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Research Article

A STUDY TO ASSESS THE CLINICAL AND BIOCHEMICAL PROFILE OF PATIENTS DIAGNOSED WITH HEPATITIS E IN A LARGE TEACHING HOSPITAL OF SOUTHERN INDIA

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ABSTRACT

Objective: Hepatitis E has been identified as a major health problem in developing countries and recently developed countries. To study the profile of patients diagnosed with hepatitis E infection in a tertiary care hospital in south India.

Methods: A cross-sectional record-based study with the records of patients diagnosed with hepatitis E infection over a 40-month period from a teaching hospital in southern India and fulfilling the following criteria was performed.

Results: The cases were predominant in the age group of 21-30 years with relative sparing of children. No seasonal variation in the occurrence or secondary cases was observed. Temporary derangement of liver function tests was recorded in all cases. The study showed a male preponderance. As documented in previous studies, the disease proved fatal in a primigravida who developed fulminant hepatic failure. Another interesting feature was the presence of leptospirosis, scrub typhus, and hepatitis A as co-infection with hepatitis E.

Conclusion: In India, the awareness of the disease is also low, therefore, the diagnosis is usually not made in the majority of cases. Hence, the availability of data regarding the clinical pattern of presentation and biochemical profile is restricted. However, there are some questions still unanswered like the preference of the virus to infect individuals in the age group of 20-40 years, sparing of children, and increased rate of infection among the males. The cause of the increased morbidity and mortality of this virus in pregnant women is still not known. A larger sample size and the data on the seroprevalence of this disease in the population under study are necessary for a meaningful interpretation of its epidemiological pattern.

Keywords: Alanine transaminase, Alkaline phosphatase, Aspartate aminotransferase, Bilirubin, Liver.

INTRODUCTION

Hepatitis E is a viral infection affecting the liver. It is caused by positive-sense single-stranded RNA virus of genus *Herpesviridae*. There are four genotypes-1, 2, 3, 4. The infection is transmitted mainly by the fecal-oral route, i.e., it is transmitted by contaminated food or water. Person to person transmission is rare. It can also be transmitted by blood transfusions or vertically from mother to fetus but they are even rarer. The zoonotic transmission has also been observed. The incubation period has a range of 15-60 days, with a mean of 40 days [1]. The disease may be either symptomatic or asymptomatic and is usually self-limiting although rare complications such as fulminant hepatitis can occur.

Symptoms associated are similar to that of any hepatitis include fever, fatigue, nausea, vomiting, icterus, dark colored urine, and clay-colored stools [2]. Serum bilirubin levels and liver enzymes are usually markedly elevated. Anti-IgM antibody becomes detectable days before the onset of symptoms and disappears in 4-6 months [3]. Anti-IgG antibody appears after IgM response and may persist up to 12 years after infection [4]. Chronic infections are rare and are more common in developed countries in HIV patients, transplant recipients, immunocompromised patients and in patients with the pre-existing liver disease. In hepatitis E virus (HEV) epidemics, disproportionately high rates of fulminant hepatitis with subsequent high mortality occur among pregnant women, particularly if infected in the third trimester of pregnancy and may be related to hormonal changes in pregnancy [1].

Hepatitis E is the most common cause of acute sporadic hepatitis in India and has been associated with several large-scale epidemics in the past [5]. This disease has gained its importance, as a specific diagnostic serological confirmation is possible now because of the availability of the ELISA test and a rising prevalence of this entity in its severe fulminant form in developed countries. In a developing country like India, even though hepatitis E is endemic, it is rarely diagnosed as the availability of serological confirmation is restricted and the awareness about the disease is poor. Hence, a definitive diagnosis is usually not made in the majority of cases. The availability of data regarding the clinical pattern of presentation and biochemical profile is restricted.

Background

Hepatitis E as a distinct entity was first suspected nearly 30 years ago when a waterborne outbreak of acute hepatitis in the Kashmir valley in India was found to be related neither to hepatitis A virus nor to hepatitis B virus by Khuroo *et al*. [6]. Around the same time, sera from previous outbreaks of acute hepatitis in India, including a large outbreak in New Delhi that occurred during the year 1955-56, were also found to lack markers of acute hepatitis A or B [7]. The confirmation of these observations came in 1983 when Balayan *et al*. successfully transmitted the disease into himself by oral administration of pooled stool extracts of 9 patients from a non-A, non-B hepatitis outbreak which had occurred in a soviet military camp located in Afghanistan. The virus was demonstrated in the stool specimen as a spherical virus-like particle with the help of an immune electron microscopy. The virus was cloned and sequenced by Reyes *et al*. in 1990 [6].

Ever since then, hepatitis E has been identified as a major health problem in developing countries [1] and recently developed countries [8].

In a study conducted in Kanpur, during the epidemic in 1991, 138 people who had hepatitis in the surveyed population, 89 (64.5%) were male and 49 (35.5%) were female. This shows a high attack rate in males. The age category maximally affected was 10-29 years of age. There were only 6% of cases that were in the age group 0-9 years [9].

In a study conducted during the Kashmir epidemic, 1978-79 by Khuroo, the total numbers of people affected were 275, of which the maximum number of people infected belonged to the age group of 21-30 years (89 patients). There was also an increase in male attack rate (153 of the total infected were males and 122 were females). The clinical presentation of hepatitis was similar to that of any other hepatitis [10].

Cholestatic symptoms were seen in 20% of the cases, which presented as clay colored stools and itching [10].

In a study conducted in Nellore in 2008, a total of 23915 cases of acute viral hepatitis (AVH) occurred.

During hepatitis E outbreaks, the overall attack rates range from 1% to 15% [9]. An attack rate of 5.7%, which was one of the highest attack rates reported in southern India. The findings were similar to that of other studies (increased male preponderance, relative sparing of children, etc.) [11]. Only one other epidemic has been previously reported from southern India, where 1611 hospitalized cases were reported in Hyderabad in 2005 [12]. All other outbreaks reported so far in India have been from the north. The largest epidemic reported was in Kanpur in 1991, which affected an estimated 79000 individuals [9].

Compared with enterically transmitted HAV, which has a 10-20% secondary attack rate among household contacts, HEV has relatively low infectivity, with a secondary attack rate of about 2%. A detailed epidemiologic study of intrafamilial transmission was conducted in 1991 after the HEV epidemic occurred in Kanpur, India. Secondary or "later" cases (n=111) were defined as those persons who developed illness a minimum of 2 weeks after the index case in a household. Only 8 (7.2%) of these 111 "later" cases could be attributed to possible intrafamilial transmission; most of the "later" cases had been exposed to the same source of HEV-associated with the first peak of the epidemic. Thus, among 402 household contacts of primary cases that were at risk for secondary infection, the secondary attack rate in this study was only 2% [13].

A typical feature of hepatitis E outbreaks is the occurrence of a higher disease attack rate and a higher mortality rate among pregnant women. During a large epidemic in Kashmir, India, the disease attack rates were 8.8%, 19.4%, and 18.6% among pregnant women in the first, second, and third trimesters, respectively; these rates were significantly higher than those among non-pregnant women (2.1%) and men (2.8%) [14].

Once fulminant hepatic failure (FHF) appears, the mortality rate appears to be similar among pregnant women with hepatitis E and pregnant women with other causes of severe liver injury [15]. However, since HEV infection during pregnancy is associated with high rates of symptomatic disease and FHF, it accounts for a large proportion of cases with liver failure among pregnant women in the endemic areas [16]. The reason underlying the association of hepatitis E and pregnancy is unknown though immunological or hormonal factors have been proposed [17-20].

Hepatitis E during pregnancy is also associated with prematurity and low birth weight [21]. The children born to such mothers frequently suffer from hypoglycemia and jaundice and have increased perinatal mortality.

Nargis Beegum *et al*. investigated the duration of HEV infection in pregnant and non-pregnant women with AVH or FHF by looking for the presence of HEV-RNA [22]. The proportion of HEV viremia in pregnant women with AVH and FHF at day 15 was significantly higher than in non-pregnant women (88.3% vs. 27.6%). Similarly, HEV viremia among patients with AVH was significantly higher in pregnant women compared with non-pregnant women (100% vs. 55%). HEV viremia may be prolonged in pregnancy.

Aim

To study the profile of patients diagnosed with hepatitis E infection in a tertiary care hospital in south India.

Objectives

1. To describe the clinical features of patients diagnosed with hepatitis E and the associated factors
2. To study the demographic characteristics of patients diagnosed with hepatitis E
3. To study the complications and outcome of the patients with hepatitis E and the factors associated with it.

METHODS

A cross-sectional record based study was undertaken by reviewing the records of patients diagnosed with hepatitis E infection over a 40-month period from a teaching hospital in southern India and fulfilling the following criteria was included.

Eligibility criteria

Cases with a serologically proved diagnosis of HEV infection detected or confirmed at the NABL accredited laboratory attached to the teaching Hospital, which prompted the hospital attendance, or documented during the past hospital stay.

Methodology

Permission was obtained from the Institutional Ethical Committee for performing this study (IEC 100/2013). The medical records of the patients were accessed from the Medical Record Department (MRD) after obtaining prior permission of the medical superintendent. Using a pre-designed data extraction sheet, the socio-demographic parameters such as age, gender, religion, place of residence, marital status, co-morbid conditions as well as the presenting symptom(s) and anthropometric measurements were recorded. Relevant laboratory investigations performed has been recorded and analyzed. The final diagnosis and organ system/s involved has been recorded.

Statistical analysis

Data processing and statistical analysis were done using SPSS 16.0.

RESULTS

The records of 43 patients were analyzed in the study, out of which 37 were male, and 6 were female. The maximum number of people infected belonged to the age group of 21-30 (33.3%). The distribution of subjects in accordance with age is shown in Table 1.

The most common presenting symptoms seen in the study were icterus (81%; 35 people), fever (79.1%; 34 people), vomiting (44.2%; 19 people), dark colored urine (34.9%; 15 people), abdominal pain (32.6%; 14 people), and malaise (23.3%; 10 people) as shown in Fig. 1.

Table 1: Distribution of age and gender in patients infected with hepatitis E

Age categories (in years)	Percentage	Gender	
		Male	Female
<20	14.3	4	2
21-30	33.3	12	2
31-40	19	7	1
41-50	16.7	7	0
51-60	7.1	3	0
More than 60	9.5	3	4

There was a history of hypertension and diabetes mellitus recorded in two of the patients (4.7%).

There was no pre-existing liver diseases, cardiovascular disease, HIV infection seen in any of the patients. There was a history of alcohol consumption recorded in 5 (11.6%) and smoking in 2 (4.7%) of the patients. USG showed minimal changes. Liver biopsy was not performed in any case.

In all cases, hepatitis E was confirmed by HEV IgM ELISA. Most patients came for follow-up usually after 2 weeks of discharge.

The median levels of total bilirubin were as follows: Admission: 6.56 mg/dl, discharge: 3.4 mg/dl, and follow-up: 1.3 mg/d. Table 2 shows the distribution of total bilirubin at the time of admission, discharge, and follow-up.

90.7% of patients had deranged total bilirubin at the time of admission, 77.5% had deranged bilirubin at the time of discharge, and 64% at the time of follow-up as shown in Fig. 2.

The median levels of direct bilirubin were as follows: Admission: 5.7 mg/dl, discharge: 3.1 mg/dl, and follow-up: 0.9 mg/dl. Table 3 shows the distribution of direct bilirubin at the time of admission, discharge, and follow-up.

As depicted in Fig. 3, 92.9% of patients had deranged direct bilirubin at the time of admission, 81.6% had deranged direct bilirubin at the time of discharge, and 70.8% at the time of follow-up.

The median levels of aspartate aminotransferase (AST) were as follows: Admission: 260 IU/l, discharge: 88U/L, and follow-up: 27 U/L. Table 4 shows the distribution of AST at the time of admission, discharge, and follow-up.

97% of patients had deranged AST at the time of admission, 80.5% had deranged AST at the time of discharge, and 34.6% at the time of follow-up as shown in Fig. 4.

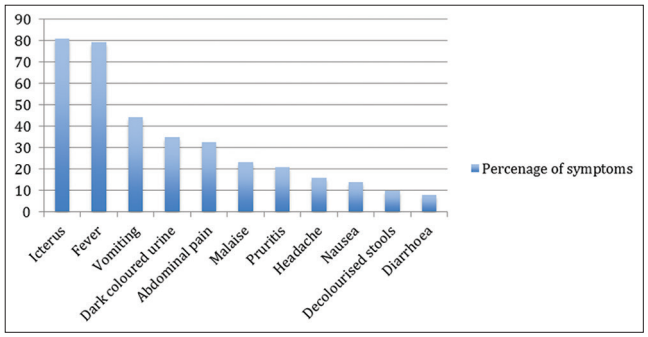

Fig. 1: The symptoms presented by patients diagnosed with hepatitis E

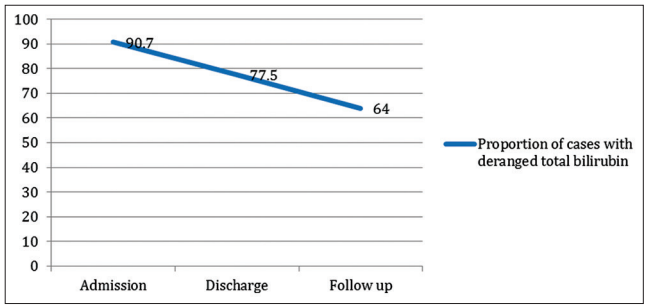

Fig. 2: Proportion of cases with deranged total bilirubin

The median levels of alanine transaminase (ALT) were as follows: Admission: 342 U/L, discharge: 136 U/L, and follow-up: 30 U/L Table 5

Table 2: Distribution of total bilirubin at time of admission, discharge, and follow-up

Parameter	Total bilirubin		
	Admission	Discharge	Follow-up
No. of cases (n)	43	40	25
Median	8.1	4.05	1.5
Minimum	0.3	0.3	0.3
Maximum	39.2	23.1	22.6
Inter quartile range	4.9, 15	1.3, 8.55	0.8, 3

Table 3: Distribution of direct bilirubin levels

Parameter	Direct bilirubin		
	Admission	Discharge	Follow-up
No. of cases	42	38	24
Median	6.95	3.55	0.9
Minimum	0.1	0.1	0.2
Maximum	31.4	18.8	18.1
Inter quartile range	4.175, 12.225	0.725, 7.4	0.4, 2.15

Table 4: Distribution of AST at time of admission, discharge, and follow-up

Parameter	AST		
	Admission	Discharge	Follow-up
No. of cases	43	41	26
Median	297	84	30
Minimum	44	17	15
Maximum	3419	1016	334
Inter quartile range	116, 705	46.5, 140.5	23.5, 60.5

AST: Aspartate aminotransferase

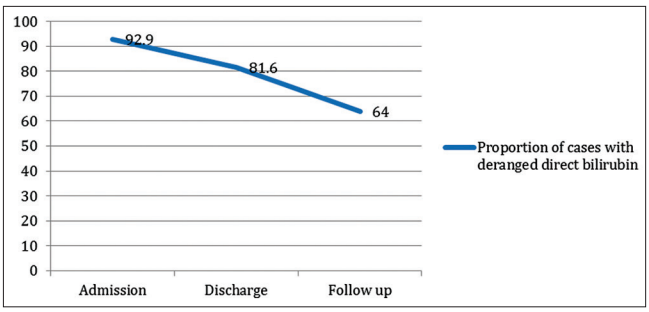

Fig. 3: Proportion of cases with deranged direct bilirubin

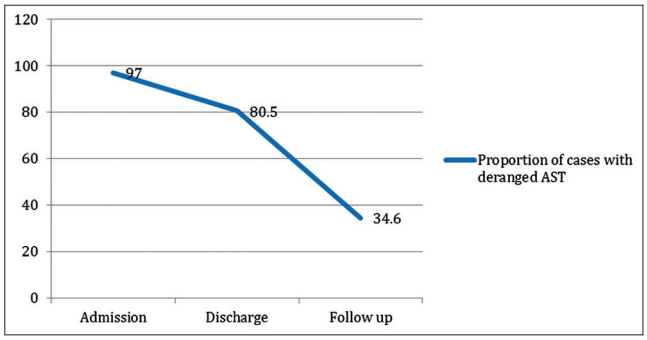

Fig. 4: Proportion of cases with deranged aspartate aminotransferase

shows the distribution of ALT at the time of admission, discharge, and follow-up.

95.3% of patients had deranged ALT at the time of admission, 87.8% had ALT at the time of discharge, and 34.6% at the time of follow-up as shown in Fig. 5.

The median levels of alkaline phosphatase (ALP) were as follows: Admission: 172.5 U/L, discharge: 143.5 U/L, and follow-up: 99.5 U/L. Table 6 shows the distribution of ALP at the time of admission, discharge, and follow-up.

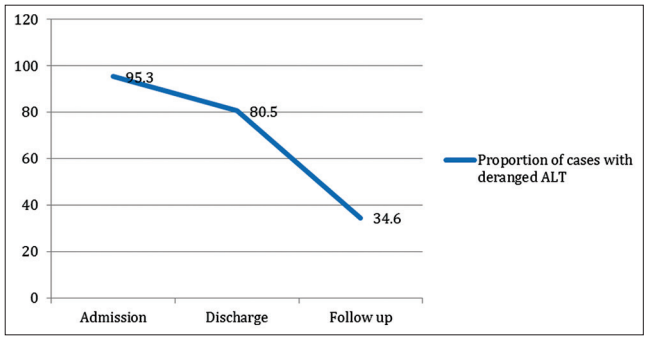

Fig. 5: Proportion of cases with deranged alanine transaminase

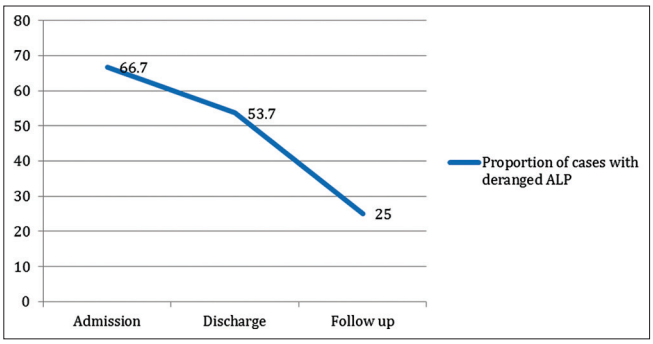

Fig. 6: Proportion of cases with deranged alanine transaminase

Table 5: Distribution of ALT at time of admission, discharge, and follow-up

Parameter	ALT		
	Admission	Discharge	Follow-up
No. of cases	43	41	26
Median	342	129	30
Minimum	19	15	8
Maximum	5618	1266	216
Inter quartile range	129,1033	68.5, 362.5	20.75, 86.75

ALT: Alanine transaminase

Table 6: Distribution of ALP at time of admission, discharge, and follow-up

Parameter	ALP		
	Admission	Discharge	Follow-up
No. of cases	42	41	24
Median	175	143	102
Minimum	63	14.7	57
Maximum	532	367	472
Inter quartile range	128, 225.5	94, 191	76, 139.25

ALP: Alkaline phosphatase

66.7% of patients had deranged ALP at the time of admission, 53.7% had deranged ALP at the time of discharge, and 25% at the time of follow-up as shown in Fig. 6.

The median levels of total serum protein were as follows: Admission: 7 g/dl, discharge: 6.4 g/dl, and follow-up: 7.6 g/dl. Table 7 shows the distribution of total serum protein at the time of admission, discharge, and follow-up. Total serum protein did not change much during the course of illness.

The median levels of serum albumin were as follows: Admission: 3.8 g/ dl, discharge: 3.35 g/dl, and follow-up: 4.6 g/dl. Table 8 shows the distribution of serum albumin at the time of admission, discharge, and follow-up. Serum albumin did not change much during the course of illness as shown in Table 8.

The median levels of prothrombin time (PT) were as follows: Admission: 3.8 g/dl, discharge: 3.35 g/dl, and follow-up: 4.6 g/dl. Table 9 shows the distribution of PT at the time of admission, discharge, and follow-up.

Most patients recovered clinically within 2-3 weeks. Liver function tests (LFTs) of most patients did not recover at the time of follow-up although most patients did not display any clinical symptoms.

Three of the patients were co-infected with scrub typhus, and two were co-infected with hepatitis A (4.7%). One patient had a history of urinary tract infection. There was no co-infection with hepatitis B, hepatitis C, hepatitis D, and Epstein-Barr virus in any of the patients.

However, we did not find any difference in the clinical course and LFT of patients of hepatitis E co-infected with hepatitis A and scrub typhus.

Table 7: Distribution of total serum protein at time of admission, discharge, and follow-up

Parameter	Total serum protein		
	Admission	Discharge	Follow-up
No. of cases	42	9	14
Median	7	6.4	7.6
Minimum	4.8	5.6	6.1
Maximum	8.9	8.3	8.3
Inter quartile range	6.5, 7.425	5.6, 7.4	7.075, 7.95

Table 8: Distribution of serum albumin at time of admission, discharge, and follow-up

Parameter	Serum albumin		
	Admission	Discharge	Follow-up
No. of cases	41	10	14
Median	3.8	3.35	4.6
Minimum	2.2	2	2
Maximum	5.2	4.7	5.2
Inter quartile range	3.15, 4.15	2.525, 3.9	3.75, 4.7

Table 9: Distribution of PT at time of admission, discharge, and follow-up

Parameter	PT		
	Admission	Discharge	Follow-up
No. of cases	26	4	1
Median	15.95	15.45	16.3
Minimum	14.1	13.6	16.3
Maximum	120	16.7	16.3
Inter quartile range	14.8, 16.95	13.825, 16.625	16.3, 16.3

PT: Prothrombin time

Among the 6 females, there was one case of hepatitis E, which occurred during pregnancy and presented with hepatic coma and FHF and eventually succumbed to her illness 7 days after her presentation.

There were two cases of prolonged cholestasis which persisted for 2 weeks and recovered during follow-up over 1 month. No patient developed hypoglycemia during the course of illness.

There was one case where the daughter developed Jaundice 4 days after the father. There were two cases where the patients develop cholestasis.

All patients were managed with symptomatic and supportive therapy and responded well. Majority improved well with these measures and was discharged within 2 weeks of admission.

DISCUSSION

The maximum number of hepatitis E patients in this study was clustered between the ages of 21-30 (33.3%). There were very few cases of hepatitis E in children aged <16 years and adults beyond 40 years of age. These results match with several other studies conducted in India like the study conducted in Delhi 1956, where the maximum numbers of people infected were among the age group of 15-35 years [7]. Similarly, in the Kashmir epidemic of hepatitis E, the peak incidence of disease was in the age group between 21 and 30 years [10].

Results similar to our study have also been reported from Asian countries like Bangladesh and Pakistan [23-25]. However, cases of sporadic hepatitis caused due to HEV have been reported in children aged 2 months to 15 years in Sudan, Egypt, and Somalia [26-28].

The cause of this age distribution of the disease is unknown.

The present study showed a higher attack rate of hepatitis E among males (86.05%), which was seen in other studies [9-12]. This might be the result of the difference in behavioral factors between the two sexes. In addition, social restrictions on women in some societies may restrict exposure to the virus. There might also be a difference in health seeking behavior between the male and female population in these societies [29].

The most common presenting complaints of hepatitis E were fever and jaundice and were similar to that of any other AVH. Hence, it is important to suspect hepatitis E when patients present with features of acute hepatitis and commonly screened viruses like hepatitis A are negative.

LFTs of almost all patients were deranged at presentation, with 2 patients going into a cholestatic phase of hepatitis-like in hepatitis A. The LFTs in all most improved over a period of 1-month, except 2 patients where it normalized in 3 months.

There were 3 patients co-infected with scrub typhus and 2 with co-infected with hepatitis A. Even though hepatitis A and scrub typhus can independently cause hepatitis, the clinical presentation, LFT and prognosis of hepatitis E co-infected with hepatitis A or scrub typhus were similar to patients only infected with hepatitis E. This finding is different from the other studies where co-infection seems to lead to more severe clinical progression than infection with other virus alone [29].

The present study had one case of hepatitis E occurring in the 1st trimester of pregnancy resulting in the death of the patient. Similar reports of increased maternal mortality have been noticed in previous studies especially in the 3rd trimester [14,22]. The cause of this increased morbidity and mortality is still unknown and is postulated to be due to the hormonal changes seen in pregnancy or immune-mediated changes [17-20].

Limitations

1. The sample size of the study was small
2. As the study cohort consisted of symptomatic patients admitted to a hospital, the subclinical form of the infection is missed.

CONCLUSION

Hepatitis E has become a major health problem in both developing and developed countries In India, the awareness of the disease is also low, therefore, the diagnosis is usually not made in the majority of cases. Hence, the availability of data regarding the clinical pattern of presentation and biochemical profile is restricted.

Since its discovery by Khuroo *et al.* in 1978, there has been a drastic increase in the knowledge obtained on hepatitis E. However, there are some questions still unanswered like the preference of the virus to infect individuals in the age group of 20-40 years, sparing of children and increased rate of infection among the males. The cause of the increased morbidity and mortality of this virus in pregnant women is still not known. Therefore, more research on hepatitis E on a large-scale is required. Since the present study showed diverse nature of the presentation of hepatitis E, it may be wise to screen for hepatitis E routinely as a cause of acute hepatitis along with other causes such as Hepatitis A, Scrub typhus, and leptospirosis. Further studies are needed to know if there is any association between hepatitis E and hepatitis A and other organisms causing hepatitis-like scrub typhus and if the prognosis is worse among these individuals.

REFERENCES

1. Teshale EH, Hu DJ, Holmberg SD. The two faces of hepatitis E virus. Clin Infect Dis 2010;51(3):328-34.
2. Hepatitis E FAQs for Health Professionals. Available from: http://www.cdc.gov/hepatitis/HEV/HEVfaq.htm. [Last accessed on 2013 Jan 16].
3. Favorov MO, Fields HA, Purdy MA, Yashina TL, Aleksandrov AG, Alter MJ, *et al.* Serologic identification of hepatitis E virus infections in epidemic and endemic settings. J Med Virol 1992;36(4):246-50.
4. Chadha MS, Walimbe AM, Arankalle VA. Retrospective serological analysis of hepatitis E patients: A long-term follow-up study. J Viral Hepat 1999;6(6):457-61.
5. Abraham P. Viral hepatitis in India. Clin Lab Med 2012;32(2):159-74.
6. Khuroo MS. Discovery of hepatitis E: The epidemic non-A, non-B hepatitis 30 years down the memory lane. Virus Res 2011;161(1):3-14.
7. Schwartz E, Jenks NP, Van Damme P, Galun E. Hepatitis E virus infection in travelers. Clin Infect Dis 1999;29(5):1312-4.
8. Khuroo MS, Kamilib S, Khurooc MS, Ashgara HA. Hepatitis E virus. Hepatology A Practical Approach. New York: Elsevier; 2004. p. 111-20.
9. Naik SR, Aggarwal R, Salunke PN, Mehrotra NN. A large waterborne viral hepatitis E epidemic in Kanpur, India. Bull World Health Organ 1992;70(5):597-604.
10. Khuroo MS. Study of an epidemic of non-A, non-B hepatitis. Possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. Am J Med 1980;68(6):818-24.
11. Vivek R, Nihal L, Illiayaraja J, Reddy PK, Sarkar R, Eapen CE, *et al.* Investigation of an epidemic of Hepatitis E in Nellore in south India. Trop Med Int Health 2010;15(11):1333-9.
12. Sailaja B, Murhekar MV, Hutin YJ, Kuruva S, Murthy SP, Reddy KS, *et al.* Outbreak of waterborne hepatitis E in Hyderabad, India, 2005. Epidemiol Infect 2009;137(2):234-40.
13. Aggarwal R, Naik SR. Hepatitis E: Intrafamilial transmission versus waterborne spread. J Hepatol 1994;21(5):718-23.
14. Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI. Incidence and severity of viral hepatitis in pregnancy. Am J Med 1981;70(2):252-5.
15. Bhatia V, Singhal A, Panda SK, Acharya SK. A 20-year single-center experience with acute liver failure during pregnancy: Is the prognosis really worse? Hepatology 2008;48(5):1577-85.
16. Aggarwal R. Clinical presentation of hepatitis E. Virus Res 2011;161(1):15-22.
17. Pal R, Aggarwal R, Naik SR, Das V, Das S, Naik S. Immunological alterations in pregnant women with acute hepatitis E. J Gastroenterol Hepatol 2005;20(7):1094-101.
18. Bose PD, Das BC, Kumar A, Gondal R, Kumar D, Kar P. High viral load and deregulation of the progesterone receptor signaling pathway: Association with hepatitis E-related poor pregnancy outcome. J Hepatol 2011;54(6):1107-13.
19. Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: Understanding the pathogenesis. Liver Int 2008;28(9):1190-9.

20. Kar P, Jilani N, Husain SA, Pasha ST, Anand R, Rai A, *et al.* Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? Am J Gastroenterol 2008;103(10):2495-501.
21. Khuroo MS, Kamili S, Khuroo MS. Clinical course and duration of viremia in vertically transmitted hepatitis E virus (HEV) infection in babies born to HEV-infected mothers. J Viral Hepat 2009;16(7):519-23.
22. Begum N, Polipalli SK, Husain SA, Kumar A, Kar P. Duration of hepatitis E viremia in pregnancy. Int J Gynaecol Obstet 2010;108(3):207-10.
23. Kane MA, Bradley DW, Shrestha SM, Maynard JE, Cook EH, Mishra RP, *et al.* Epidemic non-A, non-B hepatitis in Nepal. Recovery of a possible etiologic agent and transmission studies in marmosets. JAMA 1984;252(22):3140-5.
24. Smego RA Jr, Khaliq AA. Epidemic non-A non-B hepatitis in urban Karachi, Pakistan. Am J Trop Med Hyg 1988;38(3):628-32.
25. Malik IA, Qureshi MS, Luqman M, Qamar MA, Ahmed A, Legters LJ, *et al.* Epidemics of non-A, non-B hepatitis in Pakistan. Trop Doct 1988;18(3):99-101.
26. Goldsmith R, Yarbough PO, Reyes GR, Fry KE, Gabor KA, Kamel M, *et al.* Enzyme-linked immunosorbent assay for diagnosis of acute sporadic hepatitis E in Egyptian children. Lancet 1992;339(8789):328-31.
27. Hyams KC, Purdy MA, Kaur M, McCarthy MC, Hussain MA, el-Tigani A, *et al.* Acute sporadic hepatitis E in Sudanese children: Analysis based on a new western blot assay. J Infect Dis 1992;165(6):1001-5.
28. Mushahwar IK, Dawson GJ, Bile KM, Magnius LO. Serological studies of an enterically transmitted non-A, non-B hepatitis in Somalia. J Med Virol 1993;40(3):218-21.
29. Labrique AB, Thomas DL, Stoszek SK, Nelson KE. Hepatitis E: An emerging infectious disease. Epidemiol Rev 1999;21(2):162-79.