Etiology and outcome of patients with viral-induced acute liver failure

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ABSTRACT

Background: Acute liver failure (ALF) is a rare medical emergency and devastating clinical syndrome associated with high mortality in the absence of immediate intensive supportive care, specific treatment, or liver transplantation. Viral hepatitis is one of the main causes of ALF in the India as well in world. We aimed to determine the etiology of Viral-ALF and to compare the outcome and clinical and biochemical variables in patients with hepatitis E and non HEV group in this prospective study.

Methods: A total of 37 patients with a diagnosis of viral-ALF were included in the study. The variables evaluated were demographic, signs and symptoms, biochemical parameters, severity of liver injury, outcome, complications and duration of hospital stay.

Results: Out of 37 Viral-ALF patients, Acute HEV-induced ALF (48.6%) was most common followed by HBV (24.3%) and HAV (21.6%). There were significantly more females in HEV group (61.1%) than non HEV group (21.1%) (P = 0.014). Overall mortality was 20 (54.1%). Mortality was higher in non HEV group (73.7%) than HEV group (33.3%) (P = 0.015). The mean age in HEV group was 30±12.7 years and in non HEV group was 38±10.4 years (P = 0.042). Bilirubin, ALT, mean grade of coma and interval between jaundice and encephalopathy were significantly higher in non HEV group than HEV group. MELD Score was higher in non HEV group 32.6±7.9 than HEV group 26.3±7.2 (P = 0.012). Sepsis and renal failure occurred more frequently in non HEV group than HEV group. Duration of hospital stay was also significantly more in non HEV group 11.3±3.3 days versus HEV group was 7.9 ± 2.9 (P = 0.002).

Conclusions: HEV was the most frequently associated with Viral-ALF. HEV related ALF disproportionately affected young women. Mortality was higher in non HEV group (73.7%) than HEV group (33.3%). The marked difference in spontaneous survival between HEV and non HEV group can be explained by the severity of hepatic dysfunction on admission and more frequent complications.

Keywords: Acute liver failure, Hepatic encephalopathy, Hepatitis E virus, Viral-ALF

INTRODUCTION

Acute liver failure (ALF) also called fulminant hepatic failure, is a rare liver disorder that often leads to devastating consequences. It is one of the most challenging gastrointestinal emergencies encountered in clinical practice. ALF is a syndrome characterized by the development of hepatic encephalopathy (HE) together with signs of hepatocellular insufficiency, especially jaundice and coagulation disorders, in patients without previous liver disease.¹ Fortunately, it is a rare disease with 2000 to 3000 reported cases in the United States per year.² Reports from the developed world suggest an overall incidence of 1-8 cases per million people every year, yet it accounts for up to 7% of all liver-related deaths and is responsible for 6% of liver transplants.²⁻⁴
However, spontaneous recovery is observed in up to 45% of ALF patients, and specific treatments for known etiologies can be effective. The term acute liver failure is used to describe the development of coagulopathy, usually with an international normalized ratio (INR) of greater than 1.5, and any degree of mental alteration (encephalopathy) in a patient without pre-existing cirrhosis and with an illness of less than 26 weeks duration. Encephalopathy may vary from only subtle changes in affect, insomnia, and difficulties with concentration (stage 1) to deep coma (stage 4) by West Haven grading system for HE.

Etiology of ALF is heterogenous and shows wide geographical variation. The most important step in the management of ALF is to identify the cause which helps in the execution of targeted therapies and antidotes, when available. The main etiological factor includes: viral, drugs including herbal and traditional medications, autoimmune, toxin and indeterminate. Acetaminophen overdose is the most common cause of ALF in the United States and Europe, whereas viral hepatitis is more common in Asia and Africa, but numerous other causes have been reported, including drug-induced liver injury, viral hepatitis, ischemic liver injury, Wilson’s disease, and acute presentation of autoimmune hepatitis.

Viral hepatitis which mostly include hepatotropic (HBV, HAV, HEV, HCV, HDV, HGV) and non-hepatotropic (CMV, HSV, EBV etc.). Viral hepatitis is the commonest cause of ALF world-wide and in the Indian subcontinent alone it accounts for 90% of cases. All primary hepatotropic viruses can cause ALF with a different incidence in different countries. In developing world Hepatitis B (HBV) predominates as a cause, because of high prevalence of disease, but in India, Pakistan, China and Southeast Asia, Hepatitis E (HEV) is now the most common cause of acute liver failure. Approximately 2.2 million adult cases of HEV hepatitis are believed to occur in India annually. Major epidemics in Indian cities, include Delhi, Ahmedabad, Kolhapur, and some cities in the Kashmir Valley. HEV has a high predilection for pregnant women and development of ALF in pregnant women may further influence prognostic factors and decision to consider liver transplantation. Acute hepatitis C seems to be a cause of ALF in Asia but not in Western countries. More rare viral causes of ALF include, delta virus, cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein-Barr virus (EBV) infections.

Mortality related to ALF can be attributed to three complications in particular: cerebral edema, multorgan dysfunction syndrome, and sepsis. Liver has the unique ability to regenerate after acute, self-limiting injury. Because there is no specific therapy for ALF, treatment is limited to supportive measures that anticipate complications, allowing the liver time to regenerate. The overall management strategy starts with the identification of cause and an initial assessment of prognosis.

Although many people recover with supportive treatment; Orthotopic liver transplantation (OLT) remains the only definitive therapy for patients who are unable to achieve sufficient hepatocyte regeneration on supportive treatment. OLT has made a significant impact on survival of patients with ALF. N-Acetylcysteine (NAC) has emerged as a beneficial treatment for both paracetamol and non-paracetamol ALF. In this prospective study, we aimed to determine the clinical features, biochemical parameters, outcome and hospital course of Viral-ALF in Kashmir (North India).

METHODS

It was a single centre prospective study of adult patients with Viral-ALF. This study was carried out in the Department of Gastroenterology of Sher-i-Kashmir Institute of Medical Science (SKIMS), Soura, J and K. The study was approved by the institutional ethical committee (SKIMS). Informed consent was obtained from all the recruited subjects.

Study subjects

Total of 37 consecutive patients with diagnoses of Viral-ALF who fulfilled eligibility criteria were recruited in the study. This study was conducted over a period of three years from 2011 to 2014. Information regarding various demographics characteristics was taken through well structured questionnaires from all subjects. Besides a detailed history, physical examination and biochemical workup which included baseline investigations, liver function test (LFT), coagulogram of subjects were carried out.

Eligibility criteria

Inclusion criteria include patients having age >18 years and ALF was defined as biochemical evidence of acute liver injury with INR ≥1.5 and any degree of encephalopathy caused by the illness of duration <26 weeks in a patient with no prior known liver disease and with established viral etiology.

Exclusion criteria

- Drug-induced ALF,
- Autoimmune ALF,
- Acute on chronic liver failure,
- ALF during pregnancy,
- Hepatic shock.

After ALF was diagnosed, a detailed history was taken for any hepatotoxic drug intake, including homeopathic, herbal medications and intravenous drug abuse. Blood samples of all the patients were taken for the etiological diagnoses, which included hepatitis B surface antigen (HBsAg), hepatitis B core IgM (HBe-IgM), hepatitis A virus IgM (HAV-IgM), and hepatitis E virus IgM (HEV-
IgM), hepatitis D virus (IgG and IgM anti-HDV), anti HCV (hepatitis C virus), ANA (anti-nuclear antibody), ASMA (anti smooth muscle antibody), Wilson profile (serum ceruloplasmin, serum copper) and iron profile. HSV (herpes simplex virus), CMV (cytomegalovirus) and EBV (Epstein Barr virus) serology were done if non hepatotropic viruses were suspected as a cause of ALF. Imaging was obtained to rule out biliary processes, hepatic vascular abnormalities, and intrahepatic lesions. All the ethical considerations were taken care of during the study. Patients were given the option of liver transplant (to be done at the hospital with transplantation facility) at various stages of study when indicated.

Supportive treatment

All patients were managed with the standard supportive care treatment. The patients received treatment of and prevention for the complications of ALF. The treatment mainly involved continuous intravenous dextrose to prevent hypoglycemia; proton pump inhibitors for stress-related ulcers and lactulose enema. With the development of advanced HE, intensive care management, fluid and electrolyte balance, midazolam sedation and mannitol infusion in case of raised intracranial pressure. Intracranial hypertension was diagnosed clinically in the presence of clinical signs such as abnormal pupillary reflexes, hypertension or decerebrate posturing. Fresh frozen plasma and vitamin K was given in only those patients who had a spontaneous bleed. Blood and urine cultures were obtained in suspected cases of sepsis, which were then treated as per sensitivity. Renal impairment was defined as serum creatinine level of more than 1.5mg/dl. Response to treatment was monitored clinically (Grade of encephalopathy) and biochemically (bilirubin, PT, INR etc.).

Statistical analysis

Frequency distribution was assessed in terms of means ±SD for quantitative variables and number (percentages) for categorical variables. In univariate analysis, the categorical variables were compared by using χ2 test or Fisher exact test where appropriate. For continuous variables, the independent sample t-test was used. P values <0.05 was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA, version 21.0).

RESULTS

There were 37 patients of viral-ALF in total. Table 1 demonstrates the etiologies of Viral-ALF. Acute HEV-induced ALF (48.6%) was most common followed by hepatitis B (24.3%) and A (21.6%). One patient each of CMV (cytomegalovirus) and HSV (Herpes simplex virus). No patient had HDV induced ALF.

Table 1: Etiology of viral acute liver failure.

| Etiology          | Total (N=37) |
|-------------------|--------------|
| Acute Hepatitis E | 18 (48.6%)   |
| Acute Hepatitis A | 8 (21.6%)    |
| Acute Hepatitis B | 9 (24.3%)    |
| CMV               | 1 (2.7%)     |
| EBV               | 1 (2.7%)     |

Table 2: Clinical profile of patients with viral acute liver failure.

| Characteristics | Viral-ALF, N=37 | HEV group, N=18 | Non HEV group, N=19 | P- value* |
|-----------------|----------------|----------------|---------------------|----------|
| **Categorical variables [n (%)]** | | | | |
| Female gender | 15 (40.5%) | 11 (61.1%) | 4 (21.1%) | 0.014 |
| Hepatic-encephalopathy | | | | |
| Grade I | 15 (40.5%) | 9 (50%) | 6 (31.6%) | 0.076 |
| Grade II | 9 (24.3%) | 6 (33.3%) | 3 (15.8%) | |
| Grade III | 9 (24.3%) | 2 (11.1%) | 7 (36.8%) | |
| Grade IV | 4 (10.8%) | 1 (5.6%) | 3 (15.8%) | |
| Fever | 15 (40.5%) | 5 (27.8%) | 10 (52.6%) | 0.129 |
| Vomiting | 9 (24.3%) | 4 (22.2%) | 5 (26.3%) | 0.763 |
| Mortality | 20 (54.1%) | 6 (33.3%) | 14 (73.7%) | 0.015 |
| **Continuous variables (mean ±SD)** | | | | |
| Age (years) | 35.5±11.6 | 30±12.7 | 38.1±10.4 | 0.042 |
| INR | 2.2±0.7 | 2.1±0.7 | 2.4±0.8 | 0.115 |
| Bilirubin (mg/dl) | 18.1±8.9 | 16.5±9.2 | 22.4±7.6 | 0.041 |
| AST (mg/dl) | 1576±784 | 1330±798.3 | 1745±775.4 | 0.117 |
| ALT (mg/dl) | 1010.5±678.7 | 837.4±745 | 1296.3±530.7 | 0.037 |
| Albumin (g/dl) | 2.6±0.6 | 2.5±0.7 | 2.7±0.7 | 0.391 |
| Creatinine (mg/dl) | 1.3±0.5 | 1.2±0.6 | 1.5±0.7 | 0.171 |
| Interval between jaundice & encephalopathy (days) | 32±15.8 | 23±14.9 | 39±15.4 | 0.003 |
| Grade of coma | 2.4±0.9 | 2.0±1.1 | 2.9±0.7 | 0.005 |
| Meld score | 29.6±6.5 | 26.3±7.2 | 32.6±7.9 | 0.012 |
Table 2 shows the clinical profile of patients with viral-ALF when categorized as HEV and non HEV group. There were 18 patients in the HEV group and 19 patients in non HEV group. All the patients were of Kashmiri ethnicity. Majority of the patients were males (59.5%). There were more females in HEV group (61.1%) than non HEV group (21.1%) and the difference was statistically significant ($P = 0.014$). Coma grade at the time of admission showed that majority of patients (64.8%) had grade I and II encephalopathy. The patients in both the groups were comparable for the different grade of encephalopathy ($P = 0.076$) despite more patients in non HEV group having higher grade of encephalopathy. The two groups did not differ significantly with respect to fever and vomiting. Mortality was higher in non HEV group (73.7%) than HEV group (33.3%) and the difference was statistically significant ($P = 0.015$). The mean age in HEV group was 30±12.7 years and in non HEV group was 38±10.4 years ($P = 0.042$). INR, AST, albumin and creatinine were similar between two groups. Bilirubin and ALT were significantly higher in non HEV group than HEV group. Mean grade of coma was significantly higher in non HEV group than HEV group ($P = 0.005$). Interval between jaundice and encephalopathy was more in non HEV group than HEV group. MELD Score was 32.6±7.9 in non HEV group and 26.3±7.2 in HEV group and the difference was statistically significant ($P = 0.012$).

A total of 10 patients developed renal failure during the hospital course with 2 (11.1%) in HEV group versus 8 (42.1%) in non HEV group ($P = 0.036$). The other complication noted during hospital course included development of ascites, hypotension and UGI bleed did not differ significantly between two groups. Sepsis occurred in 4 (22.2%) patients in HEV group versus 11 (57.9%) patients in non HEV group ($P = 0.029$). Mannitol use and need for mechanical ventilation was similar between two groups. ($P = ns$) (Table 3).

**Table 3: Hospital course of viral acute liver failure.**

| Characteristics                  | HEV group N=18 | Non HEV group N=19 | P-value* |
|----------------------------------|----------------|--------------------|----------|
| Renal failure                    | 2 (11.1%)      | 8 (42.1%)          | 0.036    |
| Development of ascites           | 2 (11.1%)      | 4 (21.1%)          | 0.416    |
| Sepsis                           | 4 (22.2%)      | 11 (57.9%)         | 0.029    |
| Mannitol                         | 3 (16.7%)      | 5 (26.3%)          | 0.484    |
| Hypotension                      | 2 (11.1%)      | 5 (26.3%)          | 0.244    |
| Mechanical ventilation           | 2 (11.1%)      | 3 (15.8%)          | 0.680    |
| UGI bleeding                     | 1 (5.6%)       | 1 (5.3%)           | 0.968    |

*P-value <0.05 is considered statistically significant

The mean number of days of admission in hospital in the HEV group was 7.9±2.9 versus 11.3±3.3 in non HEV group. The difference between the two groups was statistically significant ($P = 0.002$) (Table 4).

**Table 4: Length of hospital stay in HEV group and non HEV group.**

| Duration of hospital stay (days) | HEV group Mean ±SD (range) | Non HEV group Mean ±SD (range) | P-value* |
|----------------------------------|-----------------------------|---------------------------------|----------|
|                                  | 7.9±2.9 (5-12)              | 11.3±3.3 (8-15)                 | 0.002    |

*P-value <0.05 is considered statistically significant

**DISCUSSION**

ALF refers to a highly specific and rare syndrome, characterised by an acute abnormality of liver function tests in an individual without underlying chronic liver disease. The disease process is associated with development of a coagulopathy of liver etiology, as opposed to the coagulation disturbance seen in sepsis, and clinically apparent altered level of consciousness due to HE. The condition of patients who develop coagulopathy, but do not have any alteration to their level of consciousness is defined as acute liver injury (ALI). Thus, the term ALF is appropriately used to describe patients who develop both coagulopathy and altered mentation.29 OLT has now become an established treatment option in patients with ALF. Due to lack of OLT facility NAC has emerged as a beneficial treatment for ALF.25 Clinical and etiological profile varies with geographical area and time.30 Each different etiology leads to a similar final common pathway. Trying to determine etiology is essential, however, as outcomes and the use of antidotes depend on the identification of the causative process. So, the prospective study was carried out to determine the clinical profile, hospital course and outcome of viral-ALF in Kashmir (India).

In our study HEV was etiologically associated with ALF in 48.6% patients. HEV is endemic in Kashmir, India and is the most common cause of acute viral hepatitis in this and other endemic regions of the world.10,13,31,32 Over last decade, the rate of new HEV infections in Europe has increased.33 There is apparent decrease in incidence of HEV related ALF in Kashmir numbers over the last 2 decades which may be because of improvement in
standard of living and sanitary waste disposal. HBV (24.3%) was the second most common cause of Viral-ALF in this study. Similarly, the proportion of HBV related ALF cases has not changed over the years, comprising 24.3% of cases in the previous series. HAV constituted 21.6% of ALF cases in the present study. HAV is a ubiquitous agent in developing countries, is highly pathogenic and spreads through person-to-person transmission. Although HAV is a common cause of ALF in children than adults. Das AK et al. reported higher percentage of HAV (29.8%) as cause for ALF. HCV is a very rare cause of ALF in Europe and the US, although a number of studies from Japan and India have found evidence of HCV, although no patient of HCV related ALF was found in our study. In contrast, the incidence of HCV related ALF has decreased constantly over the last 15 yr. One patient each of CMV and HSV induced ALF was seen in our study. Vaccination has led to a significant drop in the incidence of HBV cases, with a concomitant fall in HBV induced ALF.

There were more females in HEV group (61.1%) than non HEV group (21.1%) (P = 0.014). Coma grade at the time of admission showed that majority of patients (64.8%) had grade I and II encephalopathy. Mortality was higher in non HEV group (73.7%) than HEV group (33.3%) (P = 0.015). The mean age in HEV group was 30±12.7 years and in non HEV group was 38±10.4 years (P = 0.042). Bilirubin and ALT were significantly higher in non HEV group than HEV group. Mean grade of coma was significantly higher in non HEV group than HEV group (P = 0.005).

Interval between jaundice and encephalopathy was more in non HEV group than HEV group. MELD Score was significantly higher in non HEV group 32.6±7.9 than HEV group 26.3±4.72 (P = 0.012). ALF caused by HEV had a favourable outcome while those caused by non HEV group had poor outcome was also revealed by Khuroo MS, et al which can be explained by the severity of hepatic dysfunction at the time of admission and more frequent complications in non HEV group. Same study also revealed significantly more young female in HEV than non HEV group and bilirubin was also significantly higher in non HEV group while ALT which is a marker of liver injury was not significantly elevated.

In our study more patients in non HEV group (42.1%) developed renal failure as compared to HEV group (11.1%). Sepsis occurred more frequently in non HEV group (57.9%) than HEV group (22.2%). In the study by Khuroo MS, et al renal failure, sepsis and UGI bleed occurred more frequently in non HEV group than HEV which is similar to our study. Non HEV group had significantly longer hospital stay than HEV group which could be because of frequent complications of ALF in non HEV group.

**CONCLUSION**

HEV was the most frequently associated with Viral-ALF. HEV related ALF disproportionately affected young women. Mortality was higher in non HEV group (73.7%) than HEV group (33.3%). The marked difference in spontaneous survival between HEV and non HEV group can be explained by the severity of hepatic dysfunction on admission and more frequent complications. Duration of hospital stay was also significantly more in non HEV group than HEV group.

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