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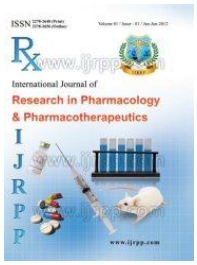

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Primary sclerosing cholangitis- a comprehensive review and update

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ABSTRACT

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology characterised by inflammation and fibrosis of the biliary tree. The aim of this review is to find out the cause, symptoms, and treatment of PSC. Remissions and relapses characterize the disease course. PSC may remain quiescent for long periods of time in some patients, however, it is progressive. The mean age at diagnosis is 40 years and men are affected twice as often as women. There is a reported annual incidence of PSC of 0.9–1.31/100,000 and point prevalence of 8.5–13.6/100,000. In most, the disease progresses to cirrhosis and liver failure. Cholangiocarcinoma develops in 8–30% of patients. PSC is thought to be immune mediated and is often associated with inflammatory bowel disease, especially ulcerative colitis. The disease is diagnosed on typical cholangiographic and histological findings and after exclusion of secondary sclerosing cholangitis. Median survival has been estimated to be 12 years from diagnosis in symptomatic patients. Patients who are asymptomatic at diagnosis, the majority of whom will develop progressive disease, have a survival rate greater than 70% at 16 years after diagnosis. Liver transplantation remains the only effective therapeutic option for patients with end-stage liver disease from PSC, although high dose ursodeoxycholic acid may have a beneficial effect.

Keywords: Primary sclerosing cholangitis(PSC), Biliary tree, Cholangiocarcinoma , Inflammatory bowel disease, Cholangiography, Ursodeoxycholic acid

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammatory destruction of the intrahepatic and/or extrahepatic bile ducts, leading to bile stasis, hepatic fibrosis, and ultimately to cirrhosis, end-stage liver disease, and need for liver transplantation. The majority of cases occur in association with inflammatory bowel disease (IBD), which often precedes the development of PSC[1, 2.]

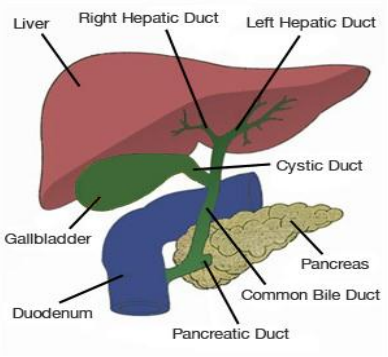

Figure 1: Biliary tree

The disease leads to irregular bile duct obliteration, including formation of multifocal bile duct strictures[3].

THE LIVER

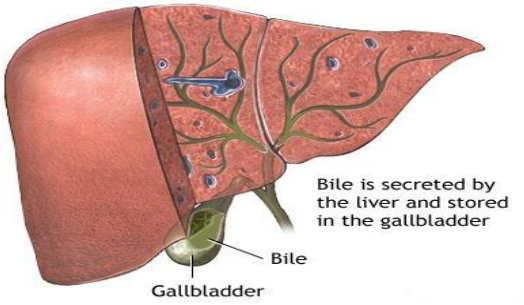

Figure 2- The liver

The liver is in the upper right part of the abdomen. It has many functions which include-

- Storing glycogen (fuel for the body), which is made from sugars. When required, glycogen is broken down into glucose which is released into the bloodstream.
- Helping to process fats and proteins from digested food.
- Making proteins that are essential for blood to clot (clotting factors).
- Processing many medicines which you may take.
- Helping to remove or process alcohol, poisons and toxins from the body.
- Making bile, this passes from the liver to the gut down the bile duct. Bile breaks down the fats in food so that they can be absorbed from the bowel[4].

CHOLANGIOGRAPHY

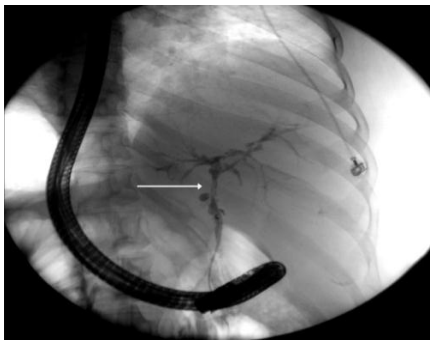

Figure 3- Endoscopic retrograde cholangiography

Cholangiography is the usual way to diagnose PSC. Endoscopic retrograde cholangiography is the test of choice[5]. Patients, who present with clinical, biochemical and histological features compatible with PSC, but have a normal cholangiogram, are classified as small duct PSC[6]. Magnetic resonance cholangiography (MRCP) for detecting PSC has emerged as an accurate, rapid, noninvasive alternative examination of the biliary tract, and is commonly used in multiple centres[7].

PRIMARY SCLEROSING CHOLANGITIS (PSC)

Primary sclerosing cholangitis (PSC) is a chronic progressive disease characterized by inflammation and fibrosis of medium size and large ducts in the intrahepatic and extrahepatic biliary tree. It was first reported in the German literature in 1867 by Hoffman, but was described in more detail in the 1920s by two French surgeons, Delbet and Lafourcade[8]. The diagnosis of this disease was based on primary findings at laparotomy until cholangiography by fiber duodenoscope introduced in 1970, that this disease become easier to diagnose and later also easier to treat[5]. The cause of PSC is unknown. While often associated with autoantibodies and closely linked to IBD, PSC is not a typical autoimmune disease and responds poorly, if at all, to typical immunosuppressive therapies[9]. Patients with PSC are at risk for the development of cholangiocarcinoma(CCA) and other extrahepatic malignancies. There is a strong but incompletely understood association between PSC and inflammatory bowel disease (IBD) [2]. Patients are often diagnosed incidentally, and nearly 50% are asymptomatic. Despite being asymptomatic at the time of diagnosis, patients with PSC have shorter average times of survival compared with matched controls from the general population[10]. The pathogenesis of PSC is unknown, but available data suggest that both immunological and non-immunological host defenses may be impaired. Hence, the normal intestinal flora or their metabolic products may play a pathogenic role[11].

INFLAMMATORY BOWEL DISEASE AND PSC

PSC is strongly associated with IBD. In most series of patients from Northern Europe and North America, the prevalence of IBD in PSC has been in the range 60%-80%. The most frequent type of IBD in PSC is UC, which is diagnosed in 48%-86% among the patients with IBD. Up to 13% have Crohn's disease (CD) which usually involves the colon[6]. Furthermore, subjects with PSC and IBD can have minimal endoscopic activity despite the presence of more active histologic inflammation[10]. IBD in primary sclerosing cholangitis represents a distinct phenotype that differs from UC and Crohn's disease and therefore requires specialized management[12].

PSC-AIH OVERLAP SYNDROME

PSC-AIH overlap syndrome is an ill-defined immune-mediated disorder which is predominantly found in children, adolescents, and young adults[13]. AIH-PSC should be suspected in patients with abnormal cholangiograms that indicate PSC, biochemical features of AIH (increased antibody titers or levels of transaminases, lymphoplasmacytic portal-based infiltrates, and significant interface hepatitis) or in patients with AIH that becomes refractory to therapy[10].

IgG4 ASSOCIATED CHOLANGITIS (IAC)

IgG4 associated cholangitis is a sclerosing cholangitis that has been acknowledged during the recent years, Due to the corticosteroid responsiveness, this condition is an important differential diagnosis to PSC[14]. In contrast to PSC, IAC is not associated with IBD[3]. Autoimmune pancreatitis (AIP) is a clinical entity characterized by stricturing of the pancreatic duct, focal or generalized pancreatic enlargement, a raised serum immunoglobulin G4 (IgG4) level, a lympho plasmacytic infiltrate on biopsy, and a response to corticosteroid therapy[6]. IgG4-associated cholangitis (IAC) and AIP are each manifestations of a systemic inflammatory condition associated with IgG4 production and deposition within the biliary system and pancreas respectively[10].

DISCUSSION

EPIDEMIOLOGY

The prevalence of primary sclerosing cholangitis (PSC) ranges from 6 to 16 cases per 100,000

individuals and an incidence of 1 per 100,000 individuals in North America and Europe[15]. Globally, there is geographical variation in the prevalence of primary sclerosing cholangitis (PSC) with similar rates in North American and Northern European countries but less in Asia and Southern Europe[7]. In contrast to most autoimmune conditions, approximately 2/3 of the PSC patients are male[16]. The highest prevalence (16.2/100,0000) has been reported within a large population based study in western Sweden with increasing trends for IBD associated PSC, large duct PSC among men/women, and PSC without IBD and predominately small-duct PSC among males[17].

ETIOLOGY

- The etiology is unknown but an autoimmune basis is suspected.
- It may also be related to infection and the ability of certain organisms to traverse the bowel wall in inflammatory bowel disease.
- It is associated with certain HLA types.
- One small study found a 100-fold increase in the risk of acquiring PSC in first-degree relatives of patients, suggesting a genetic component[18, 19].

PATHOPHYSIOLOGY

Several causative mechanisms have been proposed to explain the pathogenesis of PSC; however it still remains poorly understood. It seems that immunologic mechanisms as well as non-immunologic factors (eg;infections, toxins) could be responsible for the development of this disease[19]. Surprisingly, despite major methodological progresses in modeling various complex diseases, such as the generation of genetically modified mice, to date, no animal model has been developed that exhibits all of the desirable attributes of an 'ideal PSC model'[20]. The following describes several aspects of the etiopathogenesis of PSC, i.e. PSC as a genetic disease, as an autoimmune disease, as an inflammatory disease triggered by infectious agents and as a cholangiopathy (flowchart 1) [5]

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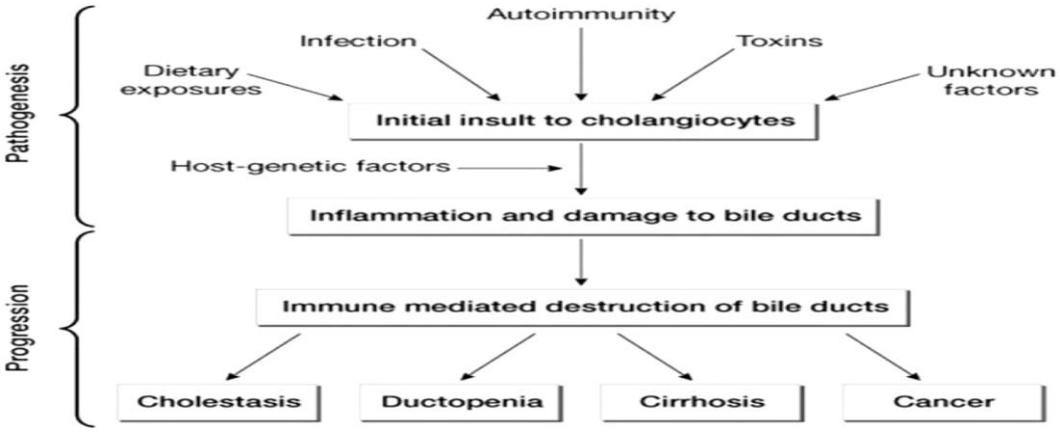

Flowchart 1- Pathogenesis

PSC AS A GENETIC DISEASE

The fact that first degree relatives of PSC patients are at significantly higher risk to develop PSC and have a higher risk of developing IBD without PSC compared with the overall population, indicates genetic associations[17]. PSC is probably acquired through inheriting a combination of genetic polymorphisms that interrelate to cause disease susceptibility. Six different HLA molecules have so far been associated with PSC[21]. The occurrence of PSC in members of the same family and definite HLA association suggest a genetic predisposition for developing this disease[22]. Early studies described an increased frequency of HLA B8 and DR3 in patients with PSC. These antigens are known to be associated with several autoimmune diseases[19].

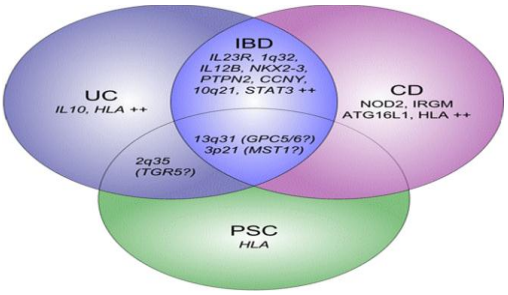

Figure 4-genetic architecture of PSC

The major histocompatibility complex (MHC) on the short arm of chromosome 6 encodes the HLA molecules having a critical role in T cell response, and along with MHC class I chain-like (MIC) α-molecules involved in the innate immune function may play a role in the pathogenesis[2]. Probably both the HLA class I and HLA class II genes contribute to the associations. However, since the HLA genes are closely linked, it has so far not been possible to conclusively dissect exactly which of the genes those are most important[16].

PSC AS AN AUTOIMMUNE DISEASE

Autoimmunity is defined as immune reactivity against self-molecules that is sufficient to cause cell and tissue injury. Evidence that PSC is an autoimmune disorder includes the presence of hyper globulinemia, multiple autoantibodies, activated immunocytes and the association with specific "autoimmune" MHC haplotypes[9]. It has been reported that 97% of patients with PSC were positive for atleast one autoantibody; whereas 81% were positive for three or more. Perinuclear antineutrophil cytoplasmic antibodies (ANCA) have been detected in approximately 85% of PSC patients[19]. Preliminary results using proteomics suggest that the auto-antigen of Panca is the nuclear envelop protein, myeloid-specific tubulin-beta isotype 5[23]. PSC also is associated with other possible autoimmune conditions such as IBD and, to a lesser extent, autoimmune hepatitis and thyroiditis. PSC is associated with multiple autoantibodies, but most closely with pANCA[24].

The autoantibodies in PSC including pANCA do not appear to play a pathological role. Nevertheless, the biliary epithelial cell appears to be the target of immune mediated injury and dense infiltrations with activated T cells and high local concentrations of pro-inflammatory cytokines with increased expression of HLA on bile ducts are common. Thus, PSC appears to be immune-mediated, but direct evidence that it is an autoimmune disease is lacking[25].

PSC AS A CHOLANGIOPATHY

PSC is a disease mainly of the large bile ducts and belongs to the cholangiopathies, a group of various hereditary or acquired diseases of the biliary tree with cholestasis as a common symptom and with cholangiocytes as primary target cells of the disease process[5]. The cholangiopathies include genetic conditions (Alagille syndrome, cystic fibrosis, fibropolycytic diseases), immune-mediated disorders (PSC, PBC, autoimmune cholangitis, allograft rejection, graft-versus-hostdisease), infections (cholangitis due to bacteria, fungi, parasites or viruses), drug-induced injury (floxuridine), ischemic damage (hepatic artery thrombosis), malignancies (cholangiocarcinoma) and diseases of unknown etiology (biliary atresia, sarcoidosis, idiopathic vanishing bile duct syndromes) [9].

PSC AS AN INFLAMMATORY REACTION

Some literatures show PSC as an immune-mediated inflammatory disease rather than as an autoimmune disease. This would be consistent with a role of bacterial or viral antigens, which enter the portal circulation through the mucosa in IBD and trigger as molecular mimics an immune reaction leading to PSC. Altogether, infectious agents probably do not directly cause PSC but could activate an immune reaction by enterohepatic lymphocyte circulation or could accelerate disease progression when leading to a biliary infection[5].

CLINICAL MANIFESTATION

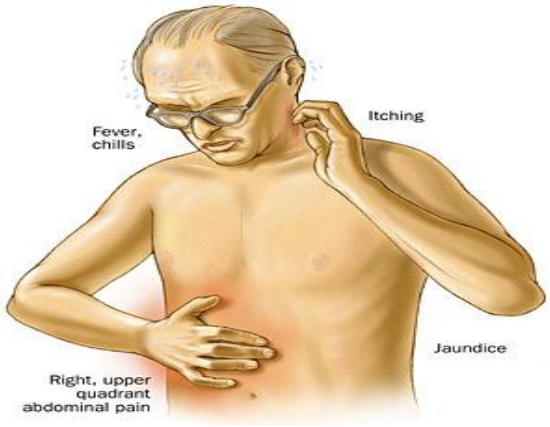

Figure 5- Symptoms of PSC

Many people have no symptoms at first and the disease is only discovered because of abnormal results of routine blood tests in patients with ulcerative colitis or Crohn's disease. Some people PSC do not produce any symptoms. Most people have few or no symptoms for many years.

Common early symptoms are:

- Tiredness
- Some abdominal discomfort in the right upper abdomen.

Late symptoms are:

- Itching
- Jaundice – yellowing of the skin and sclera of the eyes.
- Episodes of fever, shaking and chills can be distressing but are uncommon.
- Liver failure may ultimately develop[4].

PSC may be occasionally complicated by the development of bile duct cancer. PSC is closely associated with inflammatory bowel disease, usually ulcerative colitis, but also Crohn's disease[7]. Patients with PSC are susceptible to repeated episodes of bacterial cholangitis and are also prone to develop pigmented biliary stones[19].

DIAGNOSIS

The diagnosis of PSC is based on characteristic cholangiographic findings in combination with clinical, biochemical, and histologic features. It is important to exclude secondary causes of sclerosing cholangitis, such as biliary neoplasms, previous biliary surgeries, choledocholithiasis, medication-induced bile duct damage, and chronic bacterial cholangitis[19].

LABORATORY TESTS

A cholestatic picture of liver function with an elevation in serum alkaline phosphatase level is the biochemical hallmark of PSC[26]. Results of hepatic synthetic function ,i.e,serum albumin and prothrombin time become abnormal with advanced disease[21]. Hyperbilirubinemia, Hyper gammaglobulinemia, autoantibodies, and abnormal copper accumulation are also common laboratory findings[19]. As in primary biliary cirrhosis, levels of hepatic and urine copper levels are increased, as is the serum ceruloplasmin[11].

RADIOGRAPHIC FINDINGS

CHOLANGIOGRAPHIC FINDINGS

Cholangiography is the best way to identify patients with PSC. The classic features include multifocal annular structuring within the intrahepatic and/or extrahepatic bile ducts, with alternating normal or slightly dilated segments[10]. Long, confluent strictures may also be observed although these are worrisome for the development of superimposed cholangiocarcinoma[6]. The typical cholangiographic findings of PSC include multifocal strictures and dialatations that have a classic beaded appearance and may form diverticular outpouchings[19].

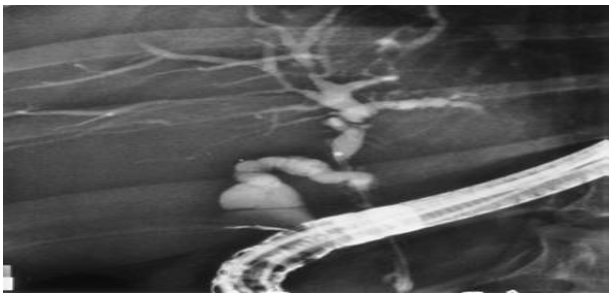

Figure 6- ERCP

In most cases, these findings affect both intrahepatic and extrahepatic bile ducts, but they can involve either alone[19]. ERCP has been the golden standard in diagnosing PSC, but it is associated with complications such as pancreatitis and sepsis[3].

NONINVASIVE IMAGING

Recent studies show that magnetic resonance cholangiopancreatography (MRCP) is a valuable technique in the diagnosis and follow-up of patients with PSC. Because of non-invasiveness, low complication rate and absent exposure to radiation, MRCP is recommended as initial diagnostic test with high sensitivity and specifity[17]. Diagnostic accuracy greater than 90% in the diagnosis of PSC was reported in one of the literature. There is some suggestion that MRCP may be superior to ERCP for intrahepatic visualization.

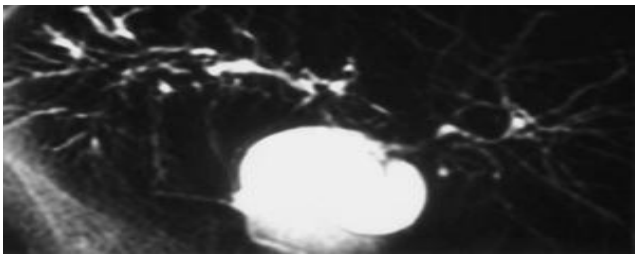

Figure 7- MRCP

MRCP has the advantage of visualizing bile ducts proximal to a complete bile duct obstruction and of providing additional diagnostic information on the liver parenchyma[5]. Other abdominal imaging studies, such as CT and ultrasonography, may suggest the diagnosis but are nonspecific[19].

HISTOLOGICAL FEATURES

Liver biopsy in this condition is more useful for staging purposes than for diagnosis itself. The characteristic finding is of concentric onionskin fibrosis surround in the bile ducts[21]. Ludwig et al described a staging system for PSC.

- Stage I - Characterized by portal hepatitis,
- Stage II - Fibrosis or hepatitis involves the periportal area.
- Stage III - Septal fibrosis or bridging necrosis occur.
- Stage IV - Characterized by biliary cirrhosis.

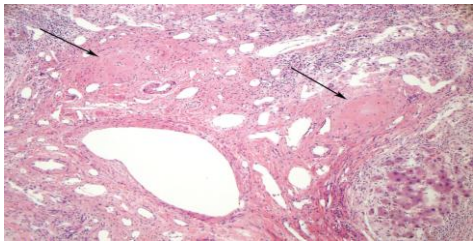

Figure 8-Liver biopsy

The role of liver biopsy in the evaluation of PSC appears to be of limited value. Liver biopsy does not reveal atypical findings and does not have any impact on the management of the patient[26]. Histologic features of PSC are often non specific and prone to sampling variations due to the heterogeneous involvement of the biliary tree[10]

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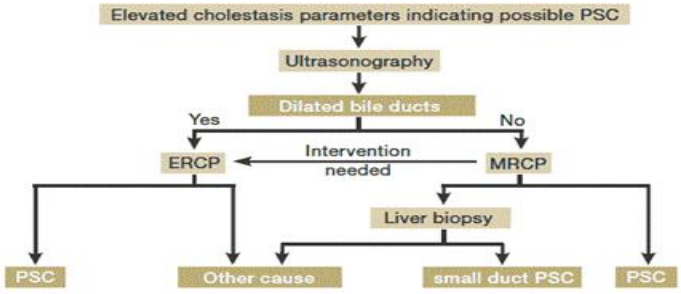

Flowchart 2- Diagnostic Algorithm

TREATMENT

PHARMACOLOGICAL TREATMENT

Ideal treatment goals are to cure the disease and prevent complications. Currently, there is no cure for PSC[7]. The scarcity of PSC patients and the long time until a primary endpoint like death or liver transplantation is reached; means that achieving an adequate study population in randomized, double blinded treatment trials in PSC is difficult[16]. The following table summarizes the current status of many clinical studies. Despite encouraging results from a few studies, none have demonstrated convincing evidence of benefit and some are associated with significant side effects[27].

Table 1- Medications evaluated in the treatment of PSC

No benefit	Possible benefit	Under consideration
Azathioprine	Metronidazole	UDCA (28 mg/kg/day to 30 mg/kg/day)
Budesonide	Minocycline	DHA
Cladribine	Silymarin	Thalidomide
Colchicine	Tacrolimus	Nor-UDCA
Cyclosporine		6-EDCA
Etanercept		Losartan
Infliximab		
Methotrexate		
Mycophenolate mofetil		
Nicotine		
Penicillamine		
Pentoxifylline		
Pirfenidone		

(6-EDCA: 6-alpha-ethyl-chenodeoxycholic acid; DHA: Docosahexanoic acid; UDCA:Ursodeoxycholic acid)

At present there is no specific treatment which either cures or slows the progression of PSC. Treatments aim to improve symptoms and also to manage any complications which may rise[9].

URSODEOXYCHOLIC ACID

UDCA, a hydrophilic bile acid, has been widely used to treat PSC. Therapy with the drug leads to a 2-3 fold increase in serum bile acid concentration. There is an increase in the biliary and urinary excretion of bile acids and an increase in bile flow[16]. Serum alkaline phosphatase (ALP) level is a long

established risk factor for disease progression in PSC[28].

A Meta analysis of 8 trials determined that treatment with UDCA did not slow the progression of PSC. Although there is no clear role for UDCA therapy at this time, the safety profile of moderate dose UDCA (17-23 mg/kg/day) indicates that it could be worth further examination in prospective trials[10].

IMMUNOSUPPRESSIVES AND OTHERS

Corticosteroids and other immuno suppressants have not demonstrated improvement in disease activity or outcome of PSC. Small randomized, placebo-controlled or pilot trials have investigated the role of agents with immune-suppressive potency like prednisolone, budesonide, azathioprine, cyclosporine, methotrexate, mycophenolate, and tacrolimus, agents with TNF-α antagonizing effects like pentoxifyllin, etanercept and anti-TNF monocolonal antibodies and anti-fibrotic agents like colchicine, penicillamine, or pirfenidone[29]. Agents in trials include immunosuppressant, anti-inflammatory and anti-fibrotic drugs. Unfortunately, none of these medications has shown a convincing long term benefit[30]. A retrospective study in adults also suggested a beneficial role of corticosteroids in a subgroup with AIH overlap features[31].

ENDOSCOPIC THERAPY

The goal of endoscopic therapy is dialation of strictures to a point that bile flow improves. Several attempts have been made to change the progressive course of PSC by endoscopic methods, including endoscopic sphincterotomy, nasobiliary lavage, stent placement, and balloon dilatation. Expansion of dominant strictures by dilation alone or dilation and stent placement can provide long term biliary drainage and reduce symptoms[10]. Biliary lavage with steroids was evaluated in a randomized, placebo-controlled trial and proved not to be effective. Several reports have shown beneficial effects of balloon dilatation or temporary stenting on clinical, biochemical, and cholangiographic findings in patients with PSC. Endoscopic intervention is usually preferred to percutaneous biliary drainage because it seems to be safer and is technically easier to perform. The incidence of dominant strictures in patients with PSC has been estimated to be as high as 45%-58%, whereas others have found a much lower frequency[26, 32].

SURGICAL THERAPY

Like the endoscopic approach, the goal of surgery is to improve bile flow, reduce jaundice and prevent further attacks of cholangitis. Inflammatory alterations in PSC can lead to almost complete stenosis of the extrahepatic biliary tree and can cause acute deterioration of liver function. Non-transplant surgical approaches include resection of the extrahepatic bile ducts with biliary-enteric bypass with or without long-term biliary stenting. Another surgical approach is to resects the extrahepatic bile ducts including the bifurcation, dilate the intrahepatic ducts and then permanently stent the bile ducts with polymeric silicon transhepatic biliary stents. Surgical treatment is now less commonly performed because of advances in endoscopic techniques[33, 5, 19].

LIVER TRANSPLANTATION

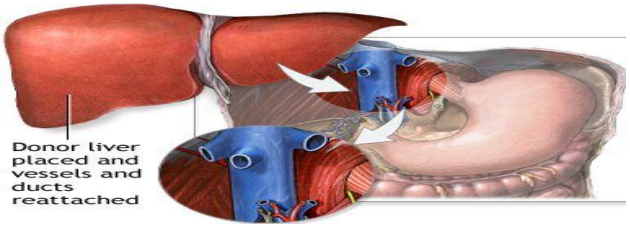

Figure 9- Liver transplantation

Liver transplantation is the only therapy of late-stage PSC that can cure advanced disease. One and ten-year survival after liver transplantation has lately been above 90% and 80%, respectively, in

experienced centers[3]. Transplantation for PSC generally involves resection of the extra-hepatic biliary tree and use of a Roux-en-Y loop[33]. In PSC patients with IBD who undergo liver transplantation, inflammatory bowel syndrome symptoms are generally improved[11]. Recurrence of PSC after liver transplantation has been reported at various rates up to a third of patients transplanted, but is difficult to define due to similarities in bile duct damage with ischemic type biliary lesions, infections, medication induced injury, preservation injury, or chronic rejection[34].

PROGNOSIS

- There is a slow progression to cirrhosis.
- Median survival has been estimated to be 12 years from diagnosis in symptomatic patients.
- The revised Mayo Clinic model for survival probability includes age, serum bilirubin, albumin, and aspartate aminotransferase levels, and history of variceal bleeding.
- PSC can be classified into small-duct or large-duct types, which seems to affect prognosis[35]:
  - Small-duct PSC has a better prognosis, with longer transplant-free survival.
  - Also, it appears that cholangiocarcinoma is unlikely with small-duct PSC.
- Prognosis after liver transplant:
  - The outcome for liver transplant in PSC is good, with a five-year survival of 75-80%.
  - PSC can recur after transplantation, and a retransplant may be required[36].

COMPLICATIONS

Complications include Bacterial cholangitis**,** Liver cirrhosis**,** Liver failure**,** Portal hypertension**,** Cholangiocarcinoma**,** Colorectal cancer[22].

FUTURE DIRECTIONS

INNOVATIVE PHARMACOTHERAPIES

Future therapeutic options in PSC may include farnesoid X receptor (FXR) agonists (e.g. obeticholic acid, 6α-ethyl chenodeoxycholic acid), and 24-norursodeoxycholic acid, a side-chain modified UDCA derivate resistant to amidation which undergoes cholehepatic shunting. FXR is a nuclear receptor that regulates bile acid homeostasis. FXR activation is also involved in antibacterial defense and protects against inflammation. The role of biologic agents such as ustekinumab and vedolizumab in the treatment of IBD is being investigated. Given the possible role of lymphocyte trafficking in the pathogenesis of PSC, monoclonal antibodies that alter this process could have a potential therapeutic benefit. Janus kinase(JAK) is a tyrosine kinase component of signaling pathways for many cytokines. Tofacitinib is a JAK inhibitor that decreases signaling by inflammatory cytokines, T-cell differentiation, and lipopolysaccharide induced innate immune responses. 24-norUDCA has been shown to be effective in an animal model for sclerosing cholangitis and biliary fibrosis. In addition, fibrates (e.g. bezafibrate, fenofibrate), which have pleiotrophic and anti-inflammatory effects and, furthermore, stimulate biliary phospholipid secretion via the PPARα-MDR3 pathway, may represent an attractive therapeutic strategy. Most promising for the near future are inhibitors of TNF action, antifibrotic agents, and inhibitors of formation of toxic bile[17, 11,10,9].

SUMMARY & CONCLUSION

Primary sclerosing cholangitis is a cholestatic liver disease strongly associated with IBD. Males are affected twice as females. PSC has been known for 100 years, but now doctors are able to diagnose it very early. This means that treatment can begin before the liver is severely damaged. Scientists are continuing to study the disease to find the cause and understand its development. Considerable advances in the understanding of its pathogenesis have been made. The idea of autoimmunity affecting genetically susceptible individuals is largely accepted, however, much remains to be explained about the origin of this disease. Despite active investigation of different therapeutic modalities with the goal of modifying disease progression, liver transplantation continues to be the only option to provide survival benefit in these patients.

PSC is a rare but important cholestatic liver disease that reduces patient survival and quality of life. Management of patients involves early recognition of the disorder, implementation of routine screening protocols to identify complications, and treating comorbid conditions. In addition, drug therapy trials, involving a large number of patients around the

world, are exploring the potential use of several additional medications to lessen the symptoms and control liver damage. In the absence of effective medical therapy for the disease itself, treatment centers on endoscopic management and referral for liver transplantation when necessary. Although our understanding of PSC and its comorbid conditions has improved, much is left to learn about its pathogenesis. Animal models and genomic-based approaches will increase our understanding of the pathophysiology and hopefully lead to new therapeutic strategies.

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