Chapter

Primary Sclerosing Cholangitis (PSC) in Children

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic liver disease of unknown aetiology affecting extrahepatic and/or intrahepatic bile ducts causing its inflammation and fibrosis with most frequent consequences including biliary cirrhosis and liver failure. The incidence of PSC in children and adolescents is 0.2 per 100,000 children per year, when in adults the reported incidence is higher and equals 0.5 to 1 in 100,000 individuals per year. PSC is more common among men and boys. The diagnosis is usually established in the second decade of life in the paediatric population with the mean age of diagnosis of 13.8 years. Many studies point out a strong correlation between IBD and PSC, especially ulcerative colitis. The prevalence of IBD among children with PSC diagnosis varies from 60 to 99%; however, the incidence of PSC is about 12% in patients with ulcerative colitis and fluctuates about 2–5% in Crohn's disease diagnosed patients. Clinical symptoms are present in approximately half of cases and they are unspecific in many of them. Elevated liver enzymes and biochemical markers of cholestasis are sometimes the only signs of PSC. Gold standard for PSC diagnosis is magnetic resonance cholangiopancreatography (MRCP) as a non-invasive procedure comparing to endoscopic retrograde cholangiopancreatography (ERCP) which is also used in some cases. The aim of the study was to review the risk factors, clinical symptoms, diagnostic methods and treatment of paediatric patients with primary sclerosing cholangitis.

Keywords: primary sclerosing cholangitis, children

Primary sclerosing cholangitis (PSC) is a chronic liver disease of unknown aetiology affecting extrahepatic and/or intrahepatic bile ducts causing its inflammation and fibrosis with most frequent consequences including biliary cirrhosis and liver failure. The incidence of PSC in children and adolescents is 0.2 per 100,000 children per year when in adults the reported incidence is higher and equals 0.5 to 1 in 100,000 individuals per year. Several studies indicate the incidence of primary sclerosing cholangitis is increasing. A similar increase has been seen in most autoimmune diseases. PSC is more common among men and boys. The diagnosis is usually established in the second decade of life in the paediatric population with the mean age of diagnosis of 13.8 years [1–9].

Many studies point out a strong correlation between IBD and PSC, especially ulcerative colitis. The prevalence of IBD among children with PSC diagnosis varies from 60 to 99%, however the incidence of PSC is about 12% in patients with ulcerative colitis and fluctuates about 2 to 5% in Crohn's disease diagnosed patients. In children, the diagnosis of IBD generally precedes the diagnosis of PSC [10–15].

1. Aetiology

The pathogenesis of PSC is unknown, but a number of mechanistic theories have been proposed. Despite the lack of scientifically proven aetiological factors, many components can be responsible for the PSC development.

1.1 Genetic background

Genetic background including an impact of HLA-A1, B8, DR3 haplotypes are one of the suspects as the diagnosis is made at a young age and family occurrence has been reported. Genome-wide comparisons of the frequency of genetic variants have provided a means of dissecting genetic risk in the many human diseases primary sclerosing cholangitis included. In the pathogenesis of PSC can play the role the presence of more non-HLA genes related to immunity and/or bile homeostasis. However most PSC genes appear to relate to adaptive immune reactions. There are limited genetic links between IBD and PSC. The HLA class 1 (expressed on all cells) and HLA class II (expressed on antigen- presenting cells) present potentially antigenic peptides derived from intra- and extracellular sources, to the T cell receptor (TCR) on CD* and CD4 T cells. But the antigenic peptides are unknown. Data suggest the presence of PSC specific TCR in the livers of patients. The predominant cell type in the portal inflammatory infiltrate in liver patients with primary sclerosing cholangitis is the T cell. It is suggested that there is cross-reaction between cholangiocytes and T-cells. Some of scientists believe that genes as PRDX5, TGR5, PSMG1, NFKB1 may play a role in innate immune reactions [11, 16–18].

1.2 Bile acids toxicity

The concentric fibrosis around the bile ducts in PSC is found in a variety of conditions and likely represents a final pathway for bile ducts injury. Defects of mechanisms protecting against bile acid toxicity can be a factor playing an important role in PSC development. The biliary epithelium shows an activated phenotype in PSC, including an expansion of the peribiliary gland system [19–21].

1.3 Autoimmunologic factors

What is more, certain autoimmune reactions in genetically susceptible individuals seem to play an important role as well. The presence of non-specific autoantibodies such as ANA, ANCA (in >80% of patients) and anti-SMA (in >60% of patients) together with autoimmune diseases such as autoimmune hepatitis (overlap syndrome PSC/AIH in 25–35%), rheumatoid arthritis, autoimmune thyroiditis or type 1 diabetes mellitus suggests that PSC can be described as an autoimmune disease. However its prevalence among men (2:1) and the lack of response to immunosuppressive therapy contributed to the concept of PSC being rather an immune-mediated disease. PSC with high immunoglobulin 4 (IgG4) levels and autoimmune hepatitis overlap syndrome have been described. But the lack of the efficacy of immunosuppressive treatment despite isolated autoimmune aetiology [11, 22–25].

1.4 Role of microbiota

The predominant coexistence of PSC and IBD led to a theory that dysregulation of gut microbiota in IBD patients causes liver T-cell activation provoking an inflammatory response in bile ducts. There is increasing appreciation of the co-metabolic functions of the gut microbiota in the bile homeostasis. The composition of the gut

microbiota in PSC has been described using sequencing technologies. However, data from other diseases suggests that reduced bacterial diversity occurs prior to and independent from clinical manifestations [26–29].

2. Clinical picture

Clinical symptoms are present in approximately half of cases and they are unspecific in many of them. Most frequently patients complain of abdominal pain, fatigue and/or abdominal pain. Malaise, jaundice, splenomegaly or pruritus are reported less often. Elevated liver enzymes and biochemical markers of cholestasis are sometimes the only signs of PSC. The diagnosis of PSC may precede that of IBD, which may even present after liver transplantation for PSC. PSC may present in an IBD patients even after colectomy. Multiple gallbladder abnormalities in the course of primary sclerosing cholangitis including: dilatation (15%), gallstones (25%), cholecystitis, hydrops, polyps (4–6%), carcinoma (2.5–3.5%) are observed more often in patients [2, 8, 17, 22, 29, 30].

2.1 Forms of PSC

1. **Classical large-duct PSC**.

2. **Small-duct PSC**. A diagnosis of small-duct PSC is made upon histological findings characteristic of PSC and clinical and biochemical abnormalities suggestive of PSC. The HLA associations with IBD in small-duct PSC resemble those of large-duct PSC and suggest shared aetiologies between large-duct PSC and small -duct PSC in the presence of IBD.

3. **PSC with high IgG4**. PSC patients with elevated IgG4 are less responsive and data suggest they may progress more rapidly than other PSC patients. IgG4 may be involved in the pathogenesis of autoimmune cholangitis and clinical response upon treatment with the anti-CD20 antibody (rituximab).

4. **PSC-AIH overlap syndrome**. Biochemical and histological features of autoimmune hepatitis are apparent in 7–14% of patients with PSC. Elevated transaminases and IgG may indicate autoimmune hepatitis, but may be elevated as a part of the biliary disease.

5. **PSC with cholangiocarcinoma**.

3. Diagnostics

The diagnosis is based on laboratory and imaging results as well as on elimination of other than PSC cholestatic diseases. When it comes to laboratory results among children, gamma-glutamyltransferase (GGT) is more specific cholestatic marker than alkaline phosphatase (ALP) as ALP levels tend to fluctuate during bone growth. Even though ultrasound (USG) is a cheap and simple way to visualise liver pathology, bile ducts abnormalities characteristic of PSC might not be visible. Gold standard for PSC diagnosis is magnetic resonance cholangiopancreatography (MRCP) with acceptable sensitivity and specificity as a non-invasive procedure comparing to endoscopic retrograde cholangiopancreatography (ERCP) which is also used in some cases. As typical cholangiographic changes define the diagnosis

of PSC, prognostic scoring system. To diagnose small duct PSC which is a type of PSC affecting intrahepatic ducts only, as well as to confirm the presence of PSC/AIH overlap syndrome it is necessary to perform liver histology. In recent years, there has been interest in the development of noninvasive tests of liver fibrosis for stratification and prognosis in PSC. Serum tests of liver fibrosis reflect fibrogenesis (APRI, Fib4 score). Liver stiffness measurement by transient elastography has been validated for the assessment of liver fibrosis in the liver diseases. Elastography in patients with PSC well correlate with the degree of fibrosis, performing best at the extremes of histological stage [5, 11, 31–34].

3.1 Differential diagnosis of PSC

1. Choledocholithiasis.
2. Congenital abnormalities of bile duct.
3. Cholangiocarcinoma without PSC.
4. Traumatic/ischemic changes in bile ducts.
5. HIV infection.
6. Infestation (ascaris, lambliosis)
7. Sarcoidosis.
8. Pyogenic cholangitis

3.2 Patients with PSC need control every 6 months

- Clinical review
- Serum liver tests
- Tumour marker: Ca 19-9, AFP
- Ultrasonography examination
- MRI/MRC if cirrhosis

4. Prognosis and complications

PSC is a progressive disease where bile ducts fibrosis lead to cirrhosis and liver failure. PSC has a highly variable natural history. Asymptomatic patients have been shown to have a better prognosis than patients with symptoms at diagnosis. Comparing to adults, PSC in children seems milder, yet 15–45% of paediatric patients will require liver transplantation within 6–12 years after the diagnosis. The increased risk of biliary cancer and colorectal cancer in PSC is firmly established and of major clinical importance. The risk of cholangiocarcinoma (CCA) is about 160 times higher than in the general population. In spite of that, only 1% of patients experience this serious complication. In a multi-centre study of 7000 PSC patients hepatobiliary malignancy was diagnosed in 10.9%. Up to 50% of

cholangiocarcinoma are detected within a year of PSC diagnosis. Unfortunately, PSC diagnosed children may also develop other types of cancers such as gallbladder, colon or hepatocellular cancer. In the majority of cases, the early stages of cholangiocarcinoma are asymptomatic. Sometimes are observed abdominal pain, weight loss, increasing jaundice. Diagnosis of cholangiocarcinoma is based on tumour marker Ca19-9, imaging modalities, biliary brush cytology. The indication for liver transplantation in patients with dysplasia and no signs of cholangiocarcinoma remain controversial. Presence of dysplasia of any grade has been reported in 83% of explant livers with PSC-cholangiocarcinoma and 36% without cholangiocarcinoma. MRI and CT may visualise early features of cholangiocarcinoma in PSC but difficulties in distinguishing inflammatory, bening and malignant lesions lead to suboptimal diagnostic accuracy. Combined MRI/cholangioMRI has the highest sensitivity and specificity and is preferred for detection of small focus cholangiocarcinoma. Liver transplantation or surgery with complete resection is the only treatments with curative intent for cholangiocarcinoma. Liver transplantation with neoadjuvant therapy (external beam radiotherapy, endoluminal brachytherapy, chemotherapy) can be considered in patients with unresectable, perihilar early stage. Systemic chemotherapy remains the palliative treatment for patients not eligible for surgery. Other palliative treatment strategies include endoscopic stenting and photodynamic therapy.

PSC-IBD whether considered UC or Crohn's disease is almost universally colonic (usually a pancolitis) with a right-sided predominance, backwash ileitis and rectal sparing. The risk of colorectal cancer is fivefold higher than in IBD without PSC and may occur at any time from diagnosis. Colonoscopy should be performed in patients with PSC regularly from the moment of diagnosis. Chromoendoscopy is being increasingly recommended to facilitate detection of flat lesions with dysplasia. Four quadrant biopsies from all colonic segments and the terminal ileum should be performed. Hepatocellular and pancreatic cancer also occur in patients with PSC, but frequencies are lower than in cirrhosis liver from other causes. Currently there are no established prognostic tools that reliably estimate prognosis of the patients [2, 35–46].

5. Treatment

Effective ways of PSC treatment are still lacking. Immunosuppressive medications did not show any benefits, while oral vancomycin therapy might be an option although more data is required. Symptomatic treatment of PSC also consists of supplementing the deficiencies of fat-soluble vitamins, preventing the development of osteoporosis and combating chronic itching: by using additional cholestyramine at a dose of 6–8 g/24 h and/or rifampicin. For patients refractory to the above-mentioned treatment, oral naloxone therapy (50 mg/24 h) may be effective.

5.1 Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is commonly used and has been proved to reduce GTP and AP levels which are both good prognostic factors improving patients' survival. However, UDCA treatment did not result in improved outcomes compared to no intervention. New therapeutic applications have been derived from this research in the form of norUDCA, to enhance general resistance to bile acid induced biliary injury. NorUDCA is slightly amidated in the liver, it is secreted into the bile in both unbound and glucuronic acid form. The biliary-hepatic flow of unbound norUDCA induces excessive secretion of bile rich in bicarbonate. Studies in mouse

models have shown that the drug is less toxic, more effectively prevents peripheral fibrosis, proliferation of hepatocytes and cholangiocytes, reduces the content of hydroxyproline and infiltrating immune cells. In addition, it improves cholestasis parameters [6, 31, 47–48].

5.2 Vankomycin

Antibiotics, particularly vancomycin, may have a positive effect on PSC either via direct effects on the microbiome or via host-mediated mechanisms. In addition vancomycin has possible immunomodulatory and anti-inflammatory mechanisms, But there is not currently sufficient evidence to support treatment recommendations. Further research is needed to establish if vancomycin is a PSC treatment [48–50].

5.3 ERCP

Bile duct strictures are possible complications in the course of the disease that can be treated with prothesis during ERCP. The generally accepted arbitrary definition is stenosis of <1.5 mm in the common bile duct or <1 mmin the hepatic duct within 2 cm of the hilum. The incidence of complications associated with ERCP in patients with PSC is 4–18% [44, 46, 48].

5.4 Liver transplantation

Liver transplantation is a life-saving procedure with generally good outcomes, however, up to 16% of paediatric patients are affected by recurrent primary sclerosing cholangitis (rPSC) after transplantation. The indications for liver transplantation in PSC are similar to other liver diseases and transplanted with a qualifying MELD/PELD score in a patient with cirrhosis [11, 29, 51].

5.5 Treatment of bacterial cholangitis

Cholangitis occurs frequently but symptoms may be atypical. Prophylactic antibiotics should be ordered prior to and following biliary interventions. Positive bacterial or fungal cultures of bile can be associated with worse prognosis. Sometimes patients with recurrent cholangitis require long-term, rotating antibiotics.

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