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Primary Biliary Cirrhosis

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Abstract

Primary biliary cirrhosis (PBC) is an idiopathic chronic autoimmune liver disease that primarily affects women. It is believed that the etiology for PBC is a combination between environmental triggers in genetically vulnerable persons. The diagnosis for PBC is made when two of the three criteria are fulfilled and they are: (1) biochemical evidence of cholestatic liver disease for at least 6 month's duration; (2) anti-mitochondrial antibody (AMA) positivity; and (3) histologic features of PBC on liver biopsy. Ursodeoxycholic acid (UDCA) is the only FDA-approved medical treatment for PBC and should be administered at a recommended dose of 13-15mg/kg/day. Unfortunately despite adequate dosing of UDCA, approximately one-third of patients does not respond adequately and may require liver transplantation. Future studies are necessary to elucidate the role of environmental exposures and overall genetic impact not only in the development of PBC, but on disease progression and variable clinical response to therapy.

Keywords

cholestasis; bile ducts; genetics; natural history

INTRODUCTION

Primary biliary cirrhosis (PBC), a chronic progressive inflammatory liver disease of unknown etiology, is characterized by high titer of serum antimitochondrial antibodies (AMA) and immune-mediated destruction of small and medium-sized intra-hepatic ducts. The histologic hallmark of the disease is a loss of biliary epithelial cells and small intrahepatic bile ducts with portal infiltration of T cells, B cells, macrophages, eosinophils, and natural killer cells [1,2]. Similar to other autoimmune diseases, PBC primarily affects women, with a 10:1 female to male ratio [3]. Addison and Gull first described a PBC-like disease in 1851, but the term PBC was not coined until a case series of 18 patients was described in 1949 [4]. The most frequently reported symptoms are fatigue and pruritus, which occur in up to 85% and 70% of patients, respectively [5,6]. The pathogenesis of PBC is thought to be related to environmental exposures in genetically vulnerable patients [7], but further studies are necessary to understand this complex interaction between genes and environment. Long-term treatment with ursodeoxycholic acid (UDCA) appears to slow disease progression and has altered the natural

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history of PBC [8]. The aim of this review is to provide an overview of current knowledge on the pathophysiology, clinical features and therapy of PBC.

EPIDEMIOLOGY

To date, all population-based studies provide only estimated prevalence and incidence rates based on the identification of cases already diagnosed. PBC primarily affects patients around the fifth decade of life and is uncommon in patients under 25 years old [3]. Initial studies published between 1974 and 1986 reported an annual incidence rates for PBC ranging between 0.6 and 13.7 cases per million population with prevalence rates varying from 23.1 and 128 cases per million population [9,10]. More recent studies observed that annual incidence rates range between 0.7 and 49 cases per million population and prevalence rates higher than studies prior to 1986, ranging between 6.7 and 402 cases per million population [11-16]. It is unclear whether a change in incidence of PBC truly reflects an epidemiological phenomenon that suggests potential environmental exposures as several studies have demonstrated geographic variation in the development of PBC or merely an improved recognition of the disease.

PATHOGENESIS

At present, the pathogenic mechanisms governing the development of PBC remains unknown. However, the development of PBC is believed to be a result from a combination of multiple genetic factors inter-playing with environmental triggers. As currently understood, PBC is initiated when tolerance to a ubiquitously expressed subunit of pyruvate dehydrogenase complex (PDC-E2) of mitochondria is lost as a result of the development of PDC-E2 specific anti-mitochondrial antibodies (AMAs) [17]. AMAs are detectable in approximately 90% of PBC patients and may be present for years prior to clinically recognizable disease [18]. The process by which self PDC-E2 moieties become antigenic in PBC has been widely studied and several mechanisms, including molecular mimicry, self alteration by xenobiotics, and intact immunogenic epitopes released by apoptotic biliary epithelia have been proposed [19]. Recent findings suggest that the autoimmune attack is triggered by the presence of intact immunoreactive PDC-E2 within apoptotic blebs of biliary epithelial cells [20]. Potentially, any of these mechanisms can contribute to the initiation of the autoimmune cascade, which is likely dependent on environmental exposure and genetic makeup.

Genetic Contributions to PBC

The genetic contribution to PBC is supported by a high disease concordance in monozygotic twins [21] and increased prevalence of other autoimmune conditions in PBC patients and their family members [22]. Familial aggregation of PBC, as recorded in prior epidemiological studies, shows familial PBC prevalence to range between 1.0%-6.4%, which is significantly higher than expected in the general population [23]. In addition to higher prevalence of PBC itself, the presence of AMA has been shown to aggregate in first degree relatives of afflicted individuals, which suggests a possible heritability component of AMA [24].

Allelic variations in the human leukocyte antigen (HLA) genes, located in the highly polymorphic major histocompatibility complex (MHC), have been shown to be associated with a large majority of autoimmune diseases. In PBC, the most commonly detected HLA association has been with MHC class II DRB1*08 allele family, specifically DRB1*0801 in European and North American Caucasians [25] and DRB1*0803 in the Japanese [26]. The recent Canadian genome-wide association study (GWAS) also provided further support for the HLA gene involvement with strong association signals across the MHC locus encompassing HLA DQB1, DPB1, DRB1, DRA, c6orf10, and BTNL2 genes [27].

Components of both the innate and adaptive immunity have also been shown to be associated with susceptibility for PBC. The A allele of the G/A polymorphism at position −308 in the tumor necrosis factor (TNF) promoter resulted in increased TNF expression [28]. Gordon and colleagues demonstrated that the carriage of −308A allele was less common in PBC patients compared to control [29], but subsequent studies reported no associations between the −308 polymorphism and PBC [30,31]. IL12, a major cytokine for the development of Th1 responses important to signaling in both innate and adaptive immunity, has also been implicated risk for PBC. Genetic variations in two genes of the IL12 signaling pathway was strongly associated with disease, second only the HLA association [27]. Cytotoxic T-lymphocyte antigen 4 (CTLA4) encodes an immunoreceptor that plays a key role in immune tolerance and autoimmunity prevention through the inhibition of T-cell activation. Genetic variations of CTLA have been associated with a variety of autoimmune diseases and have been implicated in PBC in a variety of studies [31-33].

Genetic variation in exonic sequence of three keratin (K) genes (K8/K18/K19), which are expressed in biliary epithelial cells was examined by the Italians and analysis showed an increase in carriage of pathogenic variants across the three genes in PBC patients compared to controls (OR 4.53, 95% CI 1.3-13.7, p= 0.0004), suggesting a possible deficit in cytoprotective function of these genes in PBC patients [34]. Further investigations to better understand the genetic impact and genetic architecture of this enigmatic disease are essential and will likely result in clinical benefit for affected patients.

Environmental Contributions to PBC

Multiple environmental factors have been proposed as risk factors to PBC. Two studies have examined the potential association between specific environmental exposures and the development of PBC, with several clusters of PBC cases defined in northeast England and in superfund toxic waste sites in New York City [35,36]. The possibility of autoimmune disease being triggered by an infectious agent has been examined. Cross-reactivity with self-antigens from circulating antibodies, developed in response to infection or “molecular mimicry” has been attributed to pathogenesis of PBC [37]. In two case-control studies, there was a greater than expected frequency of previous urinary tract infections in PBC patients[38,39].

Lifestyle may also have some influence the development of PBC. A population based study showed that history of smoking was observed more frequently in PBC patients (76%) compared to controls (57%) [40], which was confirmed by two subsequently case-control studies from the United States [38,39]. It is proposed that chemicals within cigarette smoke may stimulate T lymphocyte cytokine response, which predominates in PBC patients [39].

Prior studies on the use of general anesthesia as a risk for PBC development have also been explored. The United Kingdom study demonstrated a 2-fold increased risk for any type of previously surgery with developing PBC, compared to healthy controls [40]. Additionally, a previous history of tonsillectomy and cholecystectomy may also be associated with development of PBC has been suggested [38,39].

DIAGNOSIS

The diagnosis of PBC is based on the following clinical criteria: (1) biochemical evidence of cholestasis with elevation of alkaline phosphatase for at least 6 month’s duration; (2) presence of AMA; and (3) histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts on liver biopsy. The expert consensus recommends that the diagnosis of PBC is established when two of the three criteria are met [41].

In patients with biochemical evidence of cholestasis, noninvasive imaging with ultrasound of the liver and biliary tree is necessary. If the biliary system is normal on ultrasound and patient is AMA positive, then no further radiographic testing is necessary. If the diagnosis is uncertain with noninvasive testing, cholangiography maybe be necessary to exclude primary sclerosing cholangitis or other diseases of the biliary tract.

Liver biopsy may be necessary for the diagnosis of AMA-negative PBC and to exclude other concomitant disease such as autoimmune hepatitis (AIH) and non-alcoholic steatohepatitis. Additionally, liver biopsy also provides valuable prognostic information. Histology is characterized by chronic, nonsuppurative cholangitis that affects interlobular and septal bile ducts. The infiltrate is comprised of plasma cells, macrophages, polymorphonuclear cells (especially eosinophils) and sometimes epithelioid granulomas [18]. The size of the biopsy is important and at least 10-15 portal tracts should be present to adequately appreciate cholangitis and ductopenia. Histologic lesions are divided into four stages. Stage I is characterized by portal inflammation with or without florid bile duct lesion and the inflammation is confined to the portal triads. Stage II is a progression of periportal lesions to involvement of the hepatic parenchyma, which is termed as interface hepatitis. Stage III is characterized by distortion of the hepatic architecture with numerous fibrous septa. Stage IV is defined as cirrhosis with the existence of regenerative nodules [41].

CLINICAL MANIFESTATIONS AND PATIENT MANAGEMENT

PBC is now diagnosed earlier in its clinical course than in the past with more than half of patients being asymptomatic at the time of diagnosis [42]. Fatigue and pruritus are the two most common symptoms in PBC patients. Fatigue does not appear to correlate with disease severity, histologic stage, or duration and is strongly associated with excessive daytime somnolence [43]. The etiology for fatigue is unknown, but maybe related to autonomic dysfunction [44]. Fatigue may be multifactorial and other causes including anemia, hypothyroidism, depression, and sleep disorder should be explored. Treatment for clinical depression and clinical use of fluoxetine does not appear to improve underlying fatigue [45]. In an open label trial, modafinil was found to be effective at lessening fatigue [46]. Pruritus is a more specific symptom for PBC and can be local or diffuse. It is usually worse at night, but the underlying cause of pruritus in PBC is unknown [30]. Pruritogenic substances are believed to be made in the liver and excreted in bile, but due to cholestasis accumulate in tissues. The expert panel consensus recommends the use of cholestyramine as first-line treatment, with other agents like rifampicin, antidepressants, opiate antagonists, and antihistamines to be considered in refractory cases [41].

Osteoporosis is the most common bone disorder seen in PBC and can occur up to a third of patients and should treated appropriately with calcium, Vitamin D, and bisphosphonates as clinically appropriate [47]. Another common symptom is Sicca Syndrome, which is characterized by dry eyes and mouth and general treatment include artificial tears, but antiinflammatory and immunosuppressant agents have also been used to treat the dry eyes [41].

Lastly, treatment for portal hypertension and varices in patients with PBC should be same as that for other cirrhotic patients and liver transplantation should be strongly considered. Patients with cirrhosis are also at increased risk for hepatocellular carcinoma and should be screened with cross-sectional imaging every 6-12 months, with or without alpha fetoprotein [48].

NATURAL HISTORY

The rate of disease progression varies among individual patients and the natural history has become more difficult to characterize given the recognition of earlier stage disease, which

requires long-term follow-up. Prince et al., described a series of 770 patients and at diagnosis approximately 61% were asymptomatic [49]. Among the asymptomatic patients, the probability of remaining symptom-free up to 10 years after diagnosis was only 20%. Ten years from diagnosis, the cumulative incidence rates of fatigue, pruritus, jaundice, and ascites were 46%, 46%, 17%, 17%, respectively. Interestingly, the median survival was similar between the asymptomatic and symptomatic groups (9.6 vs. 8.0 years, respectively, $p = 0.212$). Notably, a majority of patients were not treated (70%) with ursodeoxycholic acid (UDCA) and therefore does not reflect the experience of contemporary patients with PBC receiving this mainstay therapy.

During the UDCA-era (circa 1990), the rate of histological progression to cirrhosis was significantly less in the UDCA group than the control group of 13% compared to 49%, respectively [50]. Additionally, in a prospective trial of 180 patients being followed over the course of 4 years, the risk of developing varices was 16% for the UDCA-treated group compared to 58% in the placebo-group, but UDCA did not appear to reduce the rate of bleeding [51]. In a study of 262 patients who received 13-15mg/kg UDCA daily for a mean of 8 years, the overall survival rates without liver transplantation were 84% at 10 years and 66% at 20 years, which was better than the spontaneous survival rate as predicted by the updated Mayo model (RR, 0.5, $p<0.01$) [52].

Interestingly, biochemical response to UDCA may be predictive of long-term prognosis. In several studies, biochemical response to UDCA has been associated with good long-term prognosis [53,54]. Since the advent of UDCA, the estimated rate of liver transplant for PBC has steadily decreased [41]. In a study from the United States, the rate of liver transplantation for PBC during 1995-2006 was reported to be decreasing yearly, while the rate of transplantation for PSC over the same indexed period remains unchanged [55].

TREATMENT

Therapy for Primary Biliary Cirrhosis

UDCA at the recommended dose of 13-15mg/kg is considered the first-line therapy for PBC [41]. UDCA is a hydrophilic naturally occurring bile acid, which has several interrelated functions including expansion of the hypdrophilic bile acid pool with direct choleretic, antiinflammatory, and anti-apoptotic properties on hepatic epithelia [56]. Multiple randomized, placebo-controlled trials demonstrated that UDCA improves both serum liver biochemistries and histology of PBC patients [57,58]. A subsequent combined analysis of the three largest clinical trials showed that UDCA prolongs survival free of liver transplantation [59].

The clinical efficacy and therapeutic effect of UDCA in PBC is controversial. Two meta-analyses have demonstrated that there was no survival difference between UDCA-treated patients compared to place-treated patients [60,61]. However, these two meta-analyses included studies of short duration and those that used an inadequate dose of UDCA. A more recent meta-analysis addressed these concerns and found that the risk of death or liver transplantation was reduced by 32% in patients treated with UDCA compared to placebo [62].

In one study comparing the three different doses of UDCA showed that the 13-15mg/kg/day is superior in terms of biochemical response and Mayo risk score compared to lower dose of 5-7 mg/kg/day, but was similar to the higher dose of 23-25mg/kg/day [63]. Unfortunately, there has been no trial to date comparing the different UDCA formulation. A pharmokinetic study in normal volunteers suggested major differences in bioavailability based on product preparation [64].

In the past three decades, a variety of adjuvant medications have been used in patients who have suboptimal response to UDCA and they include steroids, azathioprine, mycophenolate mofetil, methotrexate, colchicine, silymarin, and bezafibrate [8]. However, larger studies with longer follow-up periods are necessary to assess their effect on this disease.

Liver Transplantation

Liver transplantation has improved the survival of PBC patients. Transplantation is the only effective treatment for those with decompensated cirrhosis or liver failure. Interestingly, approximately 20% of patients will have a PBC recurrence at 5 year post-transplantation [65]. The role and long-term effect of UDCA in this setting remains unknown [66].

CONCLUSION

PBC is an autoimmune liver disease characterized by destruction of small to medium intrahepatic bile ducts, resulting in chronic cholestasis and fibrosis, with progression to cirrhosis and end-stage liver disease. The exact pathogenesis of PBC is not fully understood, but is likely the interplay between environmental exposures in genetically predisposed patients. The advancement of genetics/genomics will likely bridge this knowledge gap and provide better understanding the full scope of genetic impact on the architecture of this disease. UDCA modifies the natural history of PBC, but additional studies are required to elucidate whether this therapy is effective for all PBC patients.

Practice Points

- To date, women with PBC have persistent biochemical cholestasis but the majority are usually asymptomatic.
- The diagnosis of PBC can be established by meeting two of the three following criteria: (1) biochemical evidence of cholestasis with elevation of alkaline phosphatase; (2) presence of AMA; and (3) histopathologic evidence of nonsuppurative cholangitis with destruction of small or medium-sized bile ducts on liver biopsy.
- UDCA at the recommended dose of 13-15mg/kg is considered the first-line therapy

Research Agenda

- Future studies are necessary to elucidate the role of environmental exposures and genetic impact not only in the development of PBC, but on disease progression and variable response to therapy.
- Additional studies are required to further elucidate whether UDCA is effective for all patients within the entire spectrum of disease severity.

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