MAJOR ARTICLE

A Study of Viral Hepatitis E Infection in a Tertiary Care Hospital in Mysore, South India

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Background. In this study, we aimed to explore the clinical and epidemiological profile of all patients with hepatitis E virus (HEV) who were admitted to a tertiary care hospital in Mysore, India and to further assess various factors that influence the prognosis of these patients.

Methods. Two hundred ninety patients with HEV infection were included in the study and interviewed. They were subjected to clinical examination and laboratory investigations, including complete hemogram, renal, and liver function tests. Viral markers for HBV, HAV, HCV, and HEV by hepatitis B surface antigen, anti-HAV, anti-HCV, and anti-HEV antibodies, respectively, were done using the enzyme-linked immunosorbent assay method. Final outcome was recorded in the form of discharge or death.

Results. Males had higher (82.8%) incidence of HEV infection. Yellowish discoloration of urine was the most common symptom, and icterus was the most common sign at presentation. Hepatomegaly was most common finding on abdominal examination. Mean duration of hospital stay was higher among diabetics (10 days vs 7.11 ± 3.52 days). Overall, mortality observed was 3.45%. A higher mean age ($P = .000$) and duration of hospital stay ($P = .000$) were associated with higher mortality. Mortality was significantly higher among patients with alcohol abuse (25% vs 0%) ($P = .004$). Higher mean prothrombin time-international normalised ratio (PT-INR) (1.6 ± 0.13 vs 1.21 ± 0.32), total bilirubin (20.3 ± 5.08 vs 11.33 ± 7.26 mg/dL), and direct bilirubin (15.05 ± 3.64 vs 6.35 ± 3.71 mg/dL) were associated with higher mortality, whereas lower mean serum albumin (2.6 ± 0.11 vs 3.41 ± 0.40 gm/dL) was associated with higher mortality. Increase in renal parameters (ie, urea [97 ± 33.48 vs 32.43 ± 18.41 mg/dL] and creatinine [2.9 ± 1.38 vs 1.12 ± 0.64 mg/dL]) and electrolyte imbalances (ie, hyperkalemia [5.95 ± 1.21 vs 4.29 ± 0.51 mmol/L] and hyponatremia [123 ± 3.56 vs 136.04 ± 2.97 mmol/L]) were associated with higher mortality. There were 20-fold increases in mean serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) values (SGPT: SGOT = 1.148) and a 1-fold increase in mean alkaline phosphatase.

Conclusions. Higher mean age, duration of hospital stay, PT-INR, total bilirubin, direct bilirubin, blood urea, serum creatinine, potassium values, alcohol abuse, presence of ascites, and fulminant hepatitis were associated with higher mortality, whereas lower mean serum albumin and sodium values were associated with higher mortality. Diabetics had a higher mean duration of hospital stay.

Keywords. abnormal liver function tests (SGPT:SGOT >1); alcohol abuse; diabetes mellitus; hyponatremia and hyperkalemia; abnormal renal functions; hepatitis E.

Hepatitis E virus (HEV) is a positive-sense, single-stranded RNA icosahedral virus with a 7.5 kilobase genome. Hepatitis E virus has a fecal-oral transmission route, especially in developing countries. It is one of the five known hepatitis viruses. Initially classified in the Caliciviridae family, the virus has since been classified in the genus hepevirus [1]. This type of hepatitis, identified in India, Asia, Africa, the Middle East, and Central America, resembles infection with HAV in its primarily enteric mode of spread. The commonly recognized cases occur

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after contamination of water supplies seen after monsoon flooding, although sporadic or isolated cases can occur. Globally, 57 000 deaths and 3.4 million cases of acute hepatitis E are attributable to infection with HEV genotypes 1 and 2. Over 60% of all hepatitis E infections and 65% of all hepatitis E deaths occur in East and South Asia, where seroprevalence rates of 25% are common in some age groups. An epidemiologic feature that distinguishes HEV from other enteric agents is the rarity of secondary person-to-person spread from infected persons to their close contacts. Infections arise in populations that are immune to HAV and usually are seen in young adults [2]. In endemic areas, the prevalence of antibodies to HEV is 40%. In nonendemic areas of the world, such as the United States, clinically apparent acute hepatitis E is extremely rare; however, the prevalence of antibodies to HEV can be as high as 20% among high-risk groups such as homosexual men (15.9%), intravenous drug abusers (23%), and blood donors (21.3%) [2, 3]. The seroprevalence of HEV in the civilian noninstitutionalized US population from 1988 through 1994 was 21.0% (95% confidence interval, 19.0%–22.9%) [4]. Also, persistent infection of hepatitis E has been documented in liver transplant recipients. Epidemics of hepatitis occur frequently in the Indian subcontinent and are mostly due to HEV [5–7]. Previously reported epidemics of viral hepatitis occurred in Delhi and Kanpur [8, 9]. A study done in Central China showed higher mortality among patients with cirrhosis of liver [10]. Hepatitis E outbreak in India and Asia has a case fatality rate of 1%–2% in normal population and 10%–20% in pregnant women [2]. In view of increased reporting of cases of hepatitis E in our hospital, and because there were no reports like this earlier, a study of clinical and epidemiological profile of hepatitis E and its outcome was undertaken.

The aim of this study was to explore the clinical and epidemiological profile of all the Hepatitis E patients getting admitted to tertiary care hospital in Mysore, India and to further assess various factors that influence the prognosis of these patients.

Inclusion criteria were as follows: patients who visited JSS Hospital during the study period and who had symptoms of acute hepatitis; patients who were positive for HEV and were admitted to hospital; and patients who consented to participate in the study. Patients who belonged to pediatric age group (<18 years of age) were excluded.

MATERIALS AND METHODS

In 2012, as there were increased number of cases affected with viral hepatitis E in Mysore, a prospective observational study was conducted. Three hundred seventy-four patients were diagnosed with HEV infection using IgM anti-HEV enzyme-linked immunosorbent assay (ELISA) kits (manufactured under license from ImmunoVision USA, marketed by Amar Immunodiagnostics, Hyderabad, Andhra Pradesh, India) during a 2-year from January 2011 to December 2012 at JSS Hospital, Mysore. Among these patients, two hundred and ninety consecutive patients were admitted to the hospital and included in the study.

All of the patients who presented with features of acute hepatitis were included in study, interviewed, and subjected to clinical and laboratory examination. History obtained includes complaints with which the patient presented, food habits, alcohol abuse, and any other significant past history. Clinical examination components included general physical examination and systemic examination, with special emphasis on presence of jaundice, blood pressure, presence of organomegaly and ascites, and presence of signs of hepatic encephalopathy. Investigations did include complete hemogram, renal, and liver function tests. Viral markers for HBV, HAV, HCV, HEV were done by hepatitis B surface antigen (HBsAg), anti-HAV, anti-HCV, and anti-HEV antibodies, respectively (ELISA). Criteria for discharge were symptomatic improvement, patients feeling better, and normalization of liver function tests (progressive decline in the level of liver enzymes) repeated every 72 h. Final outcome was recorded in the form of discharge or death.

Statistical Analysis

History, clinical, and biochemical data were collected. Data were analyzed using SPSS version 15.0. A χ^2 test was applied to identify statistical significance between various categorical variables. An independent sample t test was used to compare the difference between mean quantitative parameters between those subjects who died to those who survived. A P value <.05 was considered statistically significant.

RESULTS

This study included 290 patients with proven HEV infection by anti-HEV-ELISA. The mean age of patients was 45.59 ± 14.4 years. Two hundred forty (82.8%) patients were males. The patient characteristics included demographic profile, age, duration of hospital stay, and clinical presentation and are illustrated in Table 1.

Two hundred thirty (79.3%) patients presented with yellowish discoloration of urine. The number of patients presenting with jaundice (sclera), fever, loss of appetite, myalgias, and dyspepsia were 205 (70.7%), 150 (51.1%), 90 (31%), 60 (20.7%), and 25 (8.6%), respectively. Two hundred eighty (96.6%) patients had icterus, whereas pedal edema and pallor were seen in 60 (20.7%) and 30 (10.3%) patients, respectively. Hepatomegaly was present in 175 (60.3%) patients, whereas ascites and splenomegaly were seen in 30 (6.9%) and 15 (5.2%) patients, respectively. Flapping tremors were observed in 30 (10.3%) patients. Ten (3.4%) patients had HBsAg positivity in addition to anti-HEV positivity. Mean duration of hospital stay was higher among the patients with HBV coinfection (9 days vs 7.14 ± 3.54 days) and patients with

Table 1. Demographic Profile of 290 Patients

Patient Characteristics	Numbers
Mortality	10 (3.45%)
Age (mean)	45.59 ± 14.4 years
Duration of hospital stay (mean)	15 ± 5.78 days
Yellowish discoloration of urine	230 (79.3%)
Jaundice	205 (70.7%)
Fever	150 (51.1%)
Loss of appetite	90 (31%)
Myalgia	60 (20.7%)
Dyspepsia	25 (8.6%)
Alcohol consumption	80 (27.6%)
Icterus	230 (96.6%)
Pedal edema	60 (20.7%)
Anemia	30 (10.3%)
Hepatomegaly	175 (60.3%)
Splenomegaly	15 (5.2%)
Ascites	20 (6.9%)
Fulminant hepatitis	30 (10.3%)

diabetes mellitus (10 days vs 7.11 ± 3.52 days). Thirty (10.3%) patients had fulminant hepatitis (33.45% vs 0%; $P = .001$). Incidence of fulminant hepatitis was higher in patients with history of alcohol abuse (25% vs 4.8%). Eighty (27.6%) patients had a history of alcohol abuse. Mortality was significantly higher among alcoholics who have evidence of alcoholic liver disease (ALD) compared with nonalcoholics (12.5% vs 0%; $P = .004$).

Ten (3.45%) patients died among 290 patients included in the study. Mean age among the patients who died was 69 ± 12.7 years, whereas it was 43.85 ± 12.97 years among the patients who were discharged ($P = .001$). Mean duration of hospital stay was 15 ± 5.78 days among the patients who died, whereas it was 6.63 ± 2.52 among the patients who were discharged ($P = .000$). A mean prothrombin time-international normalised ratio (PT-INR) of 1.6 ± 0.13 was seen among the patients who died, but it was 1.21 ± 0.32 among the patients who were discharged ($P = .021$). Mean total bilirubin among the patients who died was 20.3 ± 5.08 mg/dL, and it was 11.33 ± 7.26 mg/dL in patients who were discharged ($P = .019$). A mean direct bilirubin of 15.05 ± 3.64 mg/dL was seen in patients who died, and it was 6.35 ± 3.71 mg/dL in patients who were discharged ($P = .001$). Mean serum albumin in patients who died was 2.6 ± 0.11 gm/dL, and it was 3.41 ± 0.40 gm/dL in patients who were discharged ($P = .001$). There was an approximately 20-fold increase in mean serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) values, whereas mean alkaline phosphatase (ALP) was elevated by just 1-fold.

Mean blood urea was 97 ± 33.48 mg/dL in patients who died, and it was 32.43 ± 18.41 mg/dL in patients who were discharged ($P = .001$). A mean serum creatinine of 2.9 ± 1.38 mg/dL was seen in patients who died, and it was 1.12 ± 0.64 mg/dL in patients who were discharged ($P = .001$). Mean serum sodium in patients who died was 123 ± 3.56 mmol/L, and it was 136.04 ± 2.97 mmol/L in patients who were discharged ($P = .000$). A mean potassium of 5.95 ± 1.21 mmol/L was seen patients who died, and it was 4.29 ± 0.51 mmol/L among the patients who were discharged ($P = .001$).

DISCUSSION

Hepatitis E virus infection causes large epidemics of liver disease in developing countries [8, 11, 12]. In epidemic settings, HEV is transmitted by the fecal-oral route, and the most commonly attributed source of infection is feces-contaminated drinking water [9]. The incubation period after exposure ranges from 3 to 8 weeks (mean 40 days) and is dose dependent [13, 14]. Illness is generally self-limited, with death rates <4% in the general population [7], but a strikingly high death rate (10%–25%) has been reported among pregnant women [15]. Globally, there are approximately 20 million incidents of hepatitis E infections every year. One of the largest waterborne hepatitis E outbreaks occurred in Kanpur city, Uttar Pradesh, India in 1991 where over 79 000 clinical cases were reported. The source of this outbreak was traced to fecal contamination of drinking water supplied from the river Ganges [9].

Among the 290 patients, a higher percentage of males were affected, ie, male-to-female sex ratio was 4.8:1, which is in accordance with similar studies done in North India (Punjab), China, Taiwan, and Bangladesh [9–18]. However it was found to be 1:1 in an epidemic outbreak in Africa [19]. The mean age of patients was 45.59 ± 14.4 years, with the majority of patients older than 30 years of age, whereas a lower mean age (28.8 years) was seen in a study done in North India [9]. This result may be because 81.1% of the affected persons were aged 10–39 years, and in our study we have not included patients younger than 18 years of age. Yellowish discoloration of urine was the most common symptom of presentation. Among the patients included, 80 (27.6%) patients had history of alcohol abuse. On clinical examination, the majority of patients (96.6%) were found to have icterus, whereas pedal edema and pallor were seen in 60 (20.7%) and 30 (10.3%) patients, respectively. Hepatomegaly was the most common finding in abdominal examination and was seen in 175 (60.3%) patients, whereas ascites and splenomegaly was seen in 30 (6.9%) and 15 (5.2%) patients, respectively. Hepatomegaly measuring approximately 2–3 cm was seen in majority of nonalcoholics, whereas it was >5 cm in most alcoholics.

Ten (3.45%) patients died among the 290 patients included in this study, whereas mortality was higher in the study by Zhang et al (10%) [10]. In sporadic cases, mortality was associated with complications (ie, fulminant liver failure [45%]) with no higher

Table 2. Comparison between Survivors and Non survivors

Parameters	Survivors	Nonsurvivors
Mean age	43.85 ± 12.97 years	69 ± 12.7 years
Duration of hospital stay	6.63 ± 2.52 days	15 ± 5.78 days
Mean PT-INR	1.21 ± 0.32	1.6 ± 0.13
Mean total bilirubin	11.33 ± 7.26 mg/dL	20.3 ± 5.08 mg/dL
Mean direct bilirubin	6.35 ± 3.71 mg/dL	15.05 ± 3.64 mg/dL
Mean serum albumin	3.41 ± 0.40 gm/dL	2.6 ± 0.11 gm/dL
Mean blood urea	32.43 ± 18.41 mg/dL	97 ± 33.48 mg/dL
Mean serum creatinine	1.12 ± 0.64 mg/dL	2.9 ± 1.38 mg/dL
Mean serum sodium	136.04 ± 2.97 mmol/L	123 ± 3.56 mmol/L
Mean serum potassium	4.29 ± 0.51 mmol/L	5.95 ± 1.21 mmol/L

Abbreviations: INR, international normalised ratio; PT, prothrombin time.

mortality reported among pregnant women [20]. Mortality was significantly higher among alcoholics compared with nonalcoholics (12.5% vs 0%; $P = .004$). A higher mean age of 69 ± 12.7 years was seen in patients who died ($P = .001$), which was in accordance with the study done in China. The duration of hospital stay was significantly longer in patients who died compared with patients who were discharged (15 ± 5.77 vs 6.63 ± 2.52; $P = .001$).

A significantly higher mortality rate was seen in patients found to have pedal edema ($P = .001$), ascites ($P = .021$), and flapping tremors ($P = .000$) at presentation. This result probably indicates the severity of underlying disease. However, this observation has not been reported in other studies.

Ten (3.4%) patients had HBsAg positivity in addition to anti-HEV positivity, and there was no significantly higher mortality among the patients who had coinfection, but these patients had a higher mean duration of hospital stay. Patients with diabetes mellitus were found to have a higher mean duration of hospital stay.

An increase in mean PT-INR values ($P = .021$), mean total bilirubin ($P = .019$), mean direct bilirubin ($P = .001$), and low serum albumin ($P = .001$) was associated with increased mortality. Similar results were observed in the study by Zhang et al [10]. There was an approximately 20-fold increase in mean SGOT and SGPT values, whereas mean ALP was elevated by just 1-fold. Serum glutamic-pyruvic transaminase was elevated more than SGOT (mean SGPT/SGOT = 1.148), and further studies are needed to evaluate whether this ratio can be used as corroborative evidence for diagnosing HEV infection during epidemics of infective hepatitis.

Increased mean blood urea levels (97 ± 33.48) and mean serum creatinine (2.9 ± 1.38) were seen in patients who died compared with patients who were discharged, which was statistically significant ($P = .001$). These results were comparable with the study by Zhang et al [10]. Low mean sodium levels (123 ± 3.56) and high mean potassium levels (5.95 ± 1.21) were seen in patients who died (Table 2).

CONCLUSIONS

In a study of acute hepatitis E infection in the city of Mysore, South India, during the period from January 2011 to December 2012, 374 patients were diagnosed with HEV. After the initial observation, 290 consecutive cases above the age of 18 years were admitted to hospital and prospectively studied. Yellowish discoloration of urine was the most common symptom, icterus was the most common sign, and hepatomegaly was the most common finding on abdominal examination. Overall mortality observed was 3.45%. A higher mean age and longer hospital stay was seen in patients who died. Mortality was significantly higher among alcoholics (12.5%), which led us to believe that alcohol abuse can increase the severity of HEV infection, resulting in higher mortality. In our study, a univariate analysis was done, and significant association was found between alcohol abuse and hepatitis E infection. Our study results also revealed that alcohol abuse can cause decompensation in hepatitis E infection. Higher mean PT-INR, total and direct bilirubin, and lower mean serum albumin were associated with higher mortality. In general, SGOT values were increased compared with SGPT; however, this observation was significantly higher in patients with diabetes mellitus and alcohol abuse. In our study serum glutamic-pyruvic transaminase (SGPT) was elevated more than Serum glutamic-oxaloacetic transaminase (SGOT) (mean SGPT/SGOT = 1.148), and further studies are needed to evaluate whether this ratio can be used as corroborative evidence for diagnosing HEV infection during epidemics of infective hepatitis.

A higher mean blood urea, serum creatinine, potassium, and lower mean sodium values were associated with higher mortality. Literature and previous studies on hepatitis E emphasizes the mortality among pregnant women; however, the role of other comorbidities (such as Alcoholic Liver Disease (ALD)) in disease progression and mortality has not been documented. Although the pathogenesis of HEV has not been clarified due to the lack of effective animal models of HEV infection, the results may be helpful to provide us with some insight into the clinical diagnosis, management, and basic research of HEV infection.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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