

Demographics of a large cohort of urban chronic hepatitis C patients

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Abstract

Purpose Recent studies suggest that African Americans (AA) with chronic hepatitis C (CHC) differ from non-Hispanic whites (NHW) with respect to the natural history and mortality resulting from the complications of chronic liver disease. The aim of this study was to examine the demographics of a large cohort of CHC patients and identify potential differences between AA and NHW.

Methods This is a retrospective analysis, consisting of 2,739 hepatitis C antibody-positive patients seen at Wayne State University between 1995 and 2005. Patient demographics, risk factors, comorbidities, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum hepatitis C (HCV) RNA levels, genotype, and liver biopsy results were recorded.

Results AA constituted 75.4%, NHW 22.5%, and Asians or Hispanics 2.1% of the patients. Males predominated (58%), and the mean age of AA and NHW was 50.0 and 45.3 years, respectively ($P \leq 0.001$). The most common risk factor was injection drug use in 55.3% (AA 57.1% vs. NHW 49.7%; $P \leq 0.002$). HCV RNA by PCR obtained in 2,407 patients was positive in 94.8%, with a high viral load in 61%. Genotype 1 was significantly more frequent in AA (92.6%) than in NHW (70.6%, $P \leq 0.001$). AA had lower median ALT levels ($P \leq 0.001$). In those patients who

were biopsied, there was no significant difference in fibrosis between the two groups. Aspartate to platelet index calculated in those patients who were not biopsied showed significantly lower fibrosis scores in AA.

Conclusions In this large cohort of CHC patients from a single institution, AA were older at presentation, had a higher prevalence of genotype 1, but significantly lower ALT levels than NHW.

Keywords Chronic hepatitis C · Demographics · African Americans

Introduction

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States, with an estimated 3.9–5 million people having been infected [1, 2]. HCV infection can be a progressive disease, resulting in cirrhosis that can lead to liver failure and/or hepatocellular carcinoma (HCC). Decompensated cirrhosis associated with HCV infection is the most frequent indication for liver transplantation in the United States and Europe [3].

There is significant racial disparity with respect to chronic hepatitis C (CHC) in the United States, with the highest prevalence of HCV infection in African Americans (AA) (3.2%) and Hispanics (2.8%) than non-Hispanic whites (NHW) (1.5%) [2]. AA, representing 12–13% of the US population, account for 22% of the estimated 3.7 million Americans who have CHC viremia [1, 2]. AA with CHC are reported to have lower pretreatment alanine aminotransferase (ALT) levels and less fibrosis than NHW [4]. Unfortunately, AA do not respond as well as NHW to interferon (IFN)-based therapies [5–10]. The explanation for this still remains unknown.

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Although epidemiological data on patients with CHC have been reviewed in the general population [2], and selected populations, such as veterans, prison inmates, injection drug users [5, 11], and Hispanics [12, 13], there are a few studies describing the demographics of AA patients with CHC, and these have included only small numbers of patients [14–19].

Our objectives were to study the demographics of a large cohort of AA patients with CHC from a single urban medical center and to assess the clinical, biochemical, and histological differences between AA and NHW patients with CHC. Confirmation and understanding of these differences could provide insight into the differences in the natural history of the disease and, perhaps, the disparate response to IFN-based therapies between these 2 racial groups.

Materials and methods

Patients

The study population consisted of consecutive patients with a positive HCV antibody seen in our outpatient practice between January 1995 and July 2005. The majority of our patients (78%) were referred by primary care physicians from within the city of Detroit and by the General Internal Medicine clinics from within our own institution. The remaining patients were referred by primary care physicians from other metropolitan Detroit communities. Referring physicians had uniform criteria for patient referral. A positive test for HCV antibody was the most common reason for referral. Data on all patients with CHC were entered into a computer database using unique identifier numbers for each patient and medical record numbers, thereby preventing duplication of patient data. Information on age, gender, race, and risk factors for CHC, including injection drug use (IDU), intranasal drugs, blood transfusions, tattoos, multiple sexual partners, incarceration, hemodialysis, and other associated medical conditions, was obtained by experienced clinicians evaluating the patients. History of current and past alcohol intake was also recorded. These data were recorded on forms specifically created for this purpose and then entered into a computer database. Race was determined by self-reporting as AA, Asian, Hispanic, or NHW. The computer database was continually updated as data became available during patients' follow-up visits. The study was approved by the institutional review board at Wayne State University School of Medicine.

Methods

Anti-HCV serology was performed using the second generation ELISA for antibody (EIA II, Abbott Lab, Chicago,

IL). Testing for HCV RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) was accomplished using the superquant assay (PCR range: <200 to >2,000,000 copies/ml; National Genetics Institute, CA) or the AmpliCor HCV monitor test version 2.0 (PCR range: <2,500 to >2,800,000 IU/ml; Roche Molecular, Pleasanton, CA) performed in our laboratory. HCV genotype was tested using the line probe Versant Inno-LiPa HCV-II genotype assay (LiPA; Bayer Healthcare, Tarrytown, NY). Serum samples were also tested for antibodies to hepatitis A virus (anti-HAV), hepatitis B core antigen (anti-HBc), and hepatitis B surface antigen (HBsAg), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin. The Metavir score [20] for necroinflammation (grade 0 = no inflammation, grade 1 = mild inflammation, grade 2 = moderate inflammation, and grade 3 = severe inflammation) and fibrosis (stage 0 = no fibrosis, stage 1 = portal fibrosis, stage 2 = periportal fibrosis, stage 3 = bridging fibrosis, and stage 4 = established cirrhosis) were recorded for all patients who underwent liver biopsy. In order to assess the fibrosis in the remaining patients, who did not agree to liver biopsy, an AST to platelet index (APRI) was calculated as follows: $\{(AST/ULN)/Platelets(10^9/l)\} 100$.

Statistical analysis

For comparison of categorical data, Pearson's chi-square or Fisher's exact tests were used. When AA and NHW patients differed across a set of categories, follow-up comparisons were made for each category separately. For normally distributed continuous data, *t* tests were performed. For continuous data that did not meet the normality assumption, Mann-Whitney *U* tests were performed. A *P* value of <0.05 was considered statistically significant.

Results

Age, gender, and race

A total of 2,739 anti-HCV-positive patients were included in this analysis. As shown in Table 1, 2,035 patients were AA and 616 NHW. The remaining 2.1% were Asians and Hispanics. The selection criteria applied were identical in all groups. A predominance of male gender was noted. Nearly half of our patients were in their fifth decade at presentation, followed by those in their sixth decade. The mean age of AA patients was higher than that of NHW [49.98 and 45.34 years, respectively; $P \leq 0.001$]. The age distribution by decade is shown in Table 1. Most patients reported high-risk behavior in their 20s and taking into

Table 1 Characteristics of chronic hepatitis C patients seen at Wayne State University, Detroit, MI, between 1995 and 2005

	AA		NHW		<i>P</i>
	<i>n</i>	%	<i>n</i>	%	
Total subjects	2,035	75.4	616	22.5	<0.001 ^a
Gender					
Male	1,152	56.8	373	60.7	0.093 ^a
Female	875	43.2	242	39.3	
Missing	8		1		
Age (mean)	49.98		45.34		<0.001 ^b
14–29	23	1.1	28	4.6	
30–39	117	5.8	104	17.1	
40–49	851	42.2	303	49.8	
50–59	816	40.4	139	22.8	
60–69	164	8.1	24	3.9	
70+	47	2.3	11	1.8	
Unknown	17		7		
Risk factors					<0.001 ^a
Injection drug use	1,070	57.1	279	49.7	<0.002 ^c
Blood transfusion	288	15.4	104	18.5	<0.074 ^c
Intranasal drugs	135	7.2	28	5.0	0.065 ^c
Multiple	38	2.0	9	1.6	0.522 ^c
Other ^d	92	4.9	40	7.2	
None	250	13.3	101	18.0	0.006 ^c
Missing data	162		55		

^a Chi-square test for overall difference in categories for AA and whites

^b *t*-Test for overall group in means for AA and NHW

^c Chi-square test for differences in individual categories for AA and NHW

^d Other includes employment in healthcare, hemodialysis, tattoos, multiple sexual partners, and a spouse with history of injection drug use

Abbreviations: AA, African Americans; NHW, non-Hispanic whites

account the average age of AA and NHW patients (49.98 and 45.34 years, respectively), we estimated the duration of disease to be approximately 20–25 years in most patients, which was generally similar in both groups.

Risk factors

IDU was identified in most patients (two-thirds of whom had multiple risk factors) and was the most common risk factor observed, followed by blood transfusion prior to 1992 and intranasal drug use (Table 1). A significantly higher proportion of AA were injection drug users ($P \leq 0.002$). Fourteen percent of the patients had no identifiable risk factor. In the remaining patients, risk factors included employment in healthcare, hemodialysis, tattoos, multiple sexual partners, and a spouse with history

of IDU. Alcohol consumption, both past and current, was also noted to be similar in both groups (data not presented).

Laboratory data and liver histology

As shown in Table 2, HCV RNA determination by PCR (qualitative or quantitative) was available for 2,407 patients, of whom 2,282 (95%) were positive. There was no difference between AA and NHW in this regard. Quantitative PCR for HCV RNA was available for 1,928 patients. A high viral load was defined as more than 2,000,000 copies/ml or 400,000 IU/ml. Sixty-one percent of the patients had a high viral load. There was no significant difference in the viral load between AA and NHW. Genotype was available for 1,683 patients and the vast majority of AA were genotype 1 ($P \leq 0.001$). Genotypes 2, 3, and 4 were also identified but much less frequently in AA than in NHW (Table 2).

The median ALT at presentation was significantly lower in AA (66 units/l, interquartile range = 44–96) than in NHW (77, interquartile range = 50–121 $P \leq 0.001$). Mean serum albumin was significantly higher in NHW (4.07 g/dl, SD = 0.36) than AA (3.90, SD = 0.7; $P \leq 0.001$, data not shown). Although liver biopsy was offered to all patients who were seen, only 1,414 (51.6%) patients (AA = 49.6%, NHW = 57.8%) underwent biopsy. Histological scoring showed lower grades of inflammation in AA than in NHW ($P = 0.047$). NHW had a higher median score for fibrosis than AA, although this did not achieve statistical significance ($P = 0.17$). The APRI evaluated in those patients who were not biopsied showed a significant difference ($P \leq 0.04$), with a greater degree of fibrosis in NHW than in AA (Table 2).

Serological markers for hepatitis A and B

Serological markers indicating previous exposure to hepatitis A and B viruses were available in 1,740 and 1,841 patients, respectively, and showed the prevalence of both anti-HAV and anti-HBc antibodies to be significantly higher in AA than in NHW (Table 2). No difference in HBsAg prevalence was observed between the 2 groups.

Discussion

The explanation for the differences in the natural history and histological spectrum of CHC between AA and NHW is still not well established. One might have anticipated, on the basis of the decreased enzyme activity and less fibrosis that AA patients would have a more benign disease course. However, for reasons that are unclear, the complications of liver cirrhosis and the incidence of HCC are significantly

Table 2 Laboratory data and liver histology of chronic hepatitis C patients seen at Wayne State University Hospital, Detroit, MI, between 1995 and 2005

	AA		NHW		P
	n	%	n	%	
Positive HCV RNA by PCR (Qual + Quant)					0.11 ^a
Positive	1,703	95.1	507	93.4	
Negative	87	4.9	36	6.6	
Viral load					0.25 ^a
Low	534	36	200	43	
High ^b	935	64	259	57	
Genotype					<0.001 ^c
Type 1	1,171	92.6	262	70.6	<0.001 ^d
Type 2	66	5.2	40	10.8	<0.001 ^d
Type 3	18	1.7	61	16.4	<0.001 ^d
Type 4	9	0.7	8	2.2	<0.03 ^e
Missing data					
Anti-HAV IgG (total)					<0.001 ^a
Positive	569	42.9	112	30.5	
Negative	756	57.1	255	69.5	
Missing data	710		249		
Anti-HBc IgG					<0.001 ^a
Positive	826	58.8	161	41.7	
Negative	578	41.2	225	58.3	
Missing data	631		230		
HBsAg					0.24 ^c
Positive	57	3.6	21	4.9	
Negative	1,510	96.4	410	95.1	
Missing	468		185		
Liver histology					<0.04 ^f
Grade					
0 (No inflammation)	77	8.4	23	7.3	
1	454	49.2	138	44.1	
2	312	33.8	117	37.4	
3	79	8.6	31	9.9	
4	0	0	4	1.3	
Stage					0.16 ^f
0 (No fibrosis)	179	17.7	65	18.3	
1 (Portal)	274	27.2	83	23.3	
2 (Periportal)	180	17.8	62	17.4	
3 (Bridging fibrosis)	158	15.7	47	13.2	
4 (Cirrhosis) ^g	218	21.6	99	27.8	
APRI (mean)	0.65		0.78		0.04

^a Chi-square test for overall difference in categories for AA and NHW

^b High: >2 million copies/ml or >400,000 IU/ml

^c Fisher's exact test for overall difference in categories for AA and NHW

^d Chi-square test for differences in individual categories for AA and NHW

^e Fisher's exact test for differences in individual categories for AA and NHW

^f Mann-Whitney *U* test for overall group in means for AA and NHW

^g Includes those with clinically decompensated cirrhosis and those with HCC

Abbreviations: AA, African Americans; NHW, non-Hispanic whites

higher in AA than in NHW (6.1 vs. 2.8/100,000 persons, respectively) [21–23]. AA men have a mortality rate from HCC that is twice the rate observed among NHW men [23, 24]. Previous studies evaluating these issues have been limited by the heterogeneity and small size of the populations studied [4, 14–17]. Our study of 2,739 patients with CHC, of whom 2,035 were AA, constitutes the largest demographic analysis emerging from any single institution.

The higher prevalence of HCC in AA has been attributed by many investigators to a higher prevalence of coinfection with hepatitis B and hepatitis C because both entities are considered predisposing factors for the development of HCC. It is also conceivable that occult hepatitis B infection, that is, presence of anti-HBc antibody alone, could also contribute to the increased incidence of HCC in AA. In fact, we did observe a significantly higher

prevalence in AA of serologic markers of previous exposure to hepatitis B and hepatitis A than NHW. In addition, lower socioeconomic status is correlated with both hepatitis A and B infections [25, 26]. Generally lower socioeconomic status in AA patients could explain the lower serum albumin levels observed, but we did not specifically evaluate socioeconomic status in our patient population.

Race and HCV genotype have important implications in the treatment of CHC. Genotype 1 has consistently been associated with a poorer response to IFN-based therapies, especially in AA [7–10, 19, 27–29]. A significantly higher prevalence of genotype 1 in AA than in NHW was observed in our cohort. Crosse et al. [15], Reddy et al. [18], and Fleckenstein [19] have also made similar observations. The question remains as to whether the increased prevalence of genotype 1 in AA patients reflects a host genetic susceptibility or reflects a difference in mode of transmission. We also noted a higher prevalence of genotype 3 in NHW (16.4%) than 1.4% in AA. The reasons for these differences are unclear.

More recently Crosse et al. [15], in a cross-sectional analysis of 87 AA and 136 NHW with CHC, showed lower fibrosis scores in AA. In a retrospective study of 355 patients (AA = 112), Wiley et al. [4] evaluated the progression of histological changes in the liver of CHC patients over decades of exposure and noted that despite the longer duration of infection in AA, fibrosis scores were significantly lower than non-AA, especially in the third and fourth decades. Modes of transmission, estimated duration of infection, and alcohol abuse were similar in both groups. McHutchinson et al. [27] noted that AA were older at presentation, but these investigators did not observe a lower rate of cirrhosis. However, the number of AA in this large multicenter study was small, accounting for only 3% of the total patients enrolled. In contrast, Sterling et al. [16] in a study of 302 patients from a correctional facility (AA = 49%) found the overall spectrum of HCV-related liver disease to be similar in AA and NHW, without significant differences in the total histological activity index (HAI) scores for fibrosis and inflammation. Although the utility of the APRI has been controversial [30], recent studies by Snyder et al. [31] and Shaheen and Myers [32] have described the APRI to be a good estimator of hepatic fibrosis and an important tool in excluding significant HCV-related fibrosis. Hence, in order to obtain an indirect measure of the liver fibrosis in those patients who were not biopsied, we utilized the APRI and noted significantly lower fibrosis scores in AA.

This is a retrospective study with inherent limitations. Although complete information was available regarding the race, gender, age, and risk factors, information about the viral load, genotype, and liver biopsy was not available

for all patients. In addition, many patients seen between 1995 and 2000 did not have HCV RNA quantitation because access to this assay was not universally available. Even fewer patients had genotyping done. We believe the sampling obtained for each of these parameters was representative for both the NHW and the AA cohorts.

The importance of steatosis and insulin resistance on treatment response has gained emphasis more recently. Our data collection started in 1995 when these factors were not being evaluated, and hence this information was not recorded. Liver biopsy was recommended for all patients; however, those patients who did not wish to be treated often refused liver biopsy. Patient refusal of treatment and lack of adherence with follow-up visits were the 2 most common reasons for our inability to complete all components of the initial assessments.

In summary, the results derived from this large study of 2,739 patients with CHC confirm that AA when compared with NHW are older at presentation, are more likely to be injection drug users, infected with genotype 1, have lower ALT and albumin, and less hepatic fibrosis. AA also have a higher prevalence of previous exposure to hepatitis A and B. Although these findings have been observed by other investigators in much smaller groups of AA, this report confirms these observations in a much larger group of AA seen in a single institution.

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