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The Diagnosis of Primary Biliary Cirrhosis

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Abstract

Primary biliary cirrhosis (PBC) is a chronic liver disease characterized by the immune mediated destruction of small intrahepatic bile duct epithelial cells leading to cholestasis and cirrhosis. The autoimmune basis of PBC is supported by the highly specific anti-mitochondrial antibodies (AMA) and autoreactive T cells, the former being the basis for diagnosis in the vast majority of cases. Although a rare disease, the incidence rates of PBC have been increasing, possibly due to increased testing and diagnosis as opposed to a true increase in disease incidence. Presently, most cases are asymptomatic and only suspected based upon routine liver tests. Those with symptoms typically complain of pruritus and fatigue. The diagnosis of PBC is based on the presence of at least 2 of 3 key criteria including a persistently elevated serum alkaline phosphatase, the presence of serum AMA, and liver histology consistent with PBC. Anti-nuclear antibodies specific to PBC are useful in cases in which AMA are not detected and may indicate a more aggressive course. Ursodeoxycholic acid is the only proven therapy for PBC and in most cases can delay or prevent disease progression. However, a subgroup of patients does not adequately respond to ursodeoxycholic acid and for whom new therapies are needed.

Keywords

Primary biliary cirrhosis; anti-mitochondrial antibody; anti-nuclear antibody; diagnosis; epidemiology

1. Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by highly specific serum anti-mitochondrial antibody (AMA) and progressive destruction of the intrahepatic bile ducts resulting in chronic cholestasis, portal inflammation, and fibrosis that may lead to cirrhosis and ultimately liver failure. The disease predominantly affects women

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typically diagnosed in their fifth and sixth decade although younger patients have been described including rare paediatric cases [1]. The loss of bile ducts leads to intrahepatic retention of detergent bile acids, resulting in liver damage through interaction with cell membranes and organelles. The derangement of the entero-hepatic bile acid circulation is likely the cause of other pathophysiological changes, which contribute to the extra-hepatic manifestations of the disease.

The clinical features and natural history of PBC vary significantly among individual patients ranging from asymptomatic and stable or only slowly progressive to symptomatic and rapidly progressive. The typical clinical presentation has changed during the last few decades as the natural history has been modified by the recognition of earlier more indolent cases and the use of ursodeoxycholic acid (UDCA).

2. Epidemiology of PBC

2.1 Global prevalence and incidence

Large case series have reported prevalence rates of PBC ranging between 19 and 402 cases per million [2, 3]. However, serological studies of large presumably healthy cohorts demonstrate that AMA prevalence can be as high as 0.5% [4]. Differences in estimates of PBC incidence and prevalence may be due to true difference in prevalence rates between populations or secondary to variable diagnostic criteria, case-finding methods, and physician awareness. Nevertheless, a latitudinal geoepidemiological pattern of PBC occurrence has been proposed [5] with a higher frequency in Northern European and North American areas. This is supported by the highest prevalence and incidence rates being reported in Scandinavia, Great Britain, and the northern Midwest region of the US, but is contradicted by the high prevalence observed in the Spanish area of Sabadell [6]. Some authors suggest that PBC is also increasing in incidence. Indeed, incidence rates increased from 5.8 to 20.5 cases per million population among the residents of Sheffield, UK between 1980 and 1999 [7, 8] and from 11 to 32 cases in Newcastle-upon-Tyne, UK between 1976 and 1994 [9, 10]. This increase was paralleled by prevalence rates reaching more than 200 cases per million in the middle to late 1990s. Whether these changes are due to increasing disease incidence or secondary to increased detection of mild, asymptomatic cases or slowly progressing PBC remains to be determined. However, the age at diagnosis of mid-to-late-50s has remained similar across different time periods of study.

2.1 PBC Risk Factors

Although a female predominance is characteristic of most autoimmune diseases, it is particularly striking in PBC where females outnumber males with ratios reported as high as 10:1 [11]. Interestingly the presence of serum AMA in the general population has a lower sex ratio [11] suggesting that the progression from loss of tolerance to the autoantigen to clinical liver disease is more frequent in females.

In addition to female sex, several environmental factors have been associated with PBC. Notably, these include a family history of PBC, a history of urinary or vaginal infections [12], co-morbidity with other autoimmune diseases, past or present smoking, and previous pregnancies, frequent use of nail polish or hair dye [13, 14]. Chemical and infectious

exposures have also been hypothesized as potential risk factors ans have been supported by geographical clustering of cases near toxic waste sites in New York City [15] and space-time clustering in North East England [16].

3. Diagnosis of PBC

The diagnosis of PBC should be suspected when there is an elevation of serum alkaline phosphatase (ALP), other signs of cholestasis including jaundice or pruritus, and cirrhosis of unknown cause. The diagnosis of PBC can be established if two of three objective criteria are present: serum AMA at titers ≥ 1:40, unexplained elevated ALP ≥ 1.5 times the upper normal value for over 24 weeks and compatible liver histology, specifically nonsupporative cholangitis and interlobular bile duct injury (Table 1) [17, 18]. In addition, PBC patient often have elevations of aminotransferases and elevated immunoglobulins, mainly IgM.

3.1 AMA Tests

The presence of AMA in PBC sera was first recognized in 1965 by Walker and colleagues [19] and in 1987 the AMA antigens were cloned and identified [20, 21]. The epitopes recognized by AMA are often referred to as M2 antigens for historical reasons and include the lipoylated domains of the E2 and E3 binding protein (E3BP) components of the pyruvate dehydrogenase complex (PDC-E2) and the E2 components of the 2-oxo glutarate dehydrogenase (OADC-E2) and branched-chain 2-oxo acid dehydrogenase (BCOADC-E2) complexes [22, 23].

Several methods are available for AMA testing. In clinical laboratories, indirect immunofluorescence (IIF) microscopy in the past was routinely employed. However, IIF lacks both specificity and sensitivity. Enzyme-linked immunoassays (EIA) using recombinant proteins to the 3 known autoantigens are widely available and most frequently employed by commercial labs. The titer of AMA does not correlate with disease severity and whether AMA-positive individuals without biochemical abnormalities will eventually develop PBC remains debated but it is reasonable to follow them expectantly with annual liver biochemistries [17].

In contrast, when the AMA is negative, a diagnosis of PBC is based upon abnormal serum ALP levels and liver histology. Imaging by magnetic resonance or endoscopic retrograde cholangiography may be helpful to rule out primary sclerosing cholangitis or other conditions that might lead to chronic cholestasis. Additional supportive evidence can be sought by the presence of PBC specific anti-nuclear antibodies (ANA) with rim-like and multiple nuclear dot patterns[24]. EIA tests for gp210 and Sp100 are commercially available and detect most of these ANA[25]. Although AMA-negative PBC patient appear to have a similar course as AMA-positive cases, cross-sectional and longitudinal data have suggested an association between PBC-specific ANA positivity and more severe disease [26, 27].

3.2 Liver histology

The need for liver biopsy in AMA-positive PBC remains controversial. Biopsy is not required for diagnosis in these scenarios but may be clinically useful for disease staging, particularly for clinical trials. Histological staging is based on Ludwig's [28] and Scheuer's

[29] classifications ranging from portal-tract inflammation with predominantly lymphoplasmacytoid infiltrates and septal and interlobular bile ducts loss (stage I) to cirrhosis (stage IV). However, clinical management does not change significantly other than perhaps the need for hepatocellular carcinoma surveillance if cirrhosis is discovered. Liver biopsy is required when the AMA is absent in order to differentiate AMA-negative PBC from other conditions, including small-duct primary sclerosing cholangitis, sarcoidosis, or drug-induced cholestasis.

3.3 PBC-Autoimmune hepatitis overlap

Upon presentation, most case of PBC will have a mild elevation of the serum aminotransferases, many will demonstrate a mild degree of interface hepatitis on biopsy, and up to 50% will have ANA. This frequently leads to a mistaken diagnosis of an overlap of autoimmune hepatitis (AIH) with PBC. In contrast, fewer than 10% of PBC patients have a more severe hepatocellular injury and other features of AIH including responding to steroids and other immunosuppresants [30]. Several diagnostic criteria have been proposed, but none have been validated or accepted. Nevertheless, PBC/AIH overlap should be considered when the ALP to aminotransferase ratio is less than 1.5, serum IgG is elevated and anti-smooth muscle antibodies are present at greater than 1:80 titer. In these cases consideration should be given to the use of immunosuppressive agents [31].

4.0 Natural history

The natural history of PBC appears to have become significantly less severe in recent years. This may be secondary to earlier diagnosis or identification of more mild disease [32], but decreasing rates of liver transplantation for PBC in Europe and North America suggests a true change in natural history which coincides with the introduction of ursodeoxycholic acid (UDCA) for the treatment of PBC [33, 34]. Prior to its introduction, the median time from diagnosis to symptoms was 2 – 4.2 years and survival was compromised relative to a healthy population [35, 36]. Several prognostic models have been developed with the Mayo risk model which includes age, total serum bilirubin, serum albumin, prothrombin time and severity of fluid retention, being the most widely accepted [37].

5.0 Treatment of PBC

5.1 Ursodeoxycholic acid

The only currently established treatment for PBC is UDCA at 13–15 mg/kg daily divided into two to three doses [18]. The treatment is well tolerated and, with the exception of a moderate weight gain, does not lead to significant adverse effects. Results of randomized placebo-controlled trials of sufficient duration have shown that UDCA can prevent portal hypertension and the appearance of esophageal varices and delay the time to liver transplantation [38], while a significant improvement in survival is observed in patients with serum bilirubin levels greater than 1.4 mg/dl at baseline [39]. Importantly, survival rates of patients with stage I or II disease treated with UDCA are similar to age-matched healthy controls [40].

Despite the efficacy of UDCA, up to 40% of PBC patients have an incomplete biochemical response to therapy and are at greater risk of progression. Definitions of response have been developed by several groups and validated in various populations of PBC patients (Table 2) [40–44]. The largest study to date of 2,353 patients from the United Kingdom found that the Paris I criteria performed the best at discriminating between those with a good or poor prognosis [45]. According to this model, 79% of PBC patients who had received UDCA at an adequate dose for a minimum of 2 years met the Paris I criteria for a biochemical response to UDCA. Going forward, a major challenge in developing additional therapies for PBC will be whether regulatory agencies will accept any of these or other responses as sufficiently important outcomes to achieve approval.

5.2 Methotrexate

Several case series have described encouraging results with the use of methotrexate given alone or in combination with UDCA. In the most encouraging series, methotrexate in combination with colchicine significantly improved serum levels of alkaline phosphatase, aminotransferases, liver histology, and pruritus in 73 of 91 PBC patients with an inadequate response to UDCA[46]. However, no benefit on mortality or need for liver transplantation was found in a meta-analysis of five trials and a large controlled trial found no benefit from the addition of methotrexate to UDCA on survival free of liver transplantation[47, 48].

5.3 Obeticholic acid

Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist that that has pleiotropic effects including regulation of bile acid synthesis and has shown promising results in Phase 2 studies as an added therapy to UDCA in PBC patients with an incomplete response to UDCA [49]. The major adverse effect of OCA appears to be pruritus. Phase 3 studies are currently underway to determine its efficacy and safety in this patient population.

5.4 Rituximab

Rituximab is a humanized anti-CD20 monoclonal antibody which was originally developed for the treatment of B-cell lymphomas but was later shown to be effective in the treatment of rheumatoid arthritis. Two open label studies have been performed in PBC patients with incomplete responses to UDCA with only moderate effects demonstrated [50, 51]. In light of the potential toxicity including progressive multifocal leukoencephalopathy and cautionary results in animal models of PBD, future development is unlikely.

5.5 Novel approaches

The development of several animal models of PBC has allowed the dissection of the immunological basis of the induction and progression of this disease [52]. In addition, these models have served to develop the pre-clinical rational for novel approaches. Most recently, cytotoxic T lymphocyte antigen 4 immunoglobulin was shown to reduce liver inflammation after induction of PBC in mice with the xenobiotic 2-octynoic acid [53]. Finally we note a dedicated issue of the Journal of Autoimmunity devoted entirely to liver disease [54–61], as well as, for completeness, several recent descriptions of animal models of PBC [62–65].

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Highlights

- Primary biliary cirrhosis (PBC) is a chronic autoimmune disease which targets the biliary epithelial cells of the liver.
- The diagnosis of PBC is based on the presence of at least 2 of 3 key criteria including a persistent elevation of serum alkaline phosphatase, the presence of anti-mitochondrial antibodies (AMA), and liver biopsy histology consistent with PBC.
- Treatment of PBC with ursodeoxycholic acid delays disease progression in most cases, but new therapies are needed for those who have an inadequate response.

Table 1

Diagnostic criteria and clinical features of primary biliary cirrhosis

2 of 3 required criteria
Serum alkaline phosphatase > 1.5 times ULN[1]
Presence of AMA[2]
Liver histology with nonsuppurative destructive cholangitis and destruction of interlobular bile ducts
Other characteristic clinical features
PBC-specific ANA[3] (Sp100 and gp210)
Elevated serum IgM
Hypercholesterolemia/Xanthomas
Sicca syndrome
Pruritus
Fatigue

[1] ULN, upper limit of normal;

[2] AMA, anti-mitochondrial antibodies;

[3] ANA, anti-nuclear antibodies

Table 2

Definitions of biochemical response after 1 year of UDCA therapy

Paris I	*All of the following* • ALP level ≤ 3 X ULN • AST level ≤ 2 ULN • normal bilirubin level
Paris II	*All of the following* • ALP and AST level ≤ 1.5 × ULN • normal bilirubin level
Barcelona	Decrease in ALP level > 40% of baseline level or a normal level
Toronto	ALP level < 1.76 × ULN
Rotterdam	Normalization of abnormal bilirubin and/or albumin levels