Familial primary biliary cirrhosis : Like mother, like daughter ?

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Abstract

The reasons underlying why autoimmune diseases overwhelmingly affect women more than men are not clear. Nor are the reasons why autoimmune disease is more prevalent in families. This review uses primary biliary cirrhosis (PBC) as a model autoimmune disease to discuss the familial risk, focusing mainly on mother-daughter pairs. PBC is a chronic cholestatic liver disease characterised by an immune-mediated inflammatory destruction of the small intrahepatic bile ducts, with fibrosis progressing to cirrhosis and subsequent liver failure. Epidemiological studies have demonstrated that first degree relatives of PBC patients are at higher risk of developing PBC, as well as other autoimmune diseases. This is especially true for the mothers, daughters and sisters of PBC patients. Multiple case reports have highlighted the complexity of mother-daughter pairs in PBC, and the need for follow-up of these individuals when one member of the pair is diagnosed with PBC. It may be the case that diagnosis in one individual may lead to early diagnosis in the other, even if they are asymptomatic. Early management of PBC may improve the prognosis in these patients. This review will examine the literature surrounding PBC in mothers and daughters. (Acta gastroenterol. belg., **2012**, 75, **203-209**).

Key words : autoantibody, autoimmunity, autoimmune disease, familial risk, genetics, susceptibility.

Abbreviations : ALP, alkaline phosphatase ; **AMA**, antimitochondrial antibodies ; **ANA**, antinuclear antibodies ; **BEC**, biliary epithelial cells ; **γGT**, gamma-glutamyltransferase ; **PBC**, primary biliary cirrhosis ; **PDC**, pyruvate dehydrogenase complex.

Introduction

Autoimmune diseases are a heterogeneous group of chronic, progressive diseases which affect virtually every organ (1). They share a common propensity of the immune system to turning against its own cells, for reasons poorly understood (1).

Although individual autoimmune diseases are relatively rare, current projections are that approximately 5-9.4% of the North American population is affected by at least one autoimmune disease (2,3). Autoimmune diseases as a whole are the third leading cause of morbidity and mortality in the industrialized world, after heart disease and cancer (1,4,5). Some of the best known autoimmune diseases include multiple sclerosis, type 1 diabetes, Grave's disease and Hashimoto's thyroiditis, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, scleroderma, Crohn's disease and autoimmune liver diseases such as autoimmune hepatitis and primary biliary cirrhosis (PBC) (1,4,6).

Clustering of a particular autoimmune disease within families is a common feature of most autoimmune diseases (7). Familial clustering of multiple autoimmune diseases has been also noted, raising the possibility of a generalised genetic susceptibility to autoimmunity (8-11). For example, family members of patients with multiple sclerosis are usually affected with Hashimoto's thyroiditis and rheumatoid arthritis (12). Also, significant associations with the familial risk of rheumatoid arthritis in offspring according to parental proband have been observed for ankylosing spondylitis, localized scleroderma, Sjögren's syndrome and systemic lupus erythematosus (8). Clusters of multiple autoimmune diseases have been noted in type 1 diabetes (10), inflammatory bowel diseases (9) and several other autoimmune diseases. The clustering of autoimmune diseases within the same individual suggests that there is extensive genetic sharing between autoimmune diseases. Family-based association studies are more frequently being used to investigate the genetic linkage. They are also useful in estimating the effect of epigenetic and environmental factors in the development of autoimmunity. Immunological studies in families of patients with autoimmune disease have also provided interesting data, including the isolated detection of autoantibodies in asymptomatic siblings or apparently healthy relatives. It has become apparent that the presence of autoantibodies in relatives, especially of those highly-specific for the disease affecting the patient, may predict the eventual development of clinically overt autoimmune disease. The preclinical period may last for several years and even decades prior to developing tissue destruction and symptomatology.

This review uses primary biliary cirrhosis (PBC) as a model autoimmune disease to discuss the familial risk, focusing mainly on the risk in relation to mother-daughter pairs.

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Submission date : 19/08/2011
Acceptance date : 11/12/2011

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterised by an immune-mediated inflammatory destruction of the small intrahepatic bile ducts, with fibrosis progressing to cirrhosis and subsequent liver failure (13-15). The disease affects mainly middle-aged women, with more than 90% of patients being female (13-15). The disease affects up to 1 in 800 women over 40 years of age, and studies from the United Kingdom suggest that PBC is the most frequent autoimmune liver disease, followed by autoimmune hepatitis and primary sclerosing cholangitis (16). The incidence and prevalence of PBC appears to be rising in the UK, USA and Australia (16-18). Differing clinical courses have been noted between Caucasian, African American, and Hispanic patients in the USA, with non-Caucasian patients more frequently presenting with cirrhosis (19). Migration studies indicate that an individual's risk for PBC changes with geographical re-allocation, and becomes akin to that of the population into which they move. This has led to the appreciation that environmental factors play an important role in the development of the disease (17,20,21).

At diagnosis, patients with PBC can be either asymptomatic with normal biochemical tests or asymptomatic with abnormal biochemical blood tests, symptomatic or finally can have advanced liver disease (13-15). Patients usually present in early stages, and the diagnosis of PBC most often is made when the patient is still asymptomatic with an abnormal cholestatic liver biochemistry and an immunological profile compatible with the disease which is discovered at a routine check (13-15). Frequent presenting symptoms include fatigue and pruritus, and osteoporosis may be observed initially, in the absence of other signs of liver disease (13-15). The progression of PBC is usually at a slow pace, but symptoms of portal hypertension and hepatic decompensation (jaundice, ascites or variceal bleeding) can develop several years after the initial diagnosis (13-15).

The diagnosis of PBC is based on three widely accepted criteria : biochemical signs of cholestasis, seropositivity for disease-specific autoantibodies and characteristic histological features (13-15). Histological features which characterise PBC include destruction of biliary epithelial cells (BEC) and loss of small bile ducts with portal inflammatory cell infiltration, and occasionally granuloma formation (13-15). Cholestatic markers include increased levels alkaline phosphatase (ALP) and gamma-glutamyltransferase (γGT). Levels of IgM may be raised, but the most prominent immunological feature of the disease is the presence of high-titre antibodies against mitochondrial (AMA) and nuclear (ANA) antigens (13-15,22-28). While AMA do not appear to have clinical significance, disease-specific ANA can identify a subgroup of PBC cases with more advanced disease (22,23,29-40), and when present at diagnosis, they seem to be able to identify individuals who will develop advanced disease faster than those seronegative for these autoantibodies (41). It should be noted that a large number of patients present with an increase in IgM. They can also be seronegative for AMA or disease-specific ANA with conventional techniques such as that of indirect immunofluorescence (IFL) (27,42-44). A conversion to autoantibody seronegativity may be reflective of the sensitivity of the tests used for their routine autoantibody detection (27,42-44).

Disease-specific AMA are directed against components of the 2-oxo-acid dehydrogenase complexes (formerly known as M2 antigen), especially the E2 subunits of the pyruvate dehydrogenase complex (PDC), branched-chain 2-oxoacid dehydrogenase complex (BCOADC) and 2-oxoglutarate dehydrogenase complex (OGDC) (13,22,23,27,40). More than 90% of AMA positive cases with PBC have anti-PDC-E2 AMA (13,22). Additionally, the E1α and E3β subunits of PDC are subdominant targets (13,22,23,27,40). AMA isotypes may be IgG, IgA and IgM, but high titre AMA-M2 of the IgG class are found in up to 95% of patients but in less than 2% of pathological and healthy controls (13,22). Various studies have reported that the presence of AMA is much higher than the prevalence of PBC in the general population, indicating that AMA may precede the symptomatic onset of the disease (45), and indeed, studies have demonstrated that AMA-positive, asymptomatic patients often have histological features diagnostic of, or compatible with PBC (45-48). Therefore, it is commonly agreed that seropositivity for AMA is highly predictive of the development of PBC. This has raised the question as to who needs to be screened for AMA, and at what point should the screening take place (40,49).

As mentioned, disease-specific ANA are also found in PBC patients, and may be of prognostic significance. As such, there is an ongoing debate as to whether diagnostic testing needs to incorporate assays for PBC-specific ANA (40). Two PBC-specific ANA IFL patterns may be observed : the "multiple nuclear dot" pattern mainly targets the nuclear body sp100 and promyelocytic leukaemia (PML) proteins, and those giving the "nuclear membrane" (rim-like membranous) recognising gp210, nup62 and other nuclear membrane proteins (23-25,40). Approximately 30% of PBC patients have both ANA types, which show a significant disease specificity (23-25). These disease-specific patterns can be present in AMA positive and AMA negative asymptomatic individuals and also in family members of PBC patients. Other autoantibodies include those against centromere, which are mainly present in PBC cases with concomitant CREST syndrome, and their presence has been associated with more advanced disease (34,50).

As for other autoimmune diseases, genetic, epigenetic, environmental and infectious factors have been considered important for the development of the disease or its progression from early stages to more advanced, life-threatening biliary epithelial cell destruction (43,51-72). This would likely occur in the background of T cell

dysregulation (73-78). Molecular mimicry and immunological cross-reactivity involving homologous microbial and self antigens has been considered a mechanism responsible for the induction of disease-specific autoreactivity in autoimmune gastrointestinal and liver diseases, including PBC (40,58,59,63,79-94). Familial and twin studies have demonstrated that genetic and environmental factors are likely involved (51,95-97). Recent genome wide association studies (GWAS) have identified previously unknown genetic associations for PBC (43, 67,68,98-102). The mechanisms responsible for the induction of PBC-specific AMA and ANA are also not well defined (22,52,53,80,90,103,104). *In vitro* studies implicate antigen-specific B-, CD4, CD8 T-lymphocyte responses in the induction and/or maintenance of autoaggressive pathology (48,52,53,61,88,89,105). Animal models resembling the human PBC-specific immunopathology suggest that the innate and adaptive immune systems contribute to the development of the disease (53,64,66).

As mentioned above AMA positivity is highly predictive of future PBC development, and the question has been raised as to whether screening programmes for AMA (and possibly PBC-specific ANA) should be adopted, especially for female relatives of PBC patients, although no general consensus has yet been reached (40, 49). In support of this is the increased risk of developing PBC if a relative is affected, which is especially true among female relatives. It has been noted that mother-daughter pairs are particularly at risk for developing PBC, if one of the pair is affected. This review will examine the scenario of PBC in mothers and daughters, with a view of highlighting those factors of clinical relevance when treating these pairs.

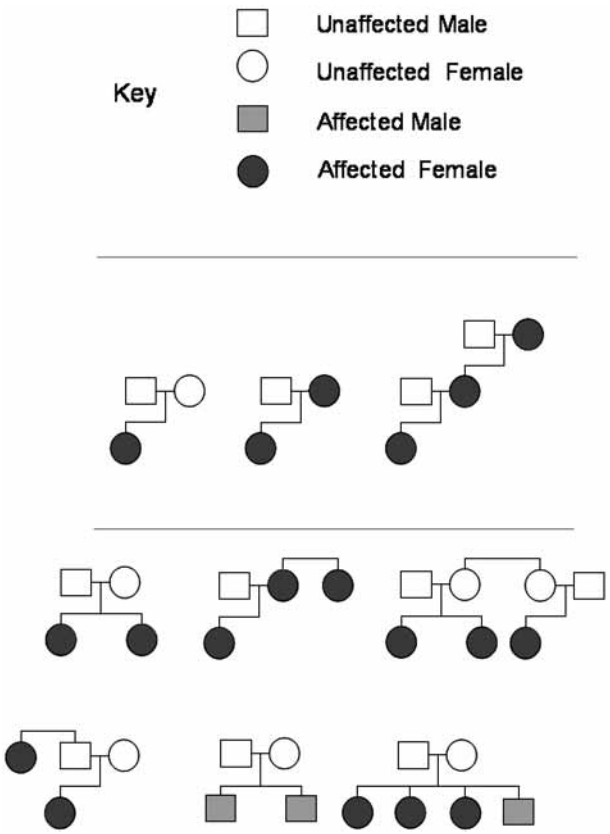

Fig. 1. — This diagram shows representative patterns of familial cases of primary biliary cirrhosis (PBC). Except for isolated cases of women with PBC, mother-daughter pairs are frequently found. Pairs of sisters or cousins have also been reported. Very rarely, affected individuals include sister-brother, or brother-brother pairs.

Primary biliary cirrhosis in mothers and daughters

The most common familial clusters of PBC cases are reported in mother-daughter pairs (106,107), followed by sisters (95,108-110), or mother-sister-daughter (111). Other patterns of familial disease have been noted and some examples are illustrated in Figure 1. An early case report by Fagan *et al*., describes a mother-daughter pair, who presented with PBC within five years of each other (111). Both mother and daughter shared a common environment, having been separated for only one year (111). Another early report of a mother and daughter pair also indicated that both women had HLA-A1 and B8, although the significance of this is not known (112). An interesting case report by Douglas and Finlayson (113) describes PBC in a mother daughter pair, as well as in a close family friend. The daughter was the first of the three to present with PBC, with the mother and close family friend providing care throughout her terminal illness (113). Within 21 months of the daughter's death, both the mother and family friend also presented with PBC (113). The short period of time between the diagnoses in the three women raised the suspicion that all three women were exposed to a common environmental factor which triggered the development of PBC. All three women were confirmed to be AMA positive (113). First degree relatives of the mother-daughter pair were tested for the presence of autoantibodies. Autoantibody positivity, including AMA, was found in several relatives, however none of these individuals were reported to have PBC (113). It is unknown as to whether any of the relatives with AMA positivity had symptoms of PBC, or were asymptomatic but with abnormal liver biochemistry. As no follow-up study was performed, it is also unknown as to whether any relatives went on to develop PBC.

When a mother-daughter pair present with PBC, further questioning regarding a family history of liver disease may demonstrate liver pathology in previous generations. However, it is difficult to determine whether these cases were indeed PBC, as the diagnostic work-up of these earlier cases was limited. Dahlan and colleagues (114) report the case of an 11 year old female who presented with abdominal pain and raised AST (48 U/L), but all other liver biochemistry tests (including ALP) were normal (γGT was not tested) (114). Her abdominal pain

continued over several years, and liver function tests demonstrated a raised γGT (107 U/L) when she was 15 years of age, at which point she was also found to be positive for AMA (114). A liver biopsy at age 16 showed stage II PBC (damaged segmental bile ducts with portal and periportal lymphoid infiltrates), and liver function tests at age 18 demonstrated a cholestatic profile with raised ALP (660 U/L) and slight increase of total bilirubin (24 μmol/L) (114). She was eventually transplanted at the age of 21 for worsening of symptoms and increasingly deranged liver biochemistry (114). Histopathological examination of the explanted liver demonstrated stage IV PBC (114). Of particular interest in that case was the apparent family history of liver disease, with the Girl's mother presenting at the age of 30 with overlapping features of PBC and autoimmune hepatitis, of which she received a liver transplantation at the age of 34 (114). Further family history revealed that the grandmother and great-grandmother on the maternal side died of liver cirrhosis of unknown origin (114). That case demonstrated that the mother-daughter relationship in PBC, may stretch over several generations, and indicate which families are in need of comprehensive follow-up. As well, it also appears that subsequent generations may be affected younger, with a more sever disease course.

In a large multicentre epidemiological study involving 1032 PBC patients, the occurrence of PBC in first degree relatives of PBC patients was reported to be 5-9%, with 1.7% of the mothers and 4.3% of sisters of PBC patients also being affected (108). A higher incidence of autoimmune disease in the mothers and sisters of PBC patients was also found (108). Similar PBC rates were found in a French epidemiological study, with 1.8% mothers and 5.5% sisters of PBC patients, also having PBC (115). That study also reported that 0.5% daughters of PBC patients also had PBC (115). These studies complement, along with earlier case reports, highlight the need for proper evaluation of female relatives (specifically mothers, daughters and sisters) of PBC patients, as they are at highest risk of developing not only PBC, but also other autoimmune disease. The proportion of AMA positive but asymptomatic mothers, daughters, and sisters of PBC patients was not indicated in the epidemiological studies. It is likely that a proportion of the non-affected individuals were indeed positive for AMA, which also gives the possibility that they would eventually develop PBC. Thus, the actual number of affected mothers-daughter may be higher than reported.

It is common practice to test liver function and AMA positivity in first degree relatives of PBC patients, and this is especially true for female relatives. This heightened level of surveillance is may lead to the identification of AMA positive, but asymptomatic individuals. Some of these asymptomatic individuals may also have abnormal liver biochemistry. As well, it is not uncommon for some AMA negative individuals to turn positive for AMA over time. Studies following the progress of AMA positive but asymptomatic patients are limited, but it is likely that a proportion of the AMA-positive asymptomatic individuals will develop abnormal liver biochemistry, and may progress to PBC (45). This change in clinical course in asymptomatic patients supports the notion that female relatives of PBC patients undergo immunological and liver function profiling, with a lengthy course of follow-up (46,49,97).

Why PBC may be more frequent in mothers and daughters : the X factor

The question remains as to why PBC is predominantly a disease of middle-aged females, and why are the daughters, mothers, and sisters of female PBC patients at a much higher risk than other relatives. Several mechanisms have been proposed to account for the mother-daughter over-representation of PBC cases, one of which deserves special attention. Recent genetic studies may shed some light on these observations. Invernizzi and co-workers have reported a higher frequency of monosomy of the X chromosome in peripheral leukocytes of female PBC patients (60,116). This is also a characteristic in other autoimmune diseases with a high female preponderance such as systemic sclerosis and autoimmune thyroid disease, which are also known to co-occur in PBC patients. This is of interest as genes involved in immunological tolerance are located on the X chromosome. These include the CD40 ligand which has been associated with increased serum levels of IgM levels, which are typically raised in PBC patients (15). It remains a possibility that X chromosome related dysregulation may contribute to the female preponderance of PBC, and that the physiological inactivation of the X chromosome could account for the prevalence of PBC occurring peri-menopause (66,116,117). Several other scenarios have been proposed to explain the role of monosomy X in the pathogenesis of PBC (53,60,116-118), but the role of monosomy X in the pathogenesis of PBC requires further exploration.

Conclusions and Prospects for Future Research

The diagnosis of PBC in a female patient also raises concerns for her first degree relatives. This is especially the case for the mothers, daughters and sisters of these patients. Due to the higher rate of PBC, and other autoimmune diseases in general among relatives of PBC patients, the question has been raised as to who should be tested for AMA positivity and abnormal liver biochemistry. This is further complicated by the fact that AMA negative individuals may become positive over time. This also raises the question as to how long the follow-up period should be. Based on case reports and epidemiological studies, it is suggested that mothers, daughters and sisters of women with PBC be tested for AMA positivity. Those studies also demonstrate that the presentation and/or diagnosis of PBC in a female relative of a PBC patient, is likely to occur within a short time period

of the original diagnosis. It is likely that this relative has early or asymptomatic PBC. As well, affected daughters of PBC patients appear to be younger, and often have a more severe clinical course. Although the reasons to this remain unclear, it is likely that environmental and genetic factors play a role. Large multi-center genetic, immunological, and clinical studies following asymptomatic relatives with or without AMA or other PBC-specific ANA are urgently warranted. Before such studies are in place, it would be very difficult to draw safe conclusions about the autoimmune component of mothers-daughters "friendship".

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