day) in adult patients was stopped early due to the observation of increased incidence of the composite primary outcome (including liver decompensation, liver transplantation and death) in patients receiving UDCA (11). As a result of these studies, some experts recommend that UDCA is no longer indicated for the treatment of PSC in adults (12). Data for the use of UDCA in children with PSC are sparse, do not include randomized, controlled clinical trials, and therefore no evidence-based recommendation can be reached.

Enteral antibiotics have been reported to improve liver enzyme values in several small case series of adults and children with PSC (13). No controlled clinical trials have yet been conducted and therefore the widespread use of these agents for children with PSC cannot yet be recommended.

Following a diagnosis of ASC, liver enzyme values improve with treatment with UDCA and immunosuppressive therapy, using corticosteroid and/or azathioprine in a similar approach to that employed for autoimmune hepatitis (4). The management of ASC has not yet been tested in controlled clinical trials and therefore no evidence-based recommendation can be reached. It is important to note that liver enzyme values improve with UDCA treatment alone in children with PSC and positive autoantibodies but no histological evidence of autoimmune hepatitis (4).

References