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BRIEF ARTICLE

Clinical features and risk factors of acute hepatitis E with severe jaundice

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Abstract

AIM: To compares the clinical features of patients infected with hepatitis E virus (HEV) with or without severe jaundice. In addition, the risk factors for HEV infection with severe jaundice were investigated.

METHODS: We enrolled 235 patients with HEV into a cross-sectional study using multi-stage sampling to select the study group. Patients with possible acute hepatitis E showing elevated liver enzyme levels were screened for HEV infection using serologic and molecular tools.HEV infection was documented by HEV antibodies and by the detection of HEV-RNA in serum. We used χ^2 analysis, Fisher's exact test, and Student's *t* test where appropriate in this study. Significant predictors in the univariate analysis were then included in a forward, stepwise multiple logistic regression model.

RESULTS: No significant differences in symptoms, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or hepatitis B virus surface antigen between the two groups were observed. HEV infected patients with severe jaundice had significantly lower peak serum levels of γ-glutamyl-transpeptidase (GGT) (median: 170.31 U/L *vs* 237.96 U/L, P = 0.007), significantly lower ALB levels (33.84 g/L *vs* 36.89 g/L, P = 0.000), significantly lower acetylcholine esterase (CHE) levels (4500.93 U/L *vs* 5815.28 U/L, P = 0.000) and significantly higher total bile acid (TBA) levels (275.56 μmol/L *vs* 147.03 μmol/L, P = 0.000) than those without severe jaundice. The median of the lowest point time tended to be lower in patients with severe jaundice (81.64% *vs* 96.12%, P = 0.000). HEV infected patients with severe jaundice had a significantly higher viral load (median: 134 *vs* 112, P = 0.025) than those without severe jaundice. HEV infected patients with severe jaundice showed a trend toward longer median hospital stay (38.17 d *vs* 18.36 d, P = 0.073). Multivariate logistic regression indicated that there were significant differences in age, sex, viral load, GGT, albumin, TBA, CHE, prothrombin index, alcohol overconsumption, and duration of admission between patients infected with acute hepatitis E with and without severe jaundice.

CONCLUSION: Acute hepatitis E patients may naturally present with severe jaundice.

Key words: Hepatitis E virus; Acute hepatitis E; Clinical features; Severe jaundice; Risk factor

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INTRODUCTION

Although hepatitis E was recognized as a new disease in 1980, the virus was first visualized in 1983 and its genome was cloned and characterized in 1991, however, the disease is probably ancient but was not recognized until modern times[1-6]. Hepatitis E is the most important or the second most important cause of acute clinical hepatitis in adults throughout Asia, the Middle East and Africa[1]. Hepatitis E virus (HEV) is a small round RNA-containing virus that is the only member of the genus Hepevirus in the family Hepeviridae[7]. The clinical course of hepatitis E is usually more severe than hepatitis A, and is frequently complicated by protracted coagulopathy and cholestasis. HEV accounts for more than 50% of acute viral hepatitis in young adults in developing countries[8]. The disease course is benign, and severe jaundice is rarely reported. Severe icteric forms are unusual in patients without cirrhosis and have been documented in immunocompromised patients[9]. These cases did not progress to fulminant hepatitis or severe acute hepatitis. However, the differences in the demography, mode of transmission, and clinical features of patients infected with HEV with and without severe jaundice have not been sufficiently studied. Thus, the present study was designed to determine the clinical features and risk factors of acute hepatitis E with severe jaundice in patients without cirrhosis. Jaundice was very marked in all patients. HEV infection was documented by HEV antibodies and by the detection of HEV-RNA in serum. Here, we studied a well-characterized population of HEV-infected individuals enrolled in a large Chinese cohort study. Acute HEV in our patients was characterized by severe jaundice with serum bilirubin levels above 171 μmol/L.

MATERIALS AND METHODS

Patients

Between December 2005 and December 2010, we diagnosed 235 cases of acute hepatitis E at Beijing YouAn Hospital affiliated to Capital Medical University in Beijing. Patients with possible acute hepatitis E showing elevated liver enzyme levels were screened for HEV infection using serologic and molecular tools. Biliary tract complications were ruled out by abdominal ultrasonography. Toxin- and drug-related causes of abnormal liver function tests were ruled out by patient history. 235 patients tested positive for serum HEV RNA. Serum samples which had been stored frozen (or below -20 ℃) were thawed prior to analysis. The samples were screened for immunoglobulin M (IgM) antibody to hepatitis A virus (Axsym System, Abbott), hepatitis B virus surface antigen (HBsAg), IgM antibody to hepatitis B core antigen (Axsym System, Abbott), polymerase chain reaction for HBV DNA and antibody to hepatitis C virus (Axsym System, Abbott). Subsequently, the serum was also tested for IgM anti-Epstein-Barr virus antibody [anti-HEV IgM, enzyme-linked immunosorbent assay (ELISA), Biotest], and IgM anti-cytomegalovirus antibody (Axsym System, Abbott). Diagnosis of drug-induced hepatitis was based on patient history and clinical course; the lymphocyte stimulation index for drugs was used as an adjunct. Acute hepatitis of unknown etiology was a diagnosis of exclusion. Acute hepatitis E was defined by the presence of HEV RNA in acute-phase sera. Drugs and alcohol were excluded as likely etiological agents by patient history and a review of patient medications. Other causes of liver disease were excluded by testing for serum ceruloplasmin, 24-h urinary copper, antinuclear antibody, antismooth muscle antibody, serum iron and iron-binding capacity and alpha-1 antitrypsin levels.

We enrolled 235 patients with HEV. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board at each institution. Informed consent was obtained from each patient.

Epidemiological survey and laboratory examinations

All patients enrolled in the study provided detailed medical history, including general data such as age, sex, onset of illness, travel history before onset of illness, history of blood transfusion, alcohol intake, medicine use, and disease complications. Acute hepatitis E with severe jaundice was defined as total bilirubin > 171 μmol/L. In this study, an underlying disease was defined as an active illness where the patient had received medical care before the onset of hepatitis. Overconsumption of alcohol was defined as daily ethanol ingestion over 50 g for 5 years or longer. To minimize recall bias and/or interview bias, we performed the following: we visited each patient at home twice in 3 mo and using an open-ended questionnaire assisted them to recall their daily ingestion and/or alcohol intake during the 2 mo preceding the onset of illness, and compared that with their current eating and drinking habits. In the laboratory examinations, total bilirubin, bilirubin direct, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), albumin (ALB), acetylcholine esterase (CHE), total bile acid (TBA) and prothrombin index (PTA) were measured, using a sequential multi-autoanalyzer at each hospital.

Detection of anti-HEV IgM

Serum samples were tested for HEV IgG and IgM using a commercial ELISA kit (Wan Tai Pharmaceutical Co., Beijing, China) produced with two recombinant peptides corresponding to amino acid residues 396-603 of the major structural protein specified by open reading frame 2 of the HEV genome. The sensitivity and specificity of the ELISA kit was demonstrated by Zhang *et al*[10]. Serum samples were tested according to the manufacturer's instructions with three negative and positive control wells included on each plate. The samples with an optical density less than the cutoff value (cutoff value for IgG was equal to the mean optical density for the three negative controls on each plate plus 0.12, and the cutoff value for IgM was equal to the mean optical density for the three

Table 1 Comparison of background characteristics and clinical manifestations, laboratory data and outcome

	Acute hepatitis E with severe jaundice	Acute hepatitis E without severe jaundice	*P* value
Characteristic			
Age, yr, mean (range)	56 (20-85)	51 (18-85)	0.015
Sex, men, *n* (%)	64 (70)	125 (165)	0.003
Occupation, *n* (%)			
Handling with animals	0	0	
Handling with raw food	0 (70)	5 (165)	0.580
Underlying disease	4 (70)	32 (165)	0.008
History, *n* (%)			
Blood transfusion	0	0	
Intake wild animals	0	0	
Intake raw pig liver or intestine	0	0	
Intake raw fish or shellfish	0 (70)	5 (165)	0.580
Alcohol overconsumption	27 (70)	16 (165)	0.003
Clinical features			
Symptoms (%)			
Fever	1.47 ± 0.737	1.35 ± 0.725	0.243
Jaundice	1.00 ± 0.000	1.01 ± 0.029	0.892
Laboratory data			
Peak ALT (U/L)	1089.23 ± 1607.77	1035.53 ± 869.49	0.741
Peak AST (U/L)	660.83 ± 675.99	604.34 ± 715.72	0.574
Peak TBil (μmol/ L)	276.31 ± 91.63	78.70 ± 48.06	0.000
Peak DBil (μmol/ L)	185.06 ± 64.64	48.52 ± 35.16	0.000
Lowest ALB (g/L)	33.84 ± 3.72	36.89 ± 4.76	0.000
Peak GGT (U/L)	170.31 ± 117.55	237.96 ± 181.18	0.007
Peak ALP (U/L)	184.96 ± 67.22	187.76 ± 89.82	0.826
Peak CHE (U/L)	4500.93 ± 175.32	5815.28 ± 151.04	0.000
Peak TBA	275.56 ± 28.81	147.03 ± 10.53	0.000
HBsAg	8 (69)	27 (159)	0.203
Lowest PTA (%)	81.64 ± 22.69	96.12 ± 24.63	0.000
PT ≤ 60%, *n* (%)	7 (60)	11 (146)	0.424
Viral load	134 ± 68	112 ± 69	0.025
Duration for admission (d)	38.17 ± 17.13	18.36 ± 91.35	0.073

TBil: Total bilirubin; DBiL: Bilirubin direct; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl-transpeptidase; ALP: Alkaline phosphatase; ALB: Albumin; CHE: Acetylcholine esterase; TBA: Total bile acid; PTA: Prothrombin index; PT: Point time; HBsAg: Hepatitis B virus surface antigen.

negative controls on each plate plus 0.26) were considered negative. Samples with an optical density greater than or equal to the cutoff value were tentatively considered reactive and were retested in duplicate to confirm the result.

Detection of HEV RNA

Using the QIAamp RNA Blood Mini Kit (QIAGEN, Germany), RNA was reverse transcribed into cDNA with 10 units of AMV Reverse Transcriptase (Promega, Madison, WI, United States) at 42 ℃ for 60 min. The primers used in this study were synthesized as previously described[10]. The primer positions indicated below are relative to the HEV strain JYI-Chisai01C (GenBank accession number AB 197674): P1: 5'AAC(T)TATGC ACAGCCGGGTTG3' (forward position 5725-5746) P2: 5'CCCTTATCCTGCTGAGCATTCTC3' (reverse position 6433-6455); P3: 5'GTC(T)ATGC(T)TC(T)TGC ATACATGGCT-3' (forward position 6010-6031) P4: 5' AGCCGACGAAATC(T)AATTCTGTC-3' (reverse position 6336-6357). The first round of polymerase chain reaction (PCR) was carried out in a 50 μL reaction volume with 8 μL cDNA, 25 pmol of each primer (P1, P2), 1 μL of 10 mmol/L dNTPs, and 0.5 μL TaKaRa Ex Taq polymerase. PCR was conducted for 35 cycles at 94 ℃ for 1 min, 55 ℃ for 45s and 72 ℃ for 1 min with a final extension time of 72 ℃ for 7 min. The second round reaction were carried out in a 50 μL volume with 8 μL of the first-round product, 25 pmol of each primer (P3/P4), and 0.5 μL TaKaRa Ex Taq polymerase. The parameters were the same as the first round. The second-round PCR products were separated by 2% agarose gel.

Statistical analysis

We used χ^2 analysis, Fisher's exact test, and Student's *t* test where appropriate in this study. Significant predictors in the univariate analysis were then included in a forward, stepwise multiple logistic regression model. A *P* value of < 0.05 was considered statistically significant; all tests were two-tailed. Data were analyzed using the statistical software StatView for Macintosh (Version 5.0 StatView, SAS Institute Inc., NC, United States).

RESULTS

Patients infected with HEV: Characteristics, laboratory data and outcome

Of the 235 patients with acute hepatitis E, 70 were diagnosed with acute hepatitis E and severe jaundice and 165 were diagnosed with acute hepatitis E without severe jaundice. Of the patients with acute hepatitis E and severe jaundice, 64 were male and 6 were female (all non-pregnant) with a median age of 56 years (range: 20-85years). Twenty-seven (39%) of these patients demonstrated alcohol overconsumption. Of the patients with acute hepatitis E without severe jaundice, 125 were male and 40 were female (all non-pregnant) with a median age of 51 years. Sixteen (10%) of these patients demonstrated alcohol overconsumption.

Comparison between patients infected with HEV

Comparison of baseline characteristics between the two groups. A comparison of characteristics between acute hepatitis E patients with severe jaundice and acute hepatitis E patients without severe jaundice is shown in Table 1.

There were significant differences in age and the male-female ratio between the two groups. There were no significant differences in occupation, history of traveling to endemic areas, blood transfusion, or the presence of underlying disease(s) between the two groups. Overconsumption of alcohol was observed in a higher proportion of patients infected with severe jaundice compared with those without severe jaundice (27/70 *vs* 16/165, $P = 0.003$). None of the patients had a history of ingesting raw wild deer, boar, bear or rabbits, or a history of blood transfusion, ingestion of raw pig liver, and/or undercooked pig intestines before the onset of illness. There were no significant differences in the intake of raw fish or shellfish between the two groups.

Table 2 Relation between acute hepatitis E with severe jaundice and risk factors

Risk factors	SE	*P* value	OR	95%CI
Viral load	0.002	0.026	1.005	1.001-1.009
Age	0.011	0.016	1.026	1.005-1.048
Sex	0.464	0.008	0.291	0.117-0.772
Fever	0.203	0.243	1.268	0.851-1.888
ALT	0.000	0.741	1.000	1.000-1.000
AST	0.000	0.573	1.000	1.000-1.001
GGT	0.001	0.009	0.997	0.995-0.999
ALP	0.002	0.825	1.000	0.996-1.003
ALB	0.036	0.000	0.857	0.799-0.919
TBA	0.001	0.000	1.006	1.004-1.009
CHE	0.000	0.000	1.000	0.999-1.000
PTA	0.007	0.000	0.975	0.963-0.988
HBsAg	0.431	0.303	1.560	0.670-3.632
Alcohol overconsumption	0.309	0.003	2.476	1.350-4.542
Duration for admission	0.009	0.000	1.038	1.020-1.056

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl-transpeptidase; ALP: Alkaline phosphatase; ALB: Albumin; CHE: Acetylcholine esterase; TBA: Total bile acid; PTA: Prothrombin index; HBsAg: Hepatitis B virus surface antigen; OR: Odds ratio.

Comparison of clinical features between the two groups

The clinical features of the study population are shown in Table 1. There were no significant differences in symptoms, ALT, AST, ALP, or HBsAg between the two groups. HEV infected patients with severe jaundice had significantly lower peak serum levels of GGT (median: 170.31 U/L *vs* 237.96 U/L, $P = 0.007$), significantly lower ALB levels (33.84 g/L *vs* 36.89 g/L, $P = 0.000$), significantly lower CHE levels (4500.93 U/L *vs* 5815.28 U/L, $P = 0.000$) and significantly higher TBA levels (275.56 μmol/L *vs* 147.03 μmol/L, $P = 0.000$) than those without severe jaundice. The lowest median PT tended to be lower in the severe jaundice group (81.64% *vs* 96.12%, $P = 0.000$). The proportion of patients with PT ⩽ 60% was not significantly different in the severe jaundice group (7/60 *vs* 11/146, $P = 0.424$). HEV infected patients with severe jaundice had a significantly higher viral load (median: 134 *vs* 112, $P = 0.025$) than those without severe jaundice. HEV infected patients with severe jaundice showed a trend toward longer median hospital stay (38.17 d *vs* 18.36 d, $P = 0.073$).

Relation between acute hepatitis E with severe jaundice and risk factors

The multivariate logistic regression analysis indicated that there were significant differences in age, sex, viral load, GGT, ALB, TBA, CHE, PTA, alcohol overconsumption, and duration of admission between acute hepatitis E patients with and without severe jaundice. The relations between acute hepatitis E patients with severe jaundice and risk factors are shown in Table 2.

DISCUSSION

Clinically, HEV usually causes a self-limiting illness, with an average incubation period of 40 d, moderate jaundice, and complete resolution of hyperbilirubinemia and normalization of aminotransferases within 1-6 wk. Laboratory findings in patients with HEV are also similar to other forms of viral hepatitis and include elevated serum bilirubin, alanine aminotransferase, aspartate transaminase, alkaline phosphatase, and gamma-glutamyl-transferaselevels[11]. The cases presented here are exceptional in that some patients had severe jaundice. We report 70 cases of acute hepatitis E with severe jaundice, no pruritus, normal serum creatinine levels, and normal PTA. Most cases of acute hepatitis E do not have severe jaundice. In this study, 70 of 235 cases with acute hepatitis E had severe jaundice. Our report is rather unique in that detailed personal interviews were performed to explore patients' exposures which may not have been recalled when the patient was originally investigated for hepatitis E. We maintained an attitude of strict neutrality during the interview to minimize recall bias and/or interview bias. The characteristics of the patients with hepatitis E and severe jaundice included in our study are summarized as follows: many patients were 4060 years of age, similar to endemic cases reported in Asia[12,13], 64 patients (90%) were male; none of the patients had a history of ingesting wild animal meat or undercooked intestines. Raw or partially cooked shellfish are a common cause of HEV infection as shellfish filter large volumes of water. Five patients (7%) had a history of ingesting raw fish or shellfish. Four patients seemed to have underlying diseases. Recently, Mizuo *et al*[14] reported that the presence of underlying disease(s) influence the severity of hepatitis E. The presence of underlying diseases was also significantly different between patients with severe jaundice and patients without severe jaundice. Sixteen patients (10%) demonstrated alcohol overconsumption. In our series, patients with severe jaundice consumed alcohol on a regular basis compared to those without severe jaundice, there were also significant differences in other background characteristics between the two groups. Alcohol overconsumption, however, was not associated with illness severity. Whether overconsumption of alcohol is associated with susceptibility to acute hepatitis E requires further research.

Physical examination revealed 235 icteric subjects, in otherwise good health, with no signs of hepatic failure. Specifically, there was no history of medication or drug use, and the patients denied taking any herbal supplements. Cholelithiasis is an unlikely explanation for jaundice, as there was no evidence of cholecystitis found on repeat imaging studies or during surgery, and there was no evidence of choledocholithiasis. There were no significant differences in symptoms, ALT, AST, ALP, or HBsAg between the two groups. Patients with severe jaundice showed more severe clinical manifestations (including laboratory data such as ALB, CHE and TBA levels, PTA and duration of hospital stay) than those without severe jaundice. Patients with severe jaundice had significantly lower peak serum GGT levels ($P = 0.007$) which requires further research. The proportion of patients with PT ⩽ 60%, however, was not significantly different between the two groups. Bernardin *et al*[15] reported that the severity of

hepatitis E was related to dose of the virus. We found that patients with severe jaundice had a significantly higher viral load than those without severe jaundice. The mechanisms underlying the development of severe jaundice during acute hepatitis E are likely to be multifactorial. It is well known that inflammatory liver cell necrosis is a factor in jaundice in the setting of acute viral hepatitis. Other cofactors of hyperbilirubinemia may include concomitant etiologies such as autoimmune cholangitis and accentuation of preoperative jaundice after laparotomy [16,17]. Such cofactors can be ruled out in our patients as none of the patients underwent abdominal surgery, and autoimmune cholangitis is unlikely since serum autoantibodies were absent. It is therefore possible to hypothesize that HEV itself had a direct effect on the development of high-grade hyperbilirubinemia in these patients. Some data indicate that HEV has not only hepatocytic but also biliary tropism, and replicates within bile epithelial cells[18-20]. However, the mechanisms underlying high-grade hyperbilirubinemia in HEV infection remain unclear.

According to our results, age, sex, GGT, ALB, CHE, TBA, viral load, and alcohol overconsumption seem to be risk factors affecting patients with acute HEV and severe jaundice (odds ratio = 1.026, 0.291, 0.997, 0.857, 1.000, 1.006, 1.005 and 2.476, respectively). In multivariate analysis, fever symptoms, ALT, AST, ALP, and HBsAg were not significant risk factors for acute HEV infection with severe jaundice. Taking into account that the majority of HEV infections in endemic areas are caused by genotype 1, a definitive picture of the differences in acute HEV infected patients with severe jaundice according to the genotype need to be obtained from more in-depth studies.

In conclusion, patients with acute hepatitis E may naturally present with severe jaundice. However, further clinical, epidemiological and virological studies are needed to elucidate HEV infection with severe jaundice and the association between HEV genotype and severe jaundice as well as its underlying mechanism.

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COMMENTS

Background

Clinically, hepatitis E virus (HEV) usually causes a self-limiting illness, with an average incubation period of 40 d, moderate jaundice, and complete resolution of hyperbilirubinemia and normalization of aminotransferases within 1-6 wk. Laboratory findings in patients with HEV are also similar to other forms of viral hepatitis and include elevated serum bilirubin, alanine aminotransferase, aspartate transaminase, alkaline phosphatase, and gamma-glutamyl-transferase levels. The clinical course of hepatitis E is usually more severe than hepatitis A, and is frequently complicated by protracted coagulopathy and cholestasis.

Research frontiers

HEV accounts for more than 50% of acute viral hepatitis in young adults in developing countries. Severe icteric forms are unusual in patients without cirrhosis and have been documented in immunocompromised patients. These cases did not progress to fulminant hepatitis or severe acute hepatitis. However, the differences in the demography, mode of transmission, and clinical features of patients infected with HEV with and without severe jaundice have not been sufficiently studied.

Innovations and breakthroughs

In this study, 70 of 235 cases with acute hepatitis E had severe jaundice, no pruritus, normal serum creatinine levels, and normal prothrombin index. Most cases of acute hepatitis E do not have severe jaundice. The report is rather unique in that detailed personal interviews were performed to explore patients' exposures which may not have been recalled when the patient was originally investigated for hepatitis E. The authors maintained an attitude of strict neutrality during the interview to minimize recall bias and/or interview bias.

Applications

The study was designed to determine the clinical features and risk factors of acute hepatitis E with severe jaundice in patients without cirrhosis. Jaundice was very marked in all patients. Acute HEV in the patients was characterized by severe jaundice with serum bilirubin levels above 171 μmol/L. These patients with severe jaundice might represent true cases of acute hepatitis E.

Terminology

The HEV is a small, non-enveloped, icosahedral, positive-sense, single-strand RNA virus. HEV is responsible for the majority of cases of what was previously called enterically transmitted non-A, non-B hepatitis. Hepatitis E is endemic in many subtropical and tropical areas. In these areas, hepatitis E occurs both epidemically and sporadically. Hepatitis E is a selflimiting disease of varying severity, presenting as acute, icteric hepatitis, with clinical and morphological findings similar to those of hepatitis A. Recent studies have found immunoglobulin G to HEV in several wild and domestic animal species native to developing and industrialized countries.Molecular evidence for natural HEV infection in swine has been reported for HEV-endemic and -nonendemic countries worldwide.

Peer review

The paper describes the characteristics of patients with a more severe jaundice than the remainder of the group.

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