Acute Hepatitis E Infection Accounts for Some Cases of Suspected Drug-Induced Liver Injury

TIMOTHY J. DAVERN,* NAGA CHALASANI,‡ ROBERT J. FONTANA,§ PAUL H. HAYASHI,‖ PETR PROTIVA,¶ DAVID E. KLEINER,# RONALD E. ENGLE,** HANH NGUYEN,** SUZANNE U. EMERSON,** ROBERT H. PURCELL,** HANS L. TILLMANN,‡‡ JIEZHUN GU,‡‡ JOSE SERRANO,§§ and JAY H. HOOFNAGLE§§ for the Drug-Induced Liver Injury Network (DILIN)

*Department of Transplantation, California Pacific Medical Center, San Francisco, California; ‡Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; §Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan; ‖Department of Internal Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ¶Department of Medicine, Yale University School of Medicine, New Haven, Connecticut; #Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; **Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; ‡‡Duke Clinical Research Institute, Durham, North Carolina; and §§Liver Disease Research Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

This article has an accompanying continuing education activity on page e14. Learning Objective: Upon completion of this CME activity, successful learners will be able to better interpret data related to drug-induced liver injury.

See Covering the Cover synopsis on page 1539.

BACKGROUND & AIMS: The diagnosis of drug-induced liver injury relies on exclusion of other causes, including viral hepatitis A, B, and C. Hepatitis E virus (HEV) infection has been proposed as another cause of suspected drug-induced liver disease. We assessed the frequency of HEV infection among patients with drug-induced liver injury in the United States. **METHODS:** The Drug-Induced Liver Injury Network (DILIN) is a prospective study of patients with suspected drug-induced liver injury; clinical information and biological samples are collected to investigate pathogenesis and disease progression. We analyzed serum samples, collected from patients enrolled in DILIN, for immunoglobulin (Ig) G and IgM against HEV; selected samples were tested for HEV RNA. **RESULTS:** Among 318 patients with suspected drug-induced liver injury, 50 (16%) tested positive for anti-HEV IgG and 9 (3%) for anti-HEV IgM. The samples that contained anti-HEV IgM (collected 2 to 24 weeks after onset of symptoms) included 4 that tested positive for HEV RNA genotype 3. Samples from the 6-month follow-up visit were available from 4 patients; they were negative for anti-HEV IgM, but levels of anti-HEV IgG increased with time. Patients who had anti-HEV IgM were mostly older men (89%; mean age, 67 years), and 2 were human immunodeficiency virus positive. Clinical reassessment of the 9 patients with anti-HEV IgM indicated that acute hepatitis E was the most likely diagnosis for 7 and might be the primary diagnosis for 2. **CONCLUSIONS: HEV infection contributes to a small but important proportion of cases of acute liver injury that are suspected to be drug induced. Serologic testing for HEV infection should be performed, particularly if clinical features are compatible with acute viral hepatitis.**

Keywords: Liver Disease; Drug Toxicity; Treatment; Cirrhosis.

Drug-induced liver injury is the leading cause of acute liver failure and the primary reason for regulatory action leading to failed drug approval, market withdrawal, usage restrictions, and warnings to practicing physicians in the United States.[1] The diagnosis of drug-induced liver injury is often difficult because of the lack of specific biomarkers and the diversity of its clinical presentation.[2] The diagnosis is primarily one of exclusion and is made only after elimination of common causes of liver disease, such as alcoholic hepatitis, metabolic and genetic liver diseases, bile duct obstruction, and hepatitis A, B, and C virus infection.

Hepatitis E virus (HEV) infection is another cause of acute liver injury but is rarely considered in the differential diagnosis of drug-induced liver injury, largely because hepatitis E is believed to be rare in the Western world and unlikely to occur unless there is a history of recent travel to an endemic area such as Asia, Africa, or Central or South America.[3] Several recent findings have served to alter this opinion. First, indigenous cases of acute hepatitis E have been reported in the United States as well as Europe, Japan, and New Zealand caused by HEV genotype 3 strains, which are endemic to domestic and wild animals, particularly swine.[4–12] In addition, recent population-based surveys in the United States have shown that at least 20% of adults are reactive for immunoglobulin (Ig) G anti-HEV and thus have serologic evidence of previous HEV infection.[13,14] Finally, a publication from the United Kingdom suggested that up to 12% of cases of acute liver injury initially attributed to medications were actually due to unsuspected acute HEV infection.[15]

Abbreviations used in this paper: DILIN, Drug-Induced Liver Injury Network; HEV, hepatitis E virus; HIV, human immunodeficiency virus.

0016-5085/$36.00
doi:10.1053/j.gastro.2011.07.051

The aims of the current study were to assess whether acute hepatitis E accounts for some cases of suspected drug-induced liver injury in the United States and whether testing for HEV infection is warranted in the routine evaluation of patients with acute liver disease of unknown cause.

Patients and Methods

Patient Identification and Causality Analysis

The Drug-Induced Liver Injury Network (DILIN) consists of multiple (previously 5, and currently 8) US clinical sites and a data coordinating center that have enrolled patients with suspected drug-induced liver injury into a prospective study since 2004. The rationale, design, and conduct of the DILIN, as well as a summary of the first 300 enrolled cases, have been described.[16,17] All enrolled cases were subjected to formal causality assessment independently by 3 investigators, and a final causality score was obtained by consensus.[18] At the same time, a Roussel Uclaf Causality Assessment score[19] was determined and cases were graded for severity using a 5-point scale developed by the DILIN.[16]

Serologic and Virologic Testing

Serum samples were obtained at the time of enrollment, which might be as long as 6 months after the onset of liver injury, and stored at −80°C in a central repository. For the current study, serum samples from the first 318 patients enrolled were tested for IgM and IgG anti-HEV using enzyme immunoassays of established sensitivity and specificity.[20,21] Samples with IgM anti-HEV and those with strongly positive reactions for IgG anti-HEV were further tested for HEV RNA using nested reverse-transcription polymerase chain reaction,[22] and the polymerase chain reaction products were separated by electrophoresis on ethidium bromide–stained agarose gels, extracted from the gel, and directly sequenced to provide the consensus sequence. A BLAST search of GenBank nucleotide sequences was performed to determine HEV genotype. Details of the enzyme-linked immunosorbent assays for anti-HEV and the polymerase chain reaction for HEV RNA are provided in Supplementary Materials and Methods.[23,24]

Histologic Analysis

When available, liver biopsy specimens (n = 3) were reviewed by a hepatic pathologist (D.E.K.) who was unaware of the medications implicated and results of HEV testing. Histologic features of inflammation, fibrosis, steatosis, cholestasis, vascular injury, and other findings were systematically recorded, along with a description of the overall pattern of injury.

Repeat Causality Analysis

Cases positive for HEV IgM were subjected to repeat causality analysis by 3 independent reviewers after the results of HEV serologic and reverse-transcription polymerase chain reaction testing were available. Cases were again judged for the likelihood that the implicated medication was responsible for the liver injury as "definite" (>95% likelihood), "highly likely" (75%–94%), "probable" (50%–74%), "possible" (25%–49%), or "unlikely" (<25%).[18] Cases were also judged using the same scale as to the likelihood that the liver injury was due to acute hepatitis E based on the clinical, biochemical, and histologic findings.

Data Analysis

Pairwise comparisons were performed between the cases with no serologic evidence of HEV infection versus patients with evidence of active or recent HEV infection (defined by presence of HEV IgM) and those with distant and resolved HEV infection (defined by presence of IgG without IgM anti-HEV). The Wilcoxon test was used for continuous variables, Fisher exact test for binary outcomes, and Pearson χ^2 test for other categorical variables.

Institutional Review Board Approval

All details of the DILIN prospective study were reviewed and approved by the institutional review boards of each clinical site and the data coordinating center. Each enrolled subject signed an informed consent that allowed future testing on archived biosamples. In addition, the protocol for anti-HEV testing was specifically approved by the institutional review board of the National Institute of Allergy and Infectious Diseases of the Intramural Program of the National Institutes of Health.

Results

Serologic Testing

Among 318 patients tested, 50 (16%) were reactive for IgG anti-HEV, 9 (3%) of whom were also reactive for IgM anti-HEV. The demographic and clinical features of patients with both IgG and IgM anti-HEV (group 1, n = 9), with IgG anti-HEV alone (group 2, n = 41), and with no markers of HEV infection (group 3, n = 268) are shown in Table 1. Comparing the 3 groups, patients with anti-HEV reactivity were on average older (67 and 62 vs 47 years; both comparisons $P = .001$) and those with IgM anti-HEV were more often men (89% vs 44% vs 39%; $P = .003$). Initial and peak serum bilirubin, alanine aminotransferase (ALT), and alkaline phosphatase levels were similar in the 3 groups of patients. Furthermore, the 3 groups did not differ in distribution of pattern of elevated serum enzyme levels, severity scores, or causality scores.

Demographic and Clinical Features of IgM Anti-HEV–Positive Cases

Selective demographic and clinical features of the 9 IgM anti-HEV–positive cases are given in Table 2, and detailed case summaries of each patient are provided as Supplementary Data. The cases included 8 men and 1 woman; 8 were non-Hispanic white subjects, and 1 was multiracial. The average age was 67 years (range, 42–83 years). Initial serum bilirubin levels ranged from 0.4 to 15.1 mg/dL (mean, 7.0 mg/dL), and peak levels were only slightly higher (mean, 10.8 mg/dL). Initial ALT levels ranged from 196 to 3838 U/L (mean, 1073 U/L) and alkaline phosphatase levels from 113 to 632 U/L (mean, 225 U/L). Based on calculation of the R score (ALT divided by alkaline phosphatase, both expressed as multiple of the upper limit of the normal range[19]), the biochemical pattern of serum enzyme elevations was hepatocellular (R > 5) in 5, cholestatic in 1 (R < 2), and "mixed" in 3 (R 2–5). Three patients gave a history of fever and one of

CLINICAL LIVER