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Primary biliary cirrhosis

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Abstract

Primary biliary cirrhosis (PBC) is a chronic, cholestatic liver disease that is characterized by progressive immune mediated destruction of the intrahepatic bile ducts. Over time, fibrosis extends out of the portal tracts and progresses to cirrhosis. Neither the etiology nor the pathogenesis are well understood; however, most of the current evidence suggests that it is an autoimmune condition that may be triggered by environmental stimuli in genetically predisposed individuals. Since the precise mechanisms involved in the pathogenesis of PBC have not been elucidated, curative therapy has not been identified and the focus has been on preventing disease progression. Ursodeoxycholic acid (UDCA), the only approved therapy for PBC, improves histology and retards disease progression. Future studies will likely combine UDCA with anti-inflammatory, immunosuppressive, immunomodulatory or antimicrobial agents. Once the etiology and pathogenesis of PBC are better delineated, more definitive therapy can be designed with curative intent.

Key words: Primary biliary cirrhosis, cholestasis, liver, ursodeoxycholic acid.

Epidemiology and presentation

PBC is primarily a disorder of middle-aged women though it can be seen in women as young as 20.[1] The prevalence of PBC in women is 9 times that of men.[2] Most patients are asymptomatic at presentation (60%), while symptomatic patients can present with fatigue, pruritus, portal hypertension, osteoporosis, skin xanthomata, fat soluble vitamin deficiencies, and/or recurrent asymptomatic urinary tract infections.[3] In symptomatic patients, advanced age, elevated serum bilirubin levels, decreased serum albumin levels, and cirrhosis each correlate with shortened survival.[1] The typical laboratory profile of a patient with PBC is characterized by an elevated alkaline phosphatase, IgM spike on electrophoresis and antimitochondrial antibody (AMA) positivity. The diagnosis of PBC can be made by fulfilling 2 of 3 internationally accepted criteria *(Table I)*.

Evidence for PBC as an autoimmune disorder

The etiology and pathogenesis of PBC is not well understood; however, autoimmunity is a prevailing hypothesis.[4] PBC has both typical and unusual features for an autoimmune disorder.

Typical features include an autoantigen (AMA) and autoreactive T cells (both $CD4^+$ and $CD8^+$) located surrounding damaged bile ducts.[5,6] This T-cell mediated apoptotic destruction of small and medium bile ducts leads to a chronic non-suppurative destructive cholangitis.[7] The AMA is a very specific autoantibody against the E2 subunit of the pyruvate dehydrogenase complex of the inner mitochondrial membrane.[9] Approximately 5% of patients with PBC do not have a positive AMA; however, studies with more sensitive assays have demonstrated the presence of AMA in virtually all patients with PBC.[9,10] In addition, PBC occurs with increased frequency among family members of affected individuals and similar to other autoimmune diseases is more prevalent in women. Furthermore, it is associated with many established autoimmune disorders such as autoimmune thyroiditis (10-15%), scleroderma/CREST (< 5-10%) and Sicca syndrome (50%), among others.[4]

Unlike most other autoimmune conditions, treatment with immunosuppressive or anti-inflammatory medications is not very effective. Although AMA is a very specific autoantibody, there is no proof that it is pathogenetic. In fact, the natural history of patients with or without a positive AMA is no different, suggesting it does not have a predominant pathogenetic role.[11]

Table I.

Diagnostic criteria for PBC (2 of 3)
Detectable AMA (> 1:40)
Increased alkaline phosphatase (> 6 months)
Compatible histology

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The effect of genetics and environment on PBC

No genetic linkage analyses have been performed in PBC, possibly due to the rarity of the disease and the complexity of obtaining DNA samples from large numbers of representative families. However, the concordance rate of PBC in monozygotic twins is among the highest for any autoimmune disease.[12] Furthermore, PBC appears in 1-6% of relatives of affected individuals and the incidence in more recent series seems to be even higher.[13] In a study from Olmstead County Minnesota, 46 cases were identified and the prevalence among family members was higher than in the general population. The relative risk of a sibling of an affected family member being diagnosed with PBC was 10.5.[14]

PBC does exhibit geographic clustering. The prevalence of PBC is highest in Scandinavia, England and some parts of the United States where prevalence rates are reported to be as high as 402 cases per million.[15] The environment likely plays an important role in triggering disease onset. Exposure to bacterial antigens is known to induce autoimmune conditions and molecular mimicry is thought to be a plausible mechanism explaining such observations. Thus, PBC may be the result of early exposure to a bacterial antigen with subsequent triggering of the immune system. Many infectious agents have been proposed to cause or trigger the onset of PBC, although convincing evidence is lacking. Of the bacterial strains invoked in the pathogenesis of PBC through molecular mimicry, *Escherichia Coli* has the most evidence, based largely on reports of increased prevalence of urinary tract infections in patients with PBC.[16] Although many bacteria and more recently, retroviruses have been implicated, recent evidence suggests *Novosphingobium aromaticivorans* may have an important role in the induction of PBC.[17]

Medical therapy for PBC

The only drug that is approved for the treatment of PBC is UDCA, a hydrophilic bile acid initially found in bear bile. Among many mechanisms of action it has immunomodulatory and antiapoptotic effects and is weakly immunosuppressive.[18] Given at a dose of 13-15 mg/kg it is well tolerated and if used early in the course of the disease, can slow disease progression.[19] In addition, UDCA improves liver chemistries, reduces AMA titer and immunoglobulin levels.

Based on the theory that PBC may have a chronic infectious etiology, two pilot studies of antiretroviral drugs (lamivudine alone then lamivudine and Combivir) have been performed.[20] The latter study showed some histologic improvement, however randomized controlled trials are needed to more rigorously assess efficacy. Immunosuppressive medications such as prednisolone, budesonide and calcineurin inhibitors have also been investigated in PBC.[21-23] Although some of these drugs improved biochemical tests and even histology, side effects in some were concerning.

Despite the benefits of UDCA, it is unable to prevent future liver decompensation or reverse it, thus at this time, liver transplantation is the only curative therapy for PBC. Future treatment may combine UDCA with anti-inflammatory, immunosuppressive, immunomodulatory or antimicrobial agents. Once the etiology and pathogenesis of PBC are better delineated, more definitive therapy can be designed with curative intent.

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