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Low Incidence of Primary Biliary Cirrhosis (PBC) in First Degree Relatives of PBC Probands after 8 Years of Follow Up

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Abstract

Background & Aims—Primary biliary cirrhosis (PBC) is characterized by chronic cholestasis and disease-specific anti-mitochondrial antibodies (AMA). A high prevalence of AMAs in first-degree relatives (FDRs) of PBC probands has been reported, though the natural history of such patients has not been described. We aimed to assess the risk of developing PBC in AMA+ FDRs of patients with PBC.

Methods—FDRs recruited to the Mayo Clinic PBC Genetic Epidemiology Registry and Biorepository were followed for disease onset after recruitment. Development of PBC was ascertained via self-report during a telephone interview and/or via proband report on a questionnaire. Chi-squared and t-tests were used to assess for differences between categorical and continuous variables, respectively. A mixed effects model was used to assess change in biochemical profiles over time.

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Results—40 AMA+ and 423 AMA– subjects were included and followed for a median of 8.9 and 8.4 years, respectively. Overall, 3% (n=15) of FDRs were diagnosed with PBC and AMA+ FDRs had a higher risk than AMA– FDRs (24% vs. 0.7%, $p<0.01$). However, among undiagnosed FDRs, only 4% of AMA+ (n=1) and 0.4% of AMA– (n=1) FDRs were diagnosed with PBC ($p=0.17$) during the follow-up period. None of the AMA+ FDRs with normal alkaline phosphatase (AP) at baseline developed PBC in follow-up.

Conclusions—Our results suggest a low risk of developing PBC over time in FDRs of PBC patients, particularly those without biochemical evidence of cholestasis at baseline. These data are useful in counseling and reassuring relatives of their overall favorable prognosis.

Keywords

familial primary biliary cirrhosis; anti-mitochondrial antibody; first-degree relative

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by chronic cholestasis and destruction of the intralobular bile ducts(1). Highly-directed, disease-specific anti-mitochondrial antibodies (AMA) are typical of PBC, being detected in more than 90% of PBC patients compared to just 0.5–1 % of controls(2, 3). In 2007, our group reported detectable AMA's in 13.1% of first degree relatives (FDRs) of PBC probands, most of whom had no biochemical evidence of cholestasis(4). The natural history of subjects with isolated elevations in AMA titer remains poorly defined, as current knowledge in this arena is largely limited to a single report from 1996 by Metcalf *et al.*, which presents outcomes in a cohort of 29 patients undergoing diagnostic investigation for suspicion of other autoimmune disease and testing positive for AMA. After 17 years of follow-up, 83% of these subjects had histologic features compatible with PBC and 55% had elevated alkaline phosphatase (AP) levels with a median time to abnormal liver tests of 5.6 years(5, 6). While no patients in this cohort developed histologic evidence of cirrhosis or died from liver related causes, this report does suggest a high frequency of PBC development among AMA positive (AMA+) patients, albeit highly selected ones. Considering this evidence, along with the known elevated risk of PBC in FDRs of PBC patients(7, 8), we hypothesized that a significant proportion of the AMA+ FDRs in our previous study would go on to develop clinically overt PBC. Thus, we performed a longitudinal follow-up of this seemingly high-risk cohort.

Patients and Methods

The cohort consisted of FDRs of probands with PBC recruited into the Mayo Clinic PBC Genetic Epidemiology (MCPGE) Registry and Biorepository since 2003. Details of this registry have been previously reported(4). Briefly, probands and their FDRs provide informed consent, complete a validated questionnaire, which collects information on personal and family medical history, and submit a blood sample from which liver enzymes and AMA are tested and genomic DNA is isolated. In 2014, a second follow-up questionnaire was administered to probands, which collected similar detailed information including personal and family medical history. FDRs did not receive a second questionnaire.

All FDRs recruited to the MCPGE who provided a blood sample for testing of liver enzymes and AMA were followed longitudinally and assessed for development of PBC after recruitment. Development of PBC was ascertained by two methods. The first was a focused 12-question telephone interview with the FDR during which subjects were asked about changes to their medical history since recruitment including if they had been diagnosed with PBC, had abnormal liver tests, or had a liver biopsy (supplementary material). The second method utilized proband responses where interval development of PBC in an FDR was defined as a positive report of PBC in the 2014 questionnaire but not in the original questionnaire (2003–2009). Absence of PBC at study enrollment was confirmed utilizing the study questionnaire provided by the FDR. FDRs were contacted with letters requesting consent to obtain external records from primary providers and available medical records were reviewed for objective assessment of liver tests. Descriptive statistics were used to define the characteristics of the cohort. Qualitative variables were summarized as proportions and continuous variables as means with standard deviations and medians with interquartile ranges. Chi-squared tests were used to assess differences between categorical variables and t-tests for differences in continuous variables between AMA+ and AMA negative (AMA–) subjects. A mixed effects model was used to assess change in biochemical profiles over time taking into account multiple measurements per person. The study was approved by the Mayo Clinic institutional review board and conforms to ethical guidelines of the 1975 Declaration of Helsinki.

Results

Between 2003 and 2009, 476 FDRs were recruited into the MCPGE and were eligible for the study. At recruitment, 11 % (n=51) of FDRs were AMA+ and 89% (n=425) were AMA–; among these, 22% (n=11) of the AMA+ FDRs and 0.5% (n=2) of the AMA– FDRs had already been diagnosed with PBC prior to study enrollment ($p<0.01$). Thus, the study cohort for interval PBC development consisted of 40 undiagnosed AMA+ FDRs and 423 undiagnosed AMA– FDRs who were followed for a median of 8.9 (7.1–10.0) and 8.4 (6.3–9.4) years, respectively (Figure 1). Of all FDRs, 22% (n=104) were parents (67% mothers), 18% (n=83) were children (65% daughters), and 60% (n=278) were siblings (65% sisters) of the PBC proband. The majority of AMA+ FDRs were female (90%) and this proportion was statistically greater than in the AMA– group (63% female, $p<0.01$). Additional characteristics of the cohort can be found in Table 1.

After excluding FDRs who died or were lost during the study interval, 31 AMA+ and 368 AMA– FDRs were available for follow-up and data from 71 % (n=22) of AMA+ FDRs and 65% (n=240) of AMA– FDRs was ultimately collected (Figure 1). Median AP levels at baseline were within the normal range in both groups, though levels were statistically higher in AMA+ FDRs ($p<0.01$) (Table 1). During the follow-up period, only 1 AMA+ FDR (4%) and 1 AMA– FDR (0.4%) were diagnosed with PBC ($p=0.17$). At the time of recruitment, a minority of AMA+ (n=5) and AMA– (n=14) FDRs had AP levels greater than the upper limit of normal (ULN). Among the two FDRs who developed PBC during the follow-up period, the AMA– FDR had a normal AP at recruitment while the AMA+ FDR entered the cohort with an elevated AP. Interestingly, none of the AMA+ FDRs with a normal AP at recruitment were diagnosed with PBC after a median 8.9 years of follow-up.

Laboratory tests were available in follow-up in 10% (n=44) of all FDRs and 17% of those who were contacted. This included data from 23% and 16% of contacted AMA+ and AMA- FDRs, respectively. After adjusting for AMA status there was no evidence to suggest AP levels changed significantly over time with a decrease in AP by 0.1 IU/mL/month after the baseline lab test (p=0.06).

A higher proportion of AMA+ compared to AMA- FDRs were deceased at the time of follow-up though this difference was not statistically significant (20% vs. 12%, p=0.13, Table 1). We were able to ascertain cause of death in 47% (n=27) subjects who died, including 63% of AMA+ FDRs and 45% of AMA- FDRs. None of the AMA+ relatives for whom the cause of death was evaluated died of liver related causes, whereas two of the 22 AMA- relatives who had cause of death data available had the primary cause of death on death certificates listed as liver failure. One of these relatives had a secondary cause of death listed as renal failure and the other had metastatic breast cancer.

Discussion

This is the first study to assess the risk of developing PBC over time in undiagnosed AMA+ FDRs of patients with PBC. We confirm that FDRs have an increased risk of developing PBC compared to the general population. In this cohort, 3% (n=15) of FDRs were diagnosed with PBC prior to or during the study interval, and AMA+ FDRs had a particularly high risk at 24% (n=12) compared to AMA- FDRs at 0.7% (n=3). That said, the risk of developing PBC over time was relatively low at 4% in AMA+ FDRs and 0.4% in AMA- FDRs - while these proportions are numerically different, this was not statistically significant. Not surprisingly, PBC developed frequently (or perhaps was already prevalent though undiagnosed) in AMA+ FDRs with an elevated AP at baseline; yet in contrast, interval development of PBC was unlikely in FDRs who had a normal AP at recruitment, even if AMA seropositive. Furthermore, AP levels remained stable over time. This suggests that while FDRs are at increased risk of developing PBC, AMA+ FDRs with normal AP levels and AMA- FDRs in general, have a low likelihood of being diagnosed with PBC over the next 8 years, and thus a low likelihood of requiring intervention with treatment.

For the purposes of this study, the presence of PBC at baseline in FDRs was defined by self-report of being diagnosed with PBC in their questionnaire at the time of recruitment. While the only AMA+ FDR who developed PBC during follow-up did have an elevated AP at baseline, this subject did not self-report a diagnosis of PBC, and thus, was not included in the group of FDRs classified as having PBC at diagnosis. Furthermore, only a single laboratory value at baseline was available for this subject (that which was obtained at recruitment), and thus, chronic cholestasis could not be confirmed. Major international societies suggest that the diagnosis of PBC can be made in the setting of histologic evidence of non-suppurative cholangitis, presence of disease specific AMAs, and/or biochemical evidence of chronic cholestasis, defined by the European Association of the Study of the Liver as an elevated AP for 6 months. That said, if this subject was considered to have PBC at diagnosis, and thus excluded from our longitudinal follow-up and analysis this would further support our finding that the risk of clinically overt PBC overtime in FDRs is

low. Including this subject suggests that among FDRs, the highest risk of PBC development over time seems to be in AMA+ FDRs with elevated AP, irrespective of chronicity.

The strength of this study is the large and unique cohort with a prolonged period of follow-up. In the end data from a total of 262 out of 399 eligible subjects including 71% of AMA+ FDRs and 65% of AMA- FDRs was included in the analysis. Limitations include incomplete follow-up and reliance on proband and/or self-reporting as a measure of interval diagnosis of PBC. Certainly, in its early stages PBC can be asymptomatic; and thus, we may underestimate the ultimate incidence if FDRs had simply not yet come to clinical attention. However, in the subset of FDRs for whom we were able to assess medical records, there was no evidence to suggest that that AP levels changed significantly over the period of follow-up. Thus, while we may underestimate the number of cases of *de novo* PBC in FDRs based on diagnostic criteria as opposed to self-report; it seems unlikely that these subjects would develop significant cholestasis, advanced liver disease, liver-related complications, or liver-related death over the period of follow-up in our study. In the 133 FDRs with whom a telephone interview was performed, 19 reported being diagnosed with any liver condition since the time of recruitment with 12 of these patients reporting interval gall stones, 4 reporting fatty liver disease, and one subject each reporting hereditary hemochromatosis, liver cysts, and methotrexate induced liver injury, respectively, suggesting overall benign disease. Furthermore, in the aforementioned study by Metcalf *et al.*, though 83% of their cohort of 29 patients developed histologic features compatible with PBC, a smaller proportion (55%) developed biochemical cholestasis which would warrant treatment and no subjects developed histologic evidence of cirrhosis or died from liver-related causes. Thus, though overall FDRs are at higher risk for developing PBC compared to the general population and thus warrant clinical follow-up, they can likely be reassured that their risk of symptomatic disease over 5 to 8 years is low. Finally, one of the methods of assessing interval PBC in FDRs required the proband to be aware of the diagnosis and to report it in their questionnaire. While this is an indirect assessment, we did confirm near perfect concordance between proband and FDR reported PBC from questionnaires at recruitment. Furthermore, this was a valuable resource as it provided data for an additional 122 subjects.

Our results differ from previous reports that suggest up to 80% of AMA+ individuals meet diagnostic criteria for PBC after a median of about 5 years(5, 6). However, there are significant differences in the studied populations to explain the disparity. For instance, the previous study followed patients who tested AMA+ during work-up for suspicion of autoimmunity, implying that this group was not truly asymptomatic. In contrast, our study focuses on FDRs of PBC patients, who while at increased risk of disease, are not necessarily presenting with symptoms at the time of AMA evaluation. The low incidence of PBC in FDRs within our cohort suggests that AMA+ FDRs may have other genetic (i.e. modifier loci) and non-genetic factors that protect them from developing PBC when compared to AMA+ individuals with other autoimmune diseases.

In summary, FDRs of patients with PBC are at risk of developing the disease, and thus, should likely be screened for detectable AMA and subsequently followed with liver biochemical tests at some regular interval. However, our findings suggest that in AMA- FDRs, and AMA+ FDRs with normal AP levels at initial testing, the risk of developing

clinically recognized PBC in the subsequent 8 years is low. While these data do not support a recommendation for a standardized approach to follow-up of FDRs of patients with PBC, this information may be useful for counseling and reassuring relatives of their overall favorable prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PBC	Primary Biliary Cirrhosis
AMA	anti-mitochondrial antibody
FDR	first degree relative
AP	alkaline phosphatase
MCPGE	Mayo Clinic PBC Genetic Epidemiology Registry and Biorepository
DNA	deoxyribonucleic acid
ALT	alanine aminotransferase

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Key Points

- First degree relatives (FDRs) of patients with PBC are at increased risk of developing PBC compared to the general population
- Disease specific anti-mitochondrial antibodies are found in up to 13% of FDRs
- After initial testing, the risk of developing clinically overt PBC in FDRs after 8 years of follow-up is low, particularly in those without biochemical evidence of cholestasis at initial assessment
- FDRs of patients with PBC can be reassured of their favorable prognosis over 5–10 years

Flow diagram of included subjects

Figure 1.

Flow diagram outlining AMA+ and AMA- FDRs included and followed up over time. The left side of the diagram outlines eligible and included AMA+ FDRs with the associated relevant data available at baseline and in follow-up and the right side provides identical information for AMA- relatives. A low proportion of contacted AMA+ FDRs (4%, 1/22) reported an interval diagnosis of PBC and this was in a subject with an elevated AP at baseline. Only 0.4% (1/240) contacted AMA- FDRs reported an interval diagnosis of PBC in follow-up and this subject had a normal AP at baseline assessment. AMA, anti-

mitochondrial antibody; AP, alkaline phosphatase; FDR, first-degree relative; PBC, primary biliary cirrhosis; QN, questionnaire; ULN, upper limit normal

Table 1

Characteristics of the cohort of 1 476 FDRs of PBC probands

	AMA +	AMA –	p
total FDRs (n)	51	425	
known PBC (%)	11 (21.5%)	2 (0.5%)	<0.01
unaffected FDRs	40	423	
age (SD)	63±16	60±15	0.26
females (%)	36 (90)	268 (63)	<0.01
mothers (%)	8 (22)	62 (23)	0.27
sisters (%)	23 (64)	157 (59)	<0.01
daughters (%)	5 (14%)	49(18%)	0.18
baseline AP×ULN (IQR)	0.7 (0.5–0.9)	0.6 (0.5–0.7)	<0.01
baseline ALT×ULN (IQR)	0.9 (0.6–1.3)	0.7 (0.5–0.9)	0.02
median f/u (yrs)	8.9 (7.1–1)	8.4 (6.3–9.4)	0.10
AP(% change/year (IU/L))*	–2.1	–0.5	0.50
ALT(% change/year (IU/L))*	–8.2	–2.7	0.37
deceased (%)	8 (20%)	49 (12%)	0.13
interval PBC diagnosis (%)	1 (4.0%)	1 (0.4%)	0.17

ALT, alanine aminotransferase; AP, alkaline phosphatase; FDR, first-degree relative; IQR, interquartile range; PBC, primary biliary cirrhosis; SD, standard deviation; ULN, upper limit normal