Autoimmunity Reviews 13 (2014) 441–444

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

The diagnosis of primary biliary cirrhosis

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ARTICLE INFO

Article history:
Accepted 13 November 2013
Available online 11 January 2014

Keywords:
Primary biliary cirrhosis
Anti-mitochondrial antibody
Anti-nuclear antibody
Diagnosis
Epidemiology

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 (AMAs) 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 AMAs, and liver histology consistent with PBC. Anti-nuclear antibodies specific to PBC are useful in cases in which AMAs 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.

Contents

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 typically diagnosed in their fifth and sixth decade although younger patients have been described including rare pediatric 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

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http://dx.doi.org/10.1016/j.autrev.2014.01.041

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.

2.2. 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 AMAs 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, previous pregnancies, and frequent use of nail polish or hair dye [13,14]. Chemical and infectious exposures have also been hypothesized as potential risk factors and 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 AMAs at titers ≥1:40, unexplained elevated ALP ≥ 1.5 times the upper normal value for over 24 weeks and compatible liver histology, specifically nonsuppurative cholangitis and interlobular bile duct injury (Table 1) [17,18]. In addition, PBC patient often have elevations of aminotransferases and elevated immunoglobulins, mainly IgM.

Table 1
Diagnostic criteria and clinical features of primary biliary cirrhosis.

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

[a] ULN, upper limit of normal.
[b] AMAs, anti-mitochondrial antibodies.
[c] ANAs, anti-nuclear antibodies.

3.1. AMA tests

The presence of AMAs 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 AMAs 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 (EIAs) using recombinant proteins to the 3 known autoantigens are widely available and most frequently employed by commercial labs. The titer of AMAs 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 (ANAs) with rim-like and multiple nuclear dot patterns [24]. EIA tests for gp210 and Sp100 are commercially available and detect most of these ANAs [25]. Although AMA-negative PBC patients 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-