Jaundice in African-American and Hispanic Patients with AIDS

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This study was presented in part as abstract at the 24th biennial scientific meeting of the International Association for the Study of the Liver, Cairo, Egypt, September 2006.

The Charles R. Drew Institutional Review Board approved this study (IRB #06-03-948-01, May 25, 2006).

Although abnormalities in hepatic biochemical tests are common in patients with acquired immunodeficiency syndrome (AIDS), overt jaundice is infrequent. The aim of this study was to investigate the etiology and outcome of jaundice in African-American and Hispanic patients with AIDS. We retrospectively reviewed medical records of 1,238 HIV-infected patients with abnormal liver chemistry over a 10-year period. Data were abstracted and analyzed for demography, medications, laboratory tests, abdominal ultrasonography, computerized tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and liver biopsy results. Of 1,238 patients with abnormal liver chemistry and HIV infection, 1,040 (84%) had AIDS. Of the 1,040 AIDS patients, 102 (10%) had jaundice (serum bilirubin >3 mg/dL). Of the 198 HIV-positive patients without AIDS and with abnormal liver chemistry, none had jaundice. The common causes of jaundice were drugs (29%) and infections (28%). Liver biopsy was performed in 20 AIDS patients, and the common findings included granulomas, *Mycobacterium avium* complex (25%) and Kaposi's sarcoma (25%). Of 102 patients with AIDS and jaundice, 72 (70%) died. Of the 198 patients without AIDS and without jaundice, 14 (7%) died. In conclusion, liver-associated enzyme abnormality was common among our patients with AIDS; however, jaundice was infrequent and associated with a high mortality; drugs, infections and alcohol were the common culprits.

Key words: jaundice ■ African Americans ■ Latinos ■ HIV/AIDS

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INTRODUCTION

African Americans account for the highest number of HIV/AIDS cases in the United States than those for all other racial/ethnic populations combined. According to a recent report by the Centers for Disease Control and Prevention (CDC), 47% of 1.2 million persons with HIV infection were non-Hispanic blacks.[1]

Highly active antiretroviral therapy (HAART) has been increasing the life expectancy of HIV-infected persons. Consequently, liver disease is becoming a major cause of morbidity and mortality in these patients.[2] CDC[1] defined AIDS: if a person has tested positive for HIV and meets one or both of the following criteria:

- The presence of one or more AIDS-related infections or illnesses
- A CD4 count that has reached or fallen below 200 cells/mm^3 of blood (normal = 450–1,200 in healthy individuals)

Although abnormalities in liver-associated enzymes are present in most HIV-infected patients, jaundice is rather infrequent.[3-5] Literature is scant about this topic, particularly in African-American and Hispanic patients. Since our large inner-city community teaching hospital predominantly serves these two populations, we undertook this study to determine the etiology and outcome of jaundice in African-American and Hispanic patients with AIDS.

METHODS

Our hospital serves a predominantly African-American and Hispanic population. We identified and reviewed retrospectively medical records of all African-American and Hispanic patients aged 19–70 years who were admitted to the hospital over 10 years (from January 1, 1996 to December 31, 2005) with the diagnosis of human immunodeficiency virus (HIV) infection and liver test abnormalities (N=1,238). Abnormal liver chemistry and hepatic injury were considered if there was an increase over 2xN (upper limit of normal) for aminotransferases (ALT, AST), alkaline phosphatase or conjugated

bilirubin. Diagnosis of drug-induced liver disease was based upon circumstantial evidence and exclusion of other causes and according to available guidelines when possible.[6-8] Jaundice was defined as total serum bilirubin levels >3mg/dL. The subanalysis showed that it was mostly indirect bilirubin. Sources of information for this study included inpatient and outpatient charts and gastroenterology consultation reports. Data were abstracted for demography, laboratory tests, abdominal ultrasonography, computerized tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and liver biopsy results. Data were analyzed using Chi-squared test for categorical data and analysis of variance (ANOVA) for continuous variables to test the significance difference between the groups. The statistical analysis was done using SPSS® (Statistical Package for Social Science version 12, 2002; SPSS Inc., Chicago, IL).

RESULTS

The study included 1,238 patients 19–70 years of age who were admitted to the hospital and diagnosed with HIV infection and had abnormal liver chemistry over a 10-year period. Seventy-seven percent (948) of the patients were African American and 23% (290) were Hispanic. Seventy-one percent of the patients were male and 50% were <30 years old (Table 1).

Of the 1,238 patients with abnormal liver chemistry and HIV infection, 1,040 (84%) had AIDS. The majority of these AIDS patients were African American (77%). Twenty-seven percent of the AIDS patients were African-American men who were 19–30 years old (Table 2).

Of the 1,040 AIDS patients, 102 (10%) had jaundice (serum bilirubin >3 mg/dL). Of 198 HIV-positive patients without AIDS and with abnormal liver chemistry, none had jaundice.

Among the 102 patients with AIDS and jaundice, 56 patients (55%) received antiretroviral therapy, 30% had multiple possible etiologies for the jaundice. One or more of the imaging studies, including abdominal ultrasound (90%), CT scan (45%) and MRI (15%), were performed in 95% of patients with jaundice, and were helpful in making a diagnosis in 23% of cases. The common potential etiologies for jaundice were drugs (29%), main possible culprits being: nevirapine, efavirenz, zidovudine, didanosine, ritonavir, isoniazid, rifampin and trimethoprim-sulfamethoxazole and acetaminophen; infections (28%), including disseminated mycobacteriosis, cytomegalovirus, toxoplasmosis, pneumocystis carinii, disseminated fungal and bacterial infections; and alcoholic liver disease (18.6%). Cholangiopathy and biliary stones were found among 8.8% of the patients. Extrahepatic neoplasm was found among 6.9%, followed by hepatocellular carcinoma (5.9%) and cholangiocarcinoma (2%) (Table 3).

Liver biopsy was performed in 20 of the 102 AIDS patients with jaundice. Indications for liver biopsy included: liver disease of uncertain etiology, clinical hepatomegaly, fever of unknown origin and unexplained deterioration of liver chemistry. There were no reports of significant complications of liver biopsy except a drop in the hematocrit and hypotension due to subcapsular hematoma in two patients, who recovered after blood transfusion. The common findings of liver biopsies were granulomas, *Mycobacterium avium* complex (25%), Kaposi's sarcoma (25%), drug-induced hepatitis (20%), lymphoma (20%) and steatohepatitis (20%) (Table 4). The diagnosis of drug-induced liver disease was presumed if serum alanine aminotransferase levels ≥3 times the upper limit of normal (ULN) plus serum

Table 1. Patient demography of 1,238 patients with HIV infection and abnormal hepatic biochemical tests

Variables	African Americans (N=948)		Hispanics (N=290)		Total
Age Groups	Males (N=674)	Females (N=274)	Males (N=208)	Females (N=82)	
(Years)	N (%)	N (%)	N (%)	N (%)	N (%)
19–30	344 (51)	131 (48)	108 (52)	41 (50)	624 (50)
31–50	237 (35)	90 (33)	75 (36)	29 (35)	431 (35)
51–70	93 (14)	53 (19)	25 (12)	12 (15)	183 (15)

Table 2. Patient demography of 1,040 AIDS patients with abnormal hepatic biochemical tests

Variables	African Americans (N=797)		Hispanics (N=243)		Total
Age Groups	Males (N=566)	Females (N=231)	Males (N=176)	Females (N=67)	
(Years)	N (%)	N (%)	N (%)	N (%)	N (%)
19–30	288 (51)	109 (47)	90 (51)	33 (49)	520 (50)
31–50	199 (35)	76 (33)	64 (36)	24 (36)	363 (35)
51–70	79 (14)	46 (20)	22 (13)	10 (15)	157 (15)

bilirubin levels ≥2 times the UNL level without evidence of biliary obstruction and absence of other known liver diseases.

Among all the 20 patients who had liver biopsy, the latest CD4 counts were low (the average was 55.4 cells/μl ± 7.4 cells/μl and the median value was 38.0 cells/μl). The latest CD4 counts did not vary significantly by the type of lesion identified in the biopsy (f=1.13, p=0.38).

Of the 102 AIDS patients with jaundice, 29 (28%) died during the index hospital admission. Of the 29 deceased patients, 24 (83%) had latest CD4 count <50 cells/μl. Further, 43 of 102 patients with AIDS and jaundice died within one year of discharge from the hospital. In 23 of 43 patients with AIDS and jaundice who died (53.5%), latest CD4 counts varied between 50–100 cells/μl, whereas the remaining 20 of 43 deceased patients' latest CD4 count was <50 cells /μl. Thus, the total deaths in the AIDS patients with jaundice were 72 of 102 (70%), as per the available records. Of the total death of 72 patients, 40 deaths (56%) occurred in years 1995–2000 and 32 deaths (44%) occurred in 2001–2005. Fourteen of 40 deaths (35%) in this group, occurring in years 1995–2000, were directly associated with liver disease, whereas 24 of 32 (75%) deaths in years 2001–2005 were related to liver disease. Deaths were assumed to be liver related if liver disease and/or hepatic failure were diagnosed clinically or as a result of autopsy findings. In our study patients, we considered the death as "related to liver disease" if the patient's clinical records or death certificate revealed ≥1 of the following: bacterial peritonitis, gastrointestinal bleeding with or without evidence of esophageal varices or portal hypertensive gastropathy, hepatic encephalopathy, coagulopathy, hepatorenal syndrome, hepatic failure with or without active viral hepatitis. Autopsy results were available only in 12 of 72 (17%) deceased patients and showed multiple organ system disease, including primary central nervous system lymphoma (n=3), progressive multifocal leukoencephalopathy (n=4), AIDS dementia complex (n=3), cryptococcal meningitis (n=3), liver cirrhosis and alcoholic liver disease (n=3), opportunistic infections (cytomegalo virus, n=3, mycobacterium avium complex, n=3, toxoplasma gondii, n=2, pneumocystis carinii, n=2), Kaposi's sarcoma (n=1), primary hepatocellular carcinoma (n=1), disseminated candidiasis (n=2) and bacterial septicemia (n=1). The liver was involved in all cases, 10 of 12 (83%) autopsy cases had multiple conditions.

Of the 198 patients without AIDS and no jaundice, 57 were hospitalized, four (7%) died during index hospitalization and 10 (5%) died within one year after discharge from the hospital. The total number of deaths in patients without AIDS and without jaundice was 14 out of 198 (7%). Their latest CD4 counts were ≥50/μl, and no deaths were directly linked to liver disease, as per available records. There was a statistically significant difference between the two groups in the odds of mortality where patients with AIDS and jaundice had higher odds of death relative to those without AIDS and jaundice [odds ratio (OR)=31.5, 95% confidence interval (CI): 15.1–67.1, p=0.00001].

Table 3. Etiology of jaundice in 102 AIDS patients*

Etiology of Jaundice	Number	Percent
Hepatocellular		
Drugs	30	29.4
Alcohol	19	18.6
Infection	29	28.4
Neoplasm	6	5.9
Biliary Ductal		
Cholangiopathy	9	8.8
Intrahepatic ductal stones	7	6.9
Cholangiocarcinoma	2	2.0
Extrahepatic		
Neoplasm	7	6.9
Biliary stones	9	8.8
Undetermined	15	14.7

*Total exceeds 102, because 31 patients (30%) had more than one conditions.

Table 4. Results of liver biopsy in patients with AIDS and jaundice (N=20)*

Lesion	Number (%)
Granulomas/*Mycobacterium avium*	5 (25)
Kaposi's sarcoma	5 (25)
Nonspecific changes consistent with hepatitis	4 (20)
Drug-induced hepatitis	4 (20)
Herpes simplex hepatitis	4 (20)
Lymphoma	4 (20)
Steatohepatitis	4 (20)
Cytomegalovirus hepatitis	3 (15)
Candida albicans hepatitis	3 (15)
Alcoholic hepatitis	2 (10)
Mycobacterium tuberculosis	1 (5)
Normal histology	0 (0)

* Total exceeds 20 because 16 (80%) biopsies had ≥1 finding.

Of the 1,238 patients with abnormal liver chemistry and HIV infection, 681 (55%) were positive for hepatitis-C virus (HCV) serology. Of the 681 HCV patients 15% received treatment for hepatitis C. Of the 1,238 patients with abnormal liver chemistry and HIV infection, 557 (45%) were positive for hepatitis-B virus (HBV) serology. Of the 557 HBV patients, 20% received treatment for hepatitis B. Of the 102 AIDS patients with jaundice, hepatitis-C serology was positive in 42 (41%), and hepatitis-B serology was positive in 60 (59%).

DISCUSSION

HIV infection has become a leading cause of morbidity and mortality throughout the world, during the last two decades following its recognition. According to a recent epidemiological survey by the World Health Organization (WHO), the number of people living with HIV globally has reached its highest level with an estimated 40.3 million people, up from an estimated 37.5 million in 2003. More than three million people died of AIDS-related illnesses in 2005.[9]

Even though African Americans make up only approximately 13% of the U.S. population, they accounted for 50% of the new cases of HIV/AIDS diagnosed in the United States in 2004.[9] Among all racial/ethnic groups, African Americans not only outnumber others in having HIV/AIDS, they inexplicably suffer from more morbidity and mortality from the disease. In 2002, HIV/AIDS was the second leading cause of death for all African Americans aged 35–44 and the number-one cause of death for African-American women aged 25–34.[10] Hispanics were the third leading racial/ethnic group diagnosed having HIV/AIDS in 2004.[2] Older African Americans are disproportionately affected by HIV infection, and the prevalence of AIDS in these communities continues to rise.[11] In our study, the majority of the AIDS patients were African American and <50 years old.

HAART has been increasing the life expectancy of HIV-infected persons. This benefit however, comes at a cost of an increase in the drug-induced liver disease, opportunistic infections (e.g., *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Cryptococcus neoformans*, *toxoplasmosis*, disseminated candidiasis) and AIDS-associated malignancies.[12,13]

Consequently liver disease is becoming a major cause of morbidity and mortality of these patients. Bica et al. showed that mortality due to end-stage liver disease in their HIV patients increased from 11.5% in 1991 to 50% in 1999.[13] In our study, total deaths in patients with jaundice accounts for 72 of 102 (70%). Forty of these deaths occurred between 1995 and 2000, 14 of which were directly related to liver disease. Similarly, 32 deaths occurred between 2001 and 2005, with 24 deaths related to liver diseases.

Patients infected with HIV can suffer from myriad liver diseases, like any other patient who is not infected with HIV. However, many HIV-infected patients share the epidemiologic risk factors for viral hepatitis and sexually transmitted diseases, such as syphilis.[14] Immunodeficiency itself may result in more adverse outcomes of concomitant diseases. In addition, HIV patients may also suffer from opportunistic infections, HIV-associated malignancies and antiretroviral drug toxicity. The incidence of severe hepatotoxicity has been reported in up to 16% of the patients receiving HAART, and co-infection with HCV may result in an increased risk of drug toxicity, cirrhosis and hepatic decompensation.[15-18] Studies have shown that the potential causes of jaundice were drug-induced hepatitis (31%), alcoholic liver disease (13%), and opportunistic infections or neoplasm (30%).[4] In our patient population, drug-induced hepatitis, infections and alcohol were the common potential causes of jaundice. The prevalence of drug-induced hepatitis was similar to other studies; however, infections and alcoholic liver diseases were more prevalent in our study. The overall prevalence of serology for hepatitis B and C was similar in our patients to those described in the literature. However, it was higher in our AIDS patients with jaundice. The exact reason for this discrepancy is not clear; it may be due to a difference in the incidence of intravenous drug abuse, sexual practices, selection bias or yet unidentified causes.

Abnormalities in liver-associated enzymes are commonly present in HIV-infected patients, and liver histology is almost always abnormal. In a study of 501 liver biopsies performed on patients infected with HIV, Poles et al., showed that only 14 (2.8%) had normal liver histology.[19] In our study, only 20 patients had liver biopsy. However, the liver histology was abnormal in all 20 patients, and 16 (80%) had >1 finding.

While the mortality in our patients with AIDS and jaundice (70%) was much higher than the mortality reported in other studies (0.8–44%),[4,20] the mortality during hospitalization was only slightly higher in our study (28%) than in the literature (25%).[4] The exact cause of higher mortality in our patients is not clear; the severity of the disease and minority status might account for this observation. This is consistent with our previous studies,[21,22] enlightening that minority patients lack adequate education, health awareness, suffer from poverty more frequent alcohol and substance abuse, have higher incidence of chronic diseases, lack of adequate medical insurance coverage and delay in prompt access to healthcare, or yet unidentified factors, which may contribute to the increased morbidity and mortality rates.

Our study has several limitations. Since we used a retrospective review of the medical records, data reflecting other variables, such as level of education, recent immigration from areas where HIV is endemic and lifestyles, were not available. A head-to-head comparison between our study and others described in the literature may not be possible because of the nonuniformity of

study designs, methodological variations and difference in population characteristics. Causal inference cannot be drawn from our data because of the temporal ambiguity and our inability to identify the definite causes of jaundice in all patients from this retrospective data. There is a possibility of underreporting of the cases in our study probably because of undercoding in the medical records, and lack of information on patients with jaundice who possibly were unable to come to the hospital. Liver biopsies were done in only a very small number of our patients; hence, limiting our ability to identify precise liver pathology in the remaining patients with jaundice. Likewise, autopsies were done only in a few patients, and chart review may lack specificity in the underlying cause of death.

CONCLUSION

Our study shows that liver-associated enzyme abnormality was common among our patients with AIDS; however, jaundice was infrequent. Jaundice, when present, was associated with a high mortality; drugs, infections and alcohol were the common culprits among this population.

Future prospective studies of jaundice in AIDS patients that include adequate minority enrollment are needed to further examine the natural history and impact of early therapeutic interventions and possible preventive measures.

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