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Differences Between Caucasian, African American, and Hispanic Patients with Primary Biliary Cirrhosis in the United States

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Abstract

Primary biliary cirrhosis (PBC) is an uncommon chronic cholestatic liver disease that primarily afflicts young and middle-aged Caucasian women; there are limited data on the clinical presentation and disease severity among non-Caucasian patients with this disease. The goal of this study was to examine differences in the severity of liver disease between Caucasian and non-Caucasian patients with PBC screened for enrollment in a large national multicenter clinical trial. Demographic features, symptoms, physical findings, and laboratory tests obtained during screening were examined in 535 patients with PBC with respect to ethnicity, gender, and

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antimitochondrial antibody (AMA) status; 73 of 535 (13.6%) were non-Caucasian (21 were African American, and 42 were Hispanic). Non-Caucasians were more likely than Caucasians to be ineligible for participation in the clinical trial (46.5% versus 25.1%, $P = 0.0001$), primarily because of greater disease severity. African Americans and Hispanics were also more likely to have a lower activity level, more severe pruritus, and more advanced disease. However, the mean age, male-to-female ratio, and seroprevalence of AMA positivity were similar between the 2 groups.

Conclusion—Liver disease severity at clinical presentation is higher among non-Caucasians than Caucasians with PBC, and this cannot be explained by demographic or serologic features alone. Possible mechanisms underlying this health discrepancy are not clear, but increased awareness of PBC as a cause of chronic cholestatic liver disease is critical in evaluating non-Caucasian patients in the United States.

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease of unknown etiology that is thought to be autoimmune in pathogenesis. It is characterized by elevated alkaline phosphatase, high immunoglobulin M, positive antimitochondrial antibody (AMA), and characteristic liver biopsy findings. Because PBC is relatively uncommon, there have been few studies of large cohorts of patients,[1,2] with little emphasis on possible variability in disease presentation and severity between racial and ethnic groups. This study determined if liver disease severity due to PBC varied with race and ethnicity. We examined features of liver disease severity among patients with confirmed PBC who were evaluated for enrollment in a randomized controlled therapeutic trial of ursodiol with or without methotrexate (the PUMPS trial).[3] In preparation for this study, we screened a large geographically diverse group of patients in the United States from 12 different university referral centers. We evaluated these screened patients to study the demographics of PBC in university referral centers; to compare the demographics, symptoms, physical findings, and laboratory tests of all screened patients; to compare differences between ethnic groups, gender, and AMA status; and to compare those randomized to those who did not enter the study. We found significant differences between Caucasian and non-Caucasian (predominantly African American and Hispanic) patients.

Patients and Methods

Patients with PBC were screened for entry into a large US multicenter randomized controlled trial of ursodeoxycholic acid (15 mg/kg/day) with or without the addition of weekly methotrexate.[3] These patients were screened between April 1989 and January 1998 at 12 universities in 11 geographically diverse states in the United States, with each center screening between 13 and 108 patients. The inclusion criteria for the trial were as follows: cholestatic liver disease for at least 6 months, serum alkaline phosphatase at least 1.5 times the upper limit of normal, serum bilirubin less than 3.0 mg/dl, serum albumin of 3.0 g/dl or greater, detectable AMA, an age between 20 and 69 years at screening, and a willingness to practice adequate contraception throughout the study. The exclusion criteria included clinical, serologic, or histologic evidence of other forms of liver disease; epilepsy requiring the use of phenytoin; breast cancer; a history of melanoma or a diagnosis of another malignant disease within the past 5 years; positive HIV serology; a major illness that could

limit lifespan; a history of alcoholism within the previous 2 years; pregnancy; and a history of ascites, hepatic encephalopathy, or variceal bleeding. Of the 535 patients with screening data reported here, 265 patients were finally randomized into the randomized controlled study. The screening centers differed in the proportion of patients ultimately randomized to the clinical trial, in part because of the severity of PBC in the screened patients.

All potential patients underwent a screening visit and physical examination, and these data are presented in this report. The collected data included the age, race/ethnicity (self-report), sex, symptoms, medications, and reproductive status. The patients completed a questionnaire about their activity level and pruritus. The activity level was assessed on the following scale: normal health, regular activity not completely well, not able to carry out regular activity, and confined to bed most of the time or in the hospital most of the time. Pruritus was assessed as follows: none, present but not requiring treatment, relieved by medication, partially relieved but interferes with sleep, and not relieved. The physical examination included evidence of chronic liver disease, signs of cirrhosis, portal hypertension, ascites, peripheral edema, hepatomegaly, splenomegaly, asterixis, scleral icterus, xanthelasma, xanthomata, spider angiomata, telangiectasia, excoriations, hyperpigmentation, purpura, clubbing, and muscle wasting. Laboratory tests included serum liver tests (serum alkaline phosphatase and bilirubin at screening and before ursodeoxycholic acid was started), a complete blood count, the prothrombin time, serum creatinine and cholesterol, and AMA and titer by immunofluorescence. The presence of ascites, hepatic encephalopathy, or variceal bleeding was defined as severe liver disease.

Statistics

The descriptive statistical analysis included the computation of frequencies or means, standard deviations (SDs), minima, and maxima of measurements for the entire sample and within groups defined by sex, race/ethnicity, AMA status, severity of disease, and eligibility/randomization status. There were a number of cases with missing data for 1 or more measurements, and thus the sample size used in the computations varies considerably and is detailed in the results. Cases with missing data for any particular measurement were omitted from analyses involving that measurement. The performed statistics, a 2-sided *t* test with unequal variance and Fisher's exact test, are noted in the Results section, and actual numbers, not percentages, were used.

Data were available for 535 patients with PBC who were screened for entry into a large US multicenter trial of ursodeoxycholic acid with or without the addition of methotrexate. Ultimately, 385 patients were judged eligible for entry into the clinical trial, with 265 of these patients consenting to randomization and participation in the trial. The completeness of the data varied according to these eligibility groups. Demographic and medication use data were available for all patients. Data relating to medical history were available for approximately 90% of the 150 ineligible patients, approximately 95% of the 120 eligible but nonrandomized patients, and nearly 100% of the 265 randomized patients. The duration of disease was difficult to assess because many patients were asymptomatic and therefore was available only for a minority of the patients (the data are detailed in the Results section). Individual physical examination variables were available for 84%-91% of the ineligible

patients, 89%-95% of the eligible but nonrandomized patients, and 98%-100% of the randomized patients. Laboratory test results were available for 59%-86% of the ineligible patients, 73%-100% of the eligible but nonrandomized patients, and 80%-100% of the randomized patients.

Results

Demographics of the Patients

A total of 535 patients with PBC were considered for participation in the trial; they included 501 females and 34 males (6.3%), and their mean age was 52 ± 9.5 years (Table 1). The large majority was Caucasian (462, 86.3%), but the cohort included 42 (7.9%) Hispanics, 21 (3.9%) African Americans, and 10 patients of other racial and ethnic groups. For the purposes of this analysis, the patients were first classified into 2 racial groups, Caucasian (86.4%) and non-Caucasian (13.6%); the data for African Americans and Hispanics were then examined independently. Twenty percent of the patients were of child-bearing age.

Disease Severity of the Patients

The non-Caucasians appeared to have significantly more severe liver disease than the Caucasians, as assessed by history, physical examination, and laboratory features (Tables 2-4). Compared with the Caucasian patients, the African American and Hispanic patients were significantly more likely to be limited in their physical activity level ($P < 0.00001$ for each), to have severe or difficult-to-control pruritus (African Americans, $P = 0.0004$; Hispanics, $P = 0.0002$), or to have a history of ascites, hepatic encephalopathy, or variceal bleeding ($P < 0.009$ for non-Caucasians, Table 2). Any of these features of severe liver disease represented an exclusion criterion for the randomized treatment phase of the study. These differences in the severity of liver disease could also not be explained by age and body mass index, which were similar between Caucasians, African Americans, and Hispanics. The duration of disease was known for 55% of all screened patients (59% Caucasians, 24% African Americans, and 33% Hispanics) but did not differ between ethnic groups. For Caucasians, it was 3.1 ± 3.3 years (range: 0.1-17.3); for African Americans, it was 0.3 ± 0.2 years (range: 0.1-0.6); and for Hispanics, it was 2.9 ± 3.2 years (range: 0.1-11.5).

The liver disease severity was generally comparable between males and females and those who were seropositive or seronegative for AMA, although AMA-positive patients were more likely to report a history of hepatic encephalopathy (Table 2, $P < 0.03$). Non-Caucasians were also significantly more likely to have hepatomegaly, hyperpigmentation, cutaneous excoriations, discernible icterus, and muscle wasting (Table 3). Compared to Caucasians, Hispanics were more likely to have hepatomegaly (60%, $P < 0.001$), icterus (12.2%, $P = 0.003$), excoriations (25%, $P < 0.001$), hyperpigmentation (50%, $P < 0.001$), and muscle wasting (10.3%, $P = 0.02$). Compared to Caucasians, African Americans were more likely to have icterus (25%, $P = 0.0004$) and excoriations (21.1%, $P = 0.01$). Interestingly, male patients and patients who were AMA-negative were also more likely to be icteric at the time of evaluation, possibly because of delays in the diagnosis of their liver disease or because of a lower index of suspicion among these groups. In support of this

hypothesis, mean serum bilirubin levels were somewhat but not significantly higher among males and AMA-negative patients. Laboratory tests also demonstrated that liver disease was more severe among non-Caucasian patients than Caucasians. African American and Hispanic patients and non-Caucasian patients in general had significantly higher serum levels of bilirubin, alkaline phosphatase, and aspartate aminotransferase, more prolonged prothrombin times, and lower levels of albumin and hemoglobin (Table 4). Compared to Caucasians, African American patients were more likely to have received prior medications for their liver disease: colchicine (4.8% versus 1.7%), corticosteroids (14.3% versus 1.1%), and rifampin (14.3% versus 0.2%). Hispanic patients were more likely to have received prior colchicine (4.8% versus 1.7%). There was no difference in the frequency or amount of alcohol used among any of the groups: 68% of the patients did not drink alcohol, and 32% reported minimal alcohol intake.

Of the 535 patients studied, 33 (6.1%) were judged to have severe liver disease as defined by presence of ascites, encephalopathy, or variceal bleeding. Non-Caucasians as a whole were overrepresented in this group ($P = 0.001$). Specifically, African Americans ($P = 0.003$) and Hispanics ($P = 0.002$) were both significantly more likely to be in the group with severe liver disease than Caucasians. Those with severe liver disease had greater limitation in activity levels than those with mild disease ($P < 0.0001$) and had more frequent findings on physical examination associated with disease severity. However, the degree of pruritus did not correlate with clinical features of disease severity. Those who were ineligible for the study had a lower activity level ($P < 0.0001$) but did not have worse pruritus ($P = 0.08$). Hepatomegaly ($P = 0.02$), hyperpigmentation ($P = 0.02$), splenomegaly ($P < 0.001$), spider nevi ($P < 0.001$), telangiectasia ($P = 0.02$), peripheral edema ($P < 0.001$), icterus ($P < 0.001$), ascites ($P < 0.001$), and clubbing ($P = 0.007$) at the time of evaluation were all more frequently noted in those with severe liver disease, but excoriations were not more common, and this was consistent with the lack of a difference in the pruritic symptoms. The disease severity was confirmed by laboratory testing with lower serum albumin, cholesterol, hemoglobin, white cell count, and platelets and higher serum bilirubin and prothrombin time (all P values < 0.001 for a comparison of severe disease versus mild disease, except for the white cell count, for which $P < 0.02$).

Eligibility of the Patients for the Randomized Treatment Study

Of the total screened patients, 265 (49.5%) were randomized into the study. The nonrandomized subjects were split between those who were eligible for the study but did not enter it (n = 120) and those who were ineligible as they did not meet the study entry criteria (n = 150). Forty five of the 535 (8.4%) were seronegative for AMA before entry. Because AMA positivity was 1 of the entry criteria for the randomized phase of the study, these 45 were ineligible for randomization but were still included in the current analysis. A significantly greater proportion of Caucasians were randomized into the treatment arms of the study: 53.5% of Caucasians versus 23.2% of non-Caucasians ($P = 0.0005$), 14.3% of African Americans ($P = 0.003$), and 19% of Hispanics ($P = 0.0006$). This was in large part because fewer non-Caucasians met the entry criteria: 25.1% of Caucasians were ineligible versus 46.6% of non-Caucasians ($P = 0.001$), 47.6% of African Americans ($P = 0.02$), and 50% of Hispanics ($P = 0.001$). However, of the eligible patients, more Caucasians (71.7%)

than non-Caucasians (43.6%, $P = 0.001$), African Americans (27%, $P = 0.003$), or Hispanics (38%, $P = 0.002$) elected to enroll in the study. Of the 120 eligible but not randomized patients, 80 gave reasons: 21% did not want to take methotrexate, 19% did not want to undergo the procedures, and 19% refused because of the travel constraints. Similar percentages of males and females were eligible and enrolled in the study.

Discussion

This large cohort of patients is geographically and ethnically diverse, reporting from 12 different university referral centers in the United States. This is not a population-based study as all patients were at tertiary referral centers. However, few large studies of PBC have been reported because of the uncommon nature of this chronic cholestatic liver disease.[4-7] Gershwin et al.[4] studied risk factors and comorbidities for the development of PBC in a cohort of patients from the United States but did not address the severity of the disease.[4] Treatment with ursodeoxycholic acid is now the standard of care for PBC patients,[3] and most studies now investigate the long-term outcome of therapy.[8-10] Fatigue and activity level have been shown to be important in the severity of the disease.[11] In addition, there is little information about ethnic differences in PBC, although PBC has been reported in all ethnic groups.[12-15] In the United States, the majority of studies have been performed predominantly (>98% and 100%) with Caucasian patients.[4,6] Although few differences were noted between males and females in our cohort, there were significant differences between Caucasians and non-Caucasians. In particular, decreased activity level and worse pruritus were more frequently reported by African American and Hispanic patients. In addition, more African American and Hispanic patients had severe disease, as noted by history, physical findings, and laboratory tests. Even those who still met criteria for the randomized study had lower serum albumin and higher prothrombin times (data not shown). Significantly more African American and Hispanic patients failed to meet inclusion criteria or were excluded because of more severe liver disease, although they were not older than the Caucasian patients. The reasons for this are unclear. African American and Hispanic patients may have been referred for the trial at a later stage of their disease than Caucasian patients, and this could explain their more severe liver disease. However, this would imply that they had earlier onset of PBC or more rapid disease progression, and our cross-sectional study could not evaluate this. Caucasian patients may have had better access to care and thus earlier referral. Because of the length of the disease, patients vary in their time of presentation. Data on the duration of the disease were known for only 55% of the patients, but it did not differ between ethnic groups. It is possible that some of the non-Caucasians without a known duration of the disease had earlier onset of PBC. The differential diagnosis of PBC includes other chronic cholestatic liver diseases such as sarcoidosis, sclerosing cholangitis, and infectious etiologies. African American and Hispanic patients may have been initially misdiagnosed. Suggestive of this was the higher use of immunosuppressive agents in these patients before screening. It is not clear whether these patients had more rapid disease, less access to care early in their disease, or misdiagnoses due to inadequate testing, the absence of liver biopsies, or the presence of comorbidities that may have led to a delay in treatment. However, our data show that they were similar in age and disease duration to Caucasian subjects. A number of patients declined to participate because they

did not want to take methotrexate, the study took too much time, or there were too many procedures. Significantly more African American and Hispanic patients, who did meet inclusion criteria for the randomized study, did not wish to participate, perhaps because of these or other unknown factors, such as difficulties related to access to tertiary referral centers. Interestingly, similar findings were reported for African American patients with autoimmune hepatitis. Although they were diagnosed at a younger age, African American patients had cirrhosis more frequently at presentation than Caucasians. As in the current study, there was no obvious explanation for these differences.[16]

Although this study includes a large US-based cohort of patients with diverse ethnicity and is geographically representative, it may be more representative of a tertiary referral center population and not represent the demographics of the United States as a whole. It is possible that the enrollment criteria of the initial trial may have inadvertently affected the findings of the patients screened for the trial and reported in this study. However, the randomized trial enrolled patients without severe liver disease[3] and should have biased the screening group toward milder disease status. There were significant differences in ethnic representation depending on the site, reflecting the diversity of ethnic populations throughout the United States. Although PBC remains predominantly a disease of Caucasian women, a significant number of racial minority patients were screened for this study. Although similar in age, Hispanic and African American patients more often had more advanced disease by symptoms and physical findings and were excluded because of disease severity. PBC should be considered in the differential diagnosis of cholestatic liver disease in all ethnic populations.

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Abbreviations

AMA	antimitochondrial antibody
NS	not significant
PBC	primary biliary cirrhosis
PUMPS, PBC	Ursodeoxycholic Acid Methotrexate Placebo Study Group
SD	standard deviation

Table 1

Demographics of Screened PBC Patients by Gender, Ethnicity, and AMA Positivity

	All	Female	Male	Caucasian	Non-Caucasian	AMA-Positive	AMA-Negative
n	535	501	34	462	73	490	45
Age (mean ± SD)	52 ± 9.5	52 ± 9.6	53 ± 8.1	52.1 ± 9.5	51.5 ± 9.4	52.1 ± 9.4	51.2 ± 11
Female (n)	501			431	70	458	43
Race/ethnicity (n)							
Caucasian	462	431	31	–	0	427	35
African American	21	19	2	–	21	15	6
Hispanic	42	42	0	–	42	38	4
Other	10	9	1	–	10	10	0
Eligibility (n)							
Randomized	265	245	20	248*	17*	265	0
Eligible, not randomized	120	115	5	98	22	120	0
Ineligible	150	141	9	116†	34†	105	45

*Comparison of eligibility by ethnicity: $P = 0.0005$ between Caucasian and non-Caucasian by eligible randomized and not randomized.

†Comparison of eligibility by ethnicity: $P = 0.0001$ between Caucasian and non-Caucasian by eligible and ineligible.

Table 2

History of Screened PBC Patients by Gender, Ethnicity, and AMA Positivity

	All	Female	Male	*P*	Caucasian	Non-Caucasian	*P*	AMA-Positive	AMA-Negative	*P*
n	535	501	34		462	73		490	45	
Activity level				NS			0.00001*			NS
Normal	221	204	17		208	13		209	12	
Regular activity but not well	224	215	9		188	36		209	15	
Limited activity	66	60	6		47	19		57	9	
Bed-bound	1	1	0		0	1		1	0	
History of pruritus				NS			0.0001*			NS
None	240	223	17		225	15		225	15	
No treatment	151	142	9		129	22		143	8	
Medication relieved	65	63	2		45	20		57	8	
Medication partly relieved	43	40	3		34	9		38	5	
Medication unrelieved	13	12	1		10	3		13	0	
History (%)										
Ascites	4.2	4.3	3.1	NS	3.4	9.7	<0.06	3.9	8.3	NS
Hepatic encephalopathy	1.9	2.1	0	NS	1.3	5.6	<0.09	1.5	8.3	<0.03
Variceal bleeding	4.3	4.3	3.1	NS	3.4	9.9	<0.07	4.2	5.6	NS
Severe disease†	6.4	6.4	6.2	NS	4.7	16.7	<0.009	6	11.1	NS

NS, not significant.

*Chi-square comparisons of the activity level and pruritus are shown by gender (NS), Caucasian and non-Caucasian, or AMA positivity (NS).

†Severe disease includes any of the following: ascites, hepatic encephalopathy, or variceal bleeding.

Table 3

Physical Examination of Screened PBC Patients by Gender, Ethnicity, and AMA Positivity

	All	Female	Male	Caucasian	Non-Caucasian	AMA-Positive	AMA-Negative
Presence (%)							
Hepatomegaly	28.1	28.5	22.6	24.9	47.8‡	27.9	30.3
Hyperpigmentation	16.1	16.1	16.1	13	36.4‡	15.9	18.2
Splenomegaly	12.5	12.4	12.9	11.4	18.8	12.3	14.3
Spider nevi	12	10.9	29†	12	11.9	11.8	14.3
Telangiectasia	12	11.8	16.1	11.1	17.9	11.4	20.6
Excoriations	8.2	8.3	6.5	6	22.1‡	7.7	14.7
Edema	7.8	7.7	9.4	7.9	7.1	7.3	3.9
Icterus	4.9	4.4	12.9*	3	16.9‡	4.2	14.3*
Xanthelasma	4.4	4.7	0	4.6	3	4.3	5.9
Muscle wasting	3.4	3	9.7	2.8	7.5*	3	9.1
Ascites	3.1	3.1	3.1	2.7	5.6	2.7	8.3
Clubbing	1.6	1.5	3.2	1.4	3.1	1.5	3
Purpura	1.2	1.3	0	0.9	3.1	1.1	3
Asterixis	0.2	0.2	0	0	1.5	0.2	0
Xanthomata	0.2	0.2	0	0.2	0	0.2	0
Body mass index (mean ± SD)	26.7 ± 5.3	26.7 ± 5.4	25.6 ± 3.7	26.8 ± 5.3	26.2 ± 5.3	26.6 ± 5.2	27.5 ± 8.1

Comparisons of physical findings are shown by gender, Caucasian and non-Caucasian, or AMA positivity.

*$P < 0.05$.

†$P < 0.01$.

‡$P < 0.001$.

Table 4

Laboratory Data of Screened PBC Patients by Gender, Ethnicity, and AMA Positivity

	All	Female	Male	Caucasian	Non-Caucasian	AMA-Positive	AMA-Negative
n	535	501	34	462	73	490	45
Bilirubin	1.1 ± 2.1	1.1 ± 2.1	1.4 ± 2	0.9 ± 1	2.3 ± 4.8†	1.1 ± 2.1	1.3 ± 1.3
Alkaline phosphatase	349 ± 261	350 ± 266	331 ± 165	326 ± 232	489 ± 364‡	345 ± 259	392 ± 275
AST	66.4 ± 42.4	66.3 ± 42.6	68.3 ± 40.1	62.7 ± 37.2	89 ± 61.1‡	66.1 ± 42.8	70.2 ± 37.4
ALT	75.9 ± 100.1	75.2 ± 102.3	87.1 ± 56.8	74 ± 105	87.7 ± 62	75.5 ± 103	81.4 ± 51.2
Protime	11.6 ± 1.5	11.6 ± 1.5	11.7 ± 1.5	11.5 ± 1.6	11.9 ± 1.3†	11.6 ± 1.5	11.8 ± 1.5
Protein	7.8 ± 0.7	7.7 ± 0.7	7.8 ± 0.9	7.8 ± 0.7	7.7 ± 0.7	7.8 ± 0.7	7.6 ± 0.7
Albumin	4 ± 0.4	4 ± 0.5	4 ± 0.4	4 ± 0.4	3.7 ± 0.5‡	4 ± 0.5	3.9 ± 0.4
Cholesterol	250 ± 71	249 ± 70	263 ± 95	248 ± 68	266 ± 89	250 ± 70	253 ± 88
Creatinine	0.9 ± 0.3	0.9 ± 0.2	1.1 ± 0.4	0.9 ± 0.2	0.8 ± 0.3	0.9 ± 0.3	0.9 ± 0.2
Hemoglobin	13 ± 1.4	13 ± 1.3	14 ± 1.4	13.1 ± 1.3	12.3 ± 1.5‡	13.1 ± 1.4	12.6 ± 1.5*
White blood cell	6.5 ± 2	6.4 ± 2	6.6 ± 2.1	6.5 ± 2	6.2 ± 2.1	6.4 ± 1.9	6.9 ± 2.7
Absolute neutrophil	3.8 ± 1.5	3.8 ± 1.5	3.6 ± 1.3	3.8 ± 1.4	3.9 ± 2	3.7 ± 1.5	4.3 ± 2.1
Platelets	245 ± 100	244 ± 98	251 ± 125	247 ± 96	229 ± 120	245 ± 101	234 ± 91

Comparisons of physical findings are shown by gender, Caucasian and non-Caucasian, or AMA positivity. All results are depicted as means ± SD.

*$P < 0.05$.

†$P < 0.02$.

‡$P < 0.001$.