Diagnosis and therapeutic problems of primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) leads to a progressive destruction of the intra- and extrahepatic bile ducts. The cause is unknown but genetic and immunological mechanisms may play a role. The median survival time from diagnosis to death is about 12 years. MRCP is almost equal to ERCP for diagnosing PSC and shows the typical localised or multifocal strictures and interfering segments of ectatic bile ducts. Liver histology can be helpful in making the diagnosis but is often unspecific and there is a large sampling variability.

The treatment of PSC is disappointing. The combination of ursodeoxycholic acid with endoscopic dilatation is probably the best treatment. Patients with cirrhosis and/or recurrent cholangitis should be evaluated for liver transplantation as the outcome after liver transplantation is good, especially if there is no cholangio-carcinoma present and if the Child-Pugh score is not too high. There is also a need to treat the complication of PSC such as osteoporosis, cholangitis and the development of cholangiocarcinoma. (Acta gastroenterol. belg., **2003**, 66, **155-159**).

Key words : primary sclerosing cholangitis, complications, treatment, cholangiocarcinoma, osteoporosis, ursodeoxycholic acid, endoscopic treatment, colorectal cancer.

Introduction

Primary sclerosing cholangitis (PSC) is associated with a progressive destruction of the intra- and extrahepatic bile ducts. The aetiology of the biliary destruction is still unknown but genetic and immunological mechanisms play probably a role. The prevalence of PSC is between 6 to 9 /100 000 inhabitants in the USA and in Scandinavia but is much lower in Spain (2.2 / 1 000 000 inhabitants). The disease is more present in male patients, about 2/3 are men (1,2).

Natural history of PSC

Today, 15 to 45% of the patients are asymptomatic at the time of diagnosis. About 22% develop symptoms in the forthcoming 5 years. However, some asymptomatic patients can have already an advanced disease. The patients who develop symptoms are often related to cholestasis, portal hypertension, liver failure and exacerbations of PSC. The median survival time from diagnosis to death is about 12 to 18 years, but can be longer in asymptomatic patients (2,3).

Patients with histological features of PSC but with a normal cholangiogram are considered to have small duct PSC. These patients have a better prognosis in terms of survival and do not develop cholangiocarcinoma (4,5). Small duct PSC can progress to large duct PSC in only a small proportion of the patients (4,5).

Diagnosis

The diagnosis of PSC is based on biochemical, clinical, histological and most important on radiological basis.

Biochemical and clinical parameters

PSC is most frequently associated with ulcerative colitis but can also be associated with Crohn's disease. The biochemistry can show cholestasis, hyperimmunoglobinemia, with increase of IgM. About 97% of the patients have at least 1 auto-antibody. Especially the ANCA can be positive in 56% up to 88% of the patients with PSC.

Histology

A liver biopsy can be helpful in making the diagnosis of PSC. Periductal sclerosis is often associated with degeneration of the bile duct epithelium which results in the typical «onion skin» lesions. However, we should be aware of important sampling variability in patients with PSC (6). In about 50% of the patients the liver biopsy is quite atypical and an overlap syndrome with autoimmune hepatitis can be present in about 7 to 10% of the patients (7,8).

Radiology

Endoscopic retrograde cholangiography (ERC) was the golden standard for the diagnosis of PSC. However, magnetic resonance cholangiopancreaticography (MRCP) will probably replace ERC in the future for the diagnosis of PSC (9). On both ERC and MRCP, PSC is characterised by irregular stenosis and dilatations of the intrahepatic bile ducts but the common bile duct can also be involved. Most of the patients have a destruction of both intra- and extrahepatic bile ducts but 11% of the patients have only intrahepatic bile duct lesions and 2% of the patients do have only PSC of the extrahepatic bile ducts. Before making the diagnosis of PSC we should exclude all causes of secondary sclerosing cholangitis such as previous biliary surgery, bile duct neoplasia, bile duct stones disease, ischemic bile duct damage, HIV

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associated cholangiopathy and congenital biliary abnormalities.

Classification and staging of the cholangiographic abnormalities can have a prognostic value (3).

Complications of PSC

PSC is a progressive disease for which a good treatment is not available at this moment. As the disease progresses a number of complications can occur.

The complications specific for primary sclerosing cholangitis are fever, cholangitis, gallstone formation, strictures and most importantly the development of cholangio-carcinoma.

The diagnosis of ***cholangiocarcinoma*** in patients with PSC is difficult because multiple strictures and dilatations can be already present, which makes the differential diagnosis between malignant and benign lesions difficult. About 5 to 30% of the patients with PSC will develop cholangiocarcinoma and about 33% to 50% of the patients develop cholangiocarcinoma within 1 year after the diagnosis of PSC (10). The time between the diagnosis of PSC and the diagnosis of cholangiocarcinoma can vary between 1 year to 25 years. The prognosis of cholangiocarcinoma is bad, with a median survival of 6 months. The risk factors for developing cholangiocarcinoma in patients with PSC are smoking, alcohol abuse, the presence of colorectal dysplasia or carcinoma and the presence of biliary dysplasia (11). A recent study by Boberg et al showed that the presence of inflammatory bowel disease (IBD) of at least 1 year before PSC is a risk factor for the development of cholangiocarcinoma (10). After the first year after PSC diagnosis, the risk of hepatobiliary carcinoma is constant with an incidence rate of 1.5% per year (12).

When a dominant stricture is present, malignancy should be ruled out. For this reason brush cytology should always be performed in every dominant stricture. Brush cytology has a specificity of 98 to 100% but a sensitivity of only 50 to 60% (13,14). Bile fluid cytology and fine needle biopsy can also be helpful in making the differential diagnosis between malignant and benign strictures (14). CT scan and magnetic resonance imaging can help to detect a mass in the liver. The FDG-PET scan has an accuracy of 93% and the sensitivity and specificity of 92 and 93% for differentiating a dominant stricture from a cholangiocarcinoma (15,16). However, FDG-PET scan is expensive and not available in all hospitals. It is important to mention that only small studies are available about PET scan in patients with PSC and cholangiocarcinoma and it is not ruled out that important inflammation can cause false positive PET scans.

The use of tumour markers adds little in making the diagnosis for cholangiocarcinoma. However, when the CA 19.9 concentration is more than 100 U/L it can be an argument for cholangiocarcinoma but the CA 19.9 concentration can also be increased in the case of cholestasis and cholangitis. On the other hand, the Ramage score which is calculated from CA 19.9 + (CEA x 4) of more than 400 U/L can predict the presence of cholangiocarcinoma with an accuracy of about 86% (17).

Another important complication of PSC is the presence of ***cholestasis*** which can lead to important fatigue and pruritus, osteoporosis and a deficiency in fat soluble vitamins.

Finally, PSC can progress to ***endstage liver disease with portal hypertension,*** with the presence of oesophageal varices, peristomal varices, ascites, hepatorenal syndrome and encephalopathy.

In patients with PSC, complications can also occur due to associated disorders such as ***inflammatory bowel disease, chronic pancreatitis*** and ***celiac disease***.

Treatment of PSC

Because of lack of knowledge of the exact pathogenesis of PSC, treatment is difficult. PSC is a rare disease and can have a fluctuating course with spontaneous remissions. For these reasons only a few large randomised controlled prospective studies are available.

Medical therapy

At this moment, medical therapy is not very effective. Treatment with methotrexate, colchicine, D-penicillamine, cyclosporin, pentoxifylline did not show any favourable effects on histology and evolution of the disease (18). ***Ursodeoxycholic acid (UDCA)*** is the most frequently used treatment. Although several randomised controlled trials showed that UDCA in a dosage of 13 to 15 mg/kg/d improved liver tests and bilirubin levels, none of these studies showed an effect on disease progression or transplant free survival (19-22). Recent studies showed that ursodeoxycholic acid is only efficient in very high doses (20 to 30 mg/kg/day taken). At these high doses there is a positive effect on biochemical results and on cholangiographic abnormalities, and an amelioration of histology (especially on fibrosis) and of the Mayo risk score (23,24). The immuno-modulating effects of UDCA are dose dependent in patients with PSC (25).

The use of ***corticosteroids*** had some favourable effects but only small studies have been done and there is a clear worsening of osteoporosis in the patients with PSC. The same results were seen for ***budesonide***, a drug that has a high first pass effect in the liver. However, efficacy did not differ from steroids at the liver level and its use was associated with an important worsening of osteoporosis (26).

The ***combination of ursodeoxycholic acid and endoscopic dilatations*** is more effective than these both treatments alone. Probably combination of different treatment modalities will be used in the future (27).

Endoscopic therapy

Endoscopic therapy is the treatment of choice for patients with dominant strictures.

Dominant strictures are defined as a tight narrowing of the lumen in the common bile duct, common hepatic duct and right and left main hepatic ducts. The presence of dominant strictures may cause rapid clinical deterioration of the patient.

The placement of an endoprosthesis in dominant strictures is a good treatment option. However, some complications can occur. Recurrent occlusions of the stents and bacterial cholangitis have been described in such that the endoprosthesis should be exchanged regularly. For this reason only short term stenting of about 11 days can be performed. In the study of Ponsioen *et al.*, 83% of the patients improved and after 1 year of follow-up, only 20% of the patients needed retreatment (28). Balloon dilatations can be an option. Johnson *et al.* suggests that stents should be avoided in PSC and only balloon dilatation should be undertaken (29).

Some important points should be taken into consideration when performing an endoscopic treatment. All patients should receive prophylactic antibiotic therapy to prevent cholangitis. The ERC should be performed by a skilled endoscopist since bile duct perforation is not uncommon. The endoscopic therapy may certainly improve the survival of the patient, however, endoscopic therapy should never delay referral for liver transplantation (30). We should be aware that performing an ERC can in some cases lead to deterioration of the patient, especially in patients with endstage liver disease and who need liver transplantation (31).

Surgical treatment

The surgical treatment of patients with PSC becomes less necessary because of the amelioration of endoscopic techniques. Bilio-enteric bypass may reduce symptoms and prolong survival in non cirrhotic PSC patients. However, biliary manipulations may increase the risk of strictures, bacterial cholangitis and can complicate future orthotopic liver transplantation.

Orthotopic liver transplantation

Liver transplantation is probably the best treatment for patients with PSC as PSC is an evolutive and progressive disease in which medical and endoscopic therapy have never demonstrated to stop the disease progression (32). The indications for liver transplantation in patients with PSC are not only the indications for end stage liver disease but also the specific indications for PSC : progressive muscle wasting, intractable pruritus, fatigue and recurrent cholangitis (even in the absence of cirrhosis). The outcome of liver transplantation in patients with PSC in the absence of cholangiocarcinoma is very good. The 1-year survival is about 97% and 5-year survival is 80 – 85%. The presence of cholangiocarcinoma, which develops in about 5 to 30% of the patients with PSC, is not an indication for liver transplantation because of a high tumour recurrence rate. It is very important to have tools to predict survival and optimal timing for liver transplantation (32). The Mayo risk score is a very good model for predicting survival in patients with PSC. The Mayo risk score takes age, bilirubin concentration, AST concentration, presence or absence of variceal bleeding and concentration of albumin into account. However, this is a complex model to calculate survival (33).

The Child-Pugh score on the other hand is easier to calculate and there exist also a good correlation between Child-Pugh score and survival after liver transplantation. Patients with a Child-Pugh A classification have 1-year survival of 98% and a 5-year survival of 91% after transplantation. On the other hand patients with Child-Pugh C score have 1-year survival of 73% and a 5-year survival of 16% after liver transplantation. For this reason it should be advised that patients with PSC should be referred for liver transplantation at an early stage (32,34).

The factors that have a negative impact on the outcome after liver transplantation are the presence of inflammatory bowel disease, upper abdominal surgery before transplantation, the presence of ascites increased creatinine level and the presence of malignancy (35).

After liver transplantation, recurrence of the initial PSC disease can occur in about 20% of the patients. Risk factors for PSC recurrence are male sex and the presence of inflammatory bowel disease before transplantation (36). It was also found that recurrent disease do not influence patient or graft survival after a mean follow-up of 4.5 years (37). After liver transplantation, patients with PSC have a higher incidence and severity of acute and chronic rejections and hepatic artery thrombosis, especially when inflammatory bowel disease is associated (38).

Treatment of the complications

1. *Treatment of PSC complications.* When the diagnosis of acute cholangitis is made, one should always exclude the presence of lithiasis, dominant strictures or cholangiocarcinoma. Acute cholangitis can be treated endoscopically and with antibiotics. However, fever can also occur without cholangitis. Recurrent cholangitis is often difficult to treat and at that moment patients should be worked out for liver transplantation. The presence of gallbladder and biliary tract stones should be treated endoscopically (39). A cholecystectomy can be considered, however cholecystectomy in the presence of cirrhosis can be difficult and complicated.

Once liver cirrhosis is present, development of a mass in the liver, the presence of a cholangiocarcinoma or hepatocellular carcinoma should always be suspected. Incidental cholangiocarcinoma is observed in about 8 to 18% of the patients within the explanted liver.

2. *Treatment of the complications of cholestasis*. Cholestasis is often associated with an extreme ***fatigue*** for which a good therapy, except liver transplantation, is not available. ***Pruritus*** can be treated by ursodeoxycholic acid, cholestyramine, naltrexone, rifampicine and

eventually phototherapy with PUVA. However, intractable pruritus should be treated by liver transplantation. The development of ***osteoporosis*** in association with cholestasis can be prevented by the intake of calcium (1 g per day) and vitamin D (800 µg a day). Especially in female patients, cholestatic osteopenia is the result from a decreased bone formation and increased bone resorption (40). For the treatment of osteoporosis a therapy with bifosfonates should be added.

In the presence of longstanding cholestasis, *malabsorption of the fat soluble vitamins* can occur ; dosage of these vitamins (A, D, E, K) in plasma should be performed on a regular basis. When deficiency is detected, supplements should be given.

3. *Treatment of complications related to the associated disorders*.

– *Inflammatory bowel disease*.

Frequently, PSC is associated with ulcerative colitis. However, Crohn's disease and undetermined colitis can also be present. Inflammatory Bowel Disease (IBD) can occur before or at any time during the course of PSC and IBD may even develop de novo after liver transplantation. On the other hand, PSC can be diagnosed at any time during the course of IBD and PSC may develop even after proctocolectomy. The prevalence of ulcerative colitis in patients with PSC varies between 25 to 100%. The prevalence of PSC in patients with ulcerative colitis is about 5.5%. The only risk factor for colectomy because of intractable IBD after liver transplantation, is transplantation itself (41).

Patients with ulcerative colitis have an increased risk for the development of colorectal cancer, especially in patients who have a long duration of ulcerative colitis or patients who have an extensive colitis. When ulcerative colitis is associated with primary sclerosing cholangitis, there is a much higher risk for the development of colorectal cancer and dysplasia. After 25 years duration of ulcerative colitis, about 50% of the patients with PSC develop a colorectal cancer (42). These colorectal cancers are often located in the proximal colon probably due to carcinogenic secondary bile acids. A recent study by Tung *et al.* showed that patients with PSC and ulcerative colitis treated with ursodeoxycholic acid had a decreased prevalence of colorectal dysplasia (43). The risk for developing colorectal cancer is much higher after liver transplantation (44). For this reason an annual colonoscopy after transplantation has been advised.

– Fifteen to 50% of the patients with PSC have changes in the *pancreas*. In patients with an important weight loss and steatorrhea, an exocrine pancreas dysfunction should be excluded (45,46). The exocrine pancreas dysfunction can be treated with the supplement of pancreas enzymes.

The risk of pancreatic carcinoma in PSC patients is 14 times higher compared with the general Swedish population (12).

– *Celiac disease* is also associated with primary sclerosing cholangitis probably as a consequence of an immunological connection. Celiac disease can cause severe weight loss and steatorrhea. The presence of autoimmune antibodies such as antigliadin, antiendomysium together with duodenal or jejunal biopsies should confirm the diagnosis. Gluten free diet should be installed in these patients (47 ; 48).

Conclusions

The new therapeutic options for patients with PSC include the administration of high dose ursodeoxycholic acid (20 to 30 mg/kg/day). Short term stenting and/or balloon dilatations of the dominant strictures eventually in combination of ursodeoxycholic acid can be a good treatment option. As PSC progresses, an orthotopic liver transplantation is the best treatment for these patients.
In patients with PSC and ulcerative colitis the risk of colorectal cancer and dysplasia can probably be decreased by using ursodeoxycholic acid. Patients with ulcerative colitis and PSC should undergo after liver transplantation colonoscopy with biopsies. This should be done on an annual basis. New diagnostic techniques for the early detection of cholangiocarcinoma in patients with PSC are FDG-PET scan and perhaps in the future tumour markers such as P53 tumour protein and K-ras mutations in bile fluid or brushing.

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