Abstract  To be able to predict who will develop auto-immune disease would allow for early treatment which may dramatically alter the course of the disease. In some cases, it may also lead to prevention of the disease development. The prediction of disease development is based on the analysis of risk factors which have been associated with the disease in question. These factors include genetic susceptibility, as well as immunological and environmental factors. One autoimmune disease that may serve as a model for disease prediction is primary biliary cirrhosis (PBC), an autoimmune liver disease affecting the small- and medium-sized bile ducts. PBC could be an ideal model due to recent advances in elucidating its genetic associations. As well, a variety of immunological and environmental risk factors have been well established. Indeed, the presence of PBC-specific antimitochondrial antibodies and/or antinuclear antibodies has been shown to be predictor of disease development and possibly prognosis. This review will examine the current evidence which suggests that we may potentially be able to predict the development of PBC in some individuals. These concepts may also be applied to autoimmune diseases in general.

Keywords  Autoimmunity · Autoimmune disease · Genetics · Prevention · Prediction · Risk factor · Susceptibility

Abbreviations  AMA Antimitochondrial antibodies  
ANA Antinuclear antibodies  
E. coli Escherichia coli  
L. delbrueckii Lactobacillus delbrueckii  
PBC Primary biliary cirrhosis  
PDC-E2 Pyruvate dehydrogenase complex  
UTI Urinary tract infection

Introduction  
Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterised by immune-mediated destruction of the small- and medium-sized intrahepatic bile ducts, which in many individuals may progress to cirrhosis and liver failure [1, 2]. In advanced cases, transplantation may be required. At the time of diagnosis, patients may be symptomatic or asymptomatic, with asymptomatic patients having normal or abnormal biochemistry tests, possibly with cholestatic indices being raised [1–6]. Symptomatic patients typically present with non-specific symptoms such as fatigue, pruritus and arthralgias, with liver disease not being suspected initially.
It is not uncommon for PBC patients to have had several non-hepatological investigations and consultations for their symptomatology. In advanced stages of the disease, patients may present with complications from portal hypertension and hepatic decompensation, such as jaundice, ascites or variceal bleeding [1–6]. Although there may be great variation in the presenting signs and symptoms, the commonality found among patients are the presence of anti-mitochondrial (AMA) or disease-specific antinuclear antibody (ANA), which are present in almost all patients [7–9]. In order to establish the diagnosis a patient has to fulfil two from the three criteria mentioned below: elevated alkaline phosphatase (ALP), seropositivity for disease-specific AMA and/or ANA, as well as specific histological features of PBC [1, 5, 6]. Histological features of PBC are destruction of the biliary epithelial cells, ductopenia, portal inflammatory cell infiltration, as well as granuloma formation [1, 2]. Cholestatic markers include increased levels of alkaline phosphatase and γ GT [1–6, 10]. PBC is a slowly progressive disease, with the clinical course being well known as unpredictable [1–6, 10]. Medical treatment of PBC is with ursodeoxycholic acid (UDCA) administered at an appropriate dose (13–15 mg/kg/day) [1–6]. Early administration of UDCA slows the disease progression and has improved the quality of life in many patients [1–6, 11].

Epidemiological studies from the USA, UK and France have established several risk factors to be associated with PBC development [12–15]. Although risk factors vary among the studies, recurrent urinary tract infection, a history of smoking and oestrogen disturbance have been found to be risks in all studies. Female sex as well as being a first degree relative to a patient with PBC also increases the risk for disease development [12–15]. In recent years, genetic and genome wide association studies (GWAS) have identified several disease genes to be associated with PBC. A combination of genetic and environmental factors likely work together in the development of the disease.

Currently, no reliable prognostic index has been developed which can predict the course of the disease and its outcome over time in patients at early stages [1, 3–6]. However, given that several risk factors have been identified, the question remains as to whether we can predict the development of PBC in some individuals. Indeed, this question is raised not only with PBC, but with all autoimmune diseases in general. If we can predict the development of PBC, it may be possible to prevent disease development in some or detect the disease early in others. This review will examine the known risk factors for PBC development, in an attempt to analyse whether PBC development is predictable in certain individuals. This approach with PBC would perhaps be applied to other autoimmune diseases.

**PBC-specific autoantibodies as prognosticators of disease’s development**

AMA are pathognomic for PBC as they are present in up to 95 % of PBC patients, and their presence in asymptomatic individuals is generally believed to precipitate eventual disease development [1–9, 16–18]. Several studies indicate that the prevalence of AMA in the general population is <1 % [19–21]. In PBC patients, AMA react against components of the 2-oxo-acid dehydrogenase complexes and mostly recognise the E2 subunit of the pyruvate dehydrogenase complex (PDC) [1, 2, 9, 16–18, 22–26]. AMA are reactive against PDC-E2 in more than 90 % of cases, and there is also cross-reactivity with the PDC-E3 binding protein (E3BP) [27–29]. Other targets (in 20–70 % of cases) include the E2 subunits of branched-chain 2-oxoacid dehydrogenase complex (BCOADC) and 2-oxoglutarate dehydrogenase complex (OGDC) and the E1α and E1β subunits of PDC [1, 7, 8, 24, 26–29].

The Newcastle group has studied the significance of AMA in detail, and they indicate that the majority of asymptomatic, non-cholestatic patients positive for AMA, have histological features of PBC [23, 30]. Their first study included 29 patients with positive AMA (greater than 1/40 titer by indirect IFL), who were asymptomatic for liver disease [23]. The average age of the cohort was 54.7 years, 28 patients were females, and one set consisted of a mother–daughter pair [23]. All patients had normal LFTs, although raised γ-GT levels were found in 14 individuals [23]. Ten patients had elevated IgM levels, and 2 had marginally raised IgG, with an IgG subclass distribution of AMA being primarily IgG3 followed by IgG1 [23]. Histological examination of liver biopsies demonstrated that 12 individuals had changes compatible with PBC, including inflammatory cell infiltrates around damaged bile ducts with and without macrophage granulomata in the portal tracts [23]. Twelve had non-specific chronic hepatitis around bile ducts or lymphoid aggregates within the portal areas [23]. Mild fibrosis was found in seven biopsies, and only two biopsies in the entire cohort were completely normal [23]. After a mean 8.7-year follow-up, one patient had died of post-cricoid carcinoma, and five developed PBC symptoms (unexplained pruritus with malaise or malaise alone) [23]. Two of 13 patients followed-up for <4 years had developed pruritus, and 12 of 16 (all female) followed up for more than 4 years had developed abnormal LFTs [23]. These results led those authors to conclude that AMA positivity in the absence of symptoms, with or without normal liver disease-related biochemistry, is predictive of future PBC development, and many of these patients may already have histological evidence of early PBC [23]. The same group followed up the same cohort 10 years later [30]. The median follow-up of those patients...
was 17.8 years, ranging from 11–23.9 years, although five
of the original patients had died from non-liver-related
causes [30]. PBC symptoms had developed in 22 of 24
patients (76%), which included pruritus, ongoing fatigue,
and chronic right upper quadrant pain [30]. Persistently
cholestatic LFTs were reported in 24 patients (83%) [30].
Repeat liver biopsy material was available in ten patients
and showed fibrosis progression from grade 1 to 2 in two
individuals, and progression from grade 2 to 3 in another
two [30]. Cirrhosis had not developed in any of the patients
[30]. ELISA of baseline serum samples demonstrated
positive AMA in 21 of 27, all of which had initial biopsy
results compatible with PBC, confirming the presence of
PBC in asymptomatic, non-cholestatic patients with posi-
tive AMA [30].

A study of another cohort has produced similar results.
Kisand and colleagues [19] conducted an ELISA-based
study for antibodies to PDC-E2, the major PBC-specific
autoantigen, in three groups of Estonian patients. The first
group consisted of 1,461 individuals (ages 15–95 years,
mean 41 years, 637 males and 824 females), the second
497 individuals (ages 50–91 years, mean 61 years, 189
males and 308 females), and a third of 104 volunteers from
neighbouring small villages (mean age 42 years, 29 males
and 75 females) [19]. Fourteen individuals were found to
have antibodies to PDC-E2, all of which were asymptomatic
[19]. These patients were followed-up at 2, 4, 7 and
9 years [19]. Eight of the 14 were available for follow-up,
and 3 of the 8 had developed abnormal LFTs by the 9th
year of follow-up [19]. These patients also had AMA
detectable on indirect IFL, had inhibitory antibodies to
PDC and had anti-PDC of the IgG and IgA subclass,
although the IgG subclass was predominant [19]. The
remaining five AMA positive patients had low titer posi-
tivity, remained positive for AMA on follow-up, but did
not develop any evidence of cholestasis [19]. Unfortu-
nately, liver biopsies were not performed in any patients,
apparently due to lack of consent [19]. The above studies
demonstrate the strong predictive value of AMA positivity
for future PBC development.

ANA are also found in PBC, and their presence suggests
a more progressive form of the disease [1, 7, 8, 24, 26–29,
31–41]. Several PBC-specific ANA patterns have been
identified by indirect immunofluorescence (IFL). These
include the “multiple nuclear dot” and “nuclear mem-
brane/rim like” patterns [7, 8, 42, 43]. The “multiple
nuclear dot” pattern relates to autoantibodies against
Sp100, Sp140, promyelocytic leukaemia nuclear body
proteins and small ubiquitin-like modifiers [1, 7, 8, 24, 26–
29, 31–35]. The “nuclear envelope/rim like” pattern relates
to reactivities specific for gp210 and nucleoporin p62 [42].
Both patterns show disease specificity and are present in
approximately 30% of patients. These ANA may also be
present in patients who are AMA negative, in addition to
asymptomatic individuals and family members of PBC
patients [8, 17, 31–35, 44, 45].

The initiating events leading to AMA/ANA seropositivity,
as well as the pathological role of these autoantibodies,
remain unknown [1, 44, 46–49]. It has been suggested that
impaired T-regulation, apoptosis-mediated autoimmune
attack, xenobiotics-induced cellular destruction and
molecular mimicry and immunological cross-reactivity may
account for the development of autoantibodies [50–85].
Experimentally, numerical and/or functional impairment
of regulatory T cells has been demonstrated in PBC [55, 65–67,
86–89]. Apoptotic blebs of biliary epithelial cells have been
shown to contain intact immunoreactive mitochondrial
autoantigens, indicating a role for apoptosis in mediating
tissue-specific injury in PBC [1, 46, 47, 64]. The method
with which xenobiotics may induce the formation of auto-
antibodies is similar to that seen in microbial/self molecular
mimicry [1, 75, 76]. Molecular mimicry occurs when anti-
genic similarities between microbial or viral antigens and
self-targerts lead to the induction of cross-reactive immune
responses targeting both microbial and self-epitopic regions
[1, 7, 26, 46, 49–54, 56, 58, 59, 63, 68, 70–72, 83, 90]. The
immune attack against self targets may initiate a self-
perpetuating progressive inflammation and destruction of
the biliary epithelial cells [1, 7, 26, 46, 49–54, 56, 58, 59,
63, 68, 70–72, 83, 91]. A variety of environmental and
infectious agents, as well as immunological and genetic
factors have been suggested as potential triggers for
the induction of PBC-specific antibodies [50–54, 58, 59, 64,
73–83, 86–89].

The prevalence of AMA, and perhaps to a lesser extent
PBC-specific ANA, may be useful in the identification of
individuals at risk of PBC development. This is especially
the case in first-degree relatives of PBC patients, with
female relatives being at higher risk than others. Indeed,
the most common familial pairing in PBC is seen in
mother–daughter and sister pairs [92–95]. Therefore, the
screening of these individuals for disease-specific autoan-
tibodies may identify those asymptomatic ones who are
likely to go on to develop PBC. Further screening of these
patients for markers of cholestasis would be recommended,
as would early treatment.

Genetics

Bianchi et al. in this special issue discusses in great detail
the influence of environment and genetics in the develop-
ment of PBC. It appears that female relatives of PBC
patients have higher risk for PBC compared with demo-
graphically matched controls, which demonstrates the
likelihood of genetic factors being involved in the disease
development [90, 96–101]. The female preponderance of the disease may be due to genetic factors affecting the X chromosome, as a higher frequency of monosomy X in peripheral leukocytes has been found in patients with PBC [62, 102–106]. A single study in twins demonstrated a high concordance among monozygotic twins and a low concordance among dizygotic twins [107]. Genetic association studies (GWAS) have identified multiple gene loci to be associated with PBC, such as HLA DQB1, IL12A, IL12RB2, STAT4, CTLA4, IRF5-TNPO3, 17q12-21, and MMEL1, 17q12-21, DENND1B, CD80, CXCR5, TNFRSF1A, CLEC16A and NFKB1 [108, 109, 110–113]. Although GWAS and other genetic studies provide us with a list of genetic associations, it is not clear as to how many of these associations are required for disease development. As well, there is no diagnostic significance attached to these genetic associations although it is likely that future research will elucidate those genes which are responsible for fast versus slow disease progression. Genetic associations may also assist in the identification of those at higher risk of disease development, not only in PBC, but also in other conditions in which there is a strong genetic influence. Patients with a particular genetic trait (likely in combination with other clinical and demographic data) may be monitored for biochemical, immunological and clinical indices of disease development. As well, patients who have a susceptible trait may be advised in regard to risk reduction, such as hormonal therapy or smoking cessation and the aggressive treatment of recurrent UTI. All of these have been shown to be risk factors in PBC development [12–15, 114].

Recurrent urinary tract infections

Recurrent UTI has been indicated as a risk factor for PBC development [12–15, 94]. UTI was first suspected as a risk factor for PBC when investigators noted a higher incidence of bacteriuria in PBC patients compared with controls [115]. A study by Gershwin et al. [13] demonstrated that 59 % of 1,032 PBC patients reported a history of UTI. Prince and colleagues [15] reported similar associations in a study involving one group of 318 PBC patients from a geographically defined area and another involving 2,258 patients from a PBC support group [15]. UTI and PBC were found to be associated in the multivariate analysis (in both PBC groups) but not in a cohort of 3,936 demographically matched controls [15].

As a major causative organism of UTI, E. coli has been identified as an organism of interest in PBC, and it has been suggested that molecular mimicry between human and E. coli PDC-E2 may be involved in the breakdown of tolerance to PDC-E2 [116, 117]. Molecular mimicry and immunological cross-reactivity between bacterial-self peptides has been investigated as a mechanism responsible for the induction of liver autoimmunity [49, 57, 61, 63, 68–70, 91, 118–123]. At the experimental level, sera from PBC patients react with both E. coli and human PDC-E2. Also, more than half of the patients with recurrent UTI cross-recognize human PDC-E2 [124]. The significance of the disease-specific presence of antibodies against an ATP-dependent Clp protease of E. coli remains unclear [125–127]. Amino acid homologies between E. coli and human PDC-E2 sequences required for T cell epitope recognition of PDC-E2 have also been reported and pathogenic scenarios involving these epitopes in the pathogenesis of PBC have been formulated [119, 128]. Elegant studies have demonstrated that the E. coli and human PDC-E2 homologues are targets of cross-reactive responses at the CD4 T cell level [119, 129].

Several other organisms have been associated with PBC via a link with recurrent UTI, including Lactobacillus delbrueckii (L. delbrueckii). Vaginitis and vaginal infections have been found to be prevalent among PBC patients, and the question arises as to whether these are due to L. delbrueckii, which is part of the normal flora of the vagina [13, 14]. A pathogenic scenario implies that infections with L. delbrueckii increase susceptibility to vaginal infections, leading to recurrent UTI and subsequently PBC [130]. However, this hypothesis lacks experimental validation. Lactobacilli have also been linked to PBC development a 39-year-old female who received Lactobacilli vaccination for recurrent vaginitis [131]. The authors of this study have speculated that an immune response against Lactobacilli initiated a cross-reactive response targeting human PDC-E2 via a mechanism of molecular mimicry. The sera of the patient tested positive for AMA and the AMA targeting epitope from beta-galactosidase of Lactobacillus delbrueckii [131]. This is an interesting finding taking into account a previous report demonstrating that L. delbrueckii and human PDC-E2 share sequences in common which are targeted by antibodies specifically found in approximately 50 % of patients with PBC [130]. The fact that L. delbrueckii is a cause of recurrent UTI in a considerable proportion of elderly women further supports the theory involving this infectious agent in the pathogenesis of PBC [132, 133].

Despite UTI being linked to PBC, it remained unclear as to whether this association was causal or casual, as changes in mucosal immunity may infer an increased susceptibility to UTI via alterations in vaginal flora. A recent study by Varyani and colleagues [134] found that UTI preceded the diagnosis of PBC in a cohort of PBC patients. That study involved 800 PBC patients, 7,991 matched controls and 12,137 patients with chronic liver disease as controls [134]. UTI had been diagnosed within 1 year prior to PBC
diagnosis in 29 % of PBC patients, in comparison with 22 % of healthy controls and 17 % of chronic liver disease controls [134]. UTI had been diagnosed in 19 % of PBC patients within a 5-year period prior to PBC diagnosis, compared with 14 % of matched controls and 11 % chronic liver disease controls [134]. That study has demonstrated that in a large cohort of PBC patients, UTI does precede PBC diagnosis and therefore adds further evidence towards a potential role for molecular mimicry and cross reactivity. It also highlights that recurrent UTI may be a predicting factor of PBC development and may prompt aggressive antibiotic therapy for those who have further risk factors (such as family history, AMA positivity, or genetic traits).

Conclusions

To predict whether one will develop an autoimmune disease is as complex matter as the aetiology of the diseases themselves. The most important factors which must be taken into account are risk factors which have been associated with the disease and their additive effect within the individual. As with PBC, it is unlikely that genetic associations can wholly predict the disease development, but a variety of other intrinsic and extrinsic factors must also be taken into account. AMA and/or ANA positivity, the disease-specific autoantibody markers, appear to have great predictive value in both disease development and prognosis, with a history of UTI adding to the likelihood of PBC development.

New high-throughput methods are now permitting rapid screening of hundreds of autoantibodies at an affordable cost. Screening of such autoantibodies with significant positive predictive value for specific autoimmune diseases, including those seen in patients with primary biliary cirrhosis, may become a routine part of medical management in the long run. The individuals screened for such autoantibodies will only be those who have HLA and non-HLA genes conferring susceptibility to specific autoimmune diseases, as detected by genetic screening. Close monitoring for evidence of exposure to specific environmental and infectious agents that increase the risk for the development of autoimmunity may assist in the clinical management of these cases. The benefit and cost savings of such practice will be tremendous once preventative methods and cost-effective, targeted therapies become available.

Conflict of interest None.

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