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Original Research Article

Clinical profile and outcome of patients with indeterminate 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. Indeterminate ALF still forms a significant number of cases in India as well in the world. We aimed to determine the clinical profile and outcome of patients with indeterminate ALF.
Methods: A total of 30 patients with a diagnosis of Indeterminate 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: Overall mortality was 18 (60%). Majority of the patients were females (56.7%). Majority of patients (60%) had grade III and IV encephalopathy at the time of admission. The mean age in survived group was 30.6±11.6 years and in died group was 42.6±10.2 years (p=0.005). INR, bilirubin AST, ALT and creatinine were significantly higher in died group than survived group. Mean grade of coma was significantly higher in died group than survived group (p=0.010). MELD score was significantly higher in died group 35.8±6.7 than survived group 27.5±5.8 (p=0.001). Sepsis and renal failure occurred more frequently in died group. Duration of hospital stay was also significantly more in died group versus survived group (p=0.003).
Conclusions: Indeterminate ALF disproportionately affected young females. Mortality was as high as 60%. The marked difference in spontaneous survival can be explained by the severity of hepatic dysfunction on admission and more frequent complications.

Keywords: Acute liver failure, Hepatic encephalopathy, Indeterminate ALF

INTRODUCTION

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] It has also been referred to as fulminant hepatic failure. It is one of the most challenging gastrointestinal emergencies encountered in clinical practice. 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 2 and is responsible for 6% of liver transplants.[3-4] However, spontaneous recovery is observed in up to 45% of ALF patients, and specific treatments for known etiologies can be effective.[5] 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 preexisting cirrhosis and with an illness of less than 26 weeks duration.[6]

Etiology of ALF is heterogeneous 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.[7] 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.[8, 9] Viral hepatitis is the commonest cause of ALF world-wide and in the Indian subcontinent alone it accounts for 90% of cases.[10] In India, Pakistan, China and Southeast Asia, Hepatitis E (HEV) is now the most common cause of ALF.

Causation cannot be established in many cases; such seronegative or indeterminate liver failures happens worldwide and are associated with especially poor survival with medical therapy alone, and frequently need emergency transplantation.[11,12] A significant minority of ALF cases, however, cannot be linked to a clear cause. 18% to 20% of ALF cases in industrialized countries have an unknown etiology.[13] They usually present with an acute or subacute ALF phenotype.[14] A proportion of these patients may have taken drugs or xenobiotics, which they do not (or cannot) recall. Others provide a history compatible with a viral phenotype, although no specific viral etiological agent can be identified.[15] Some subsequently present with immune-mediated features, suggesting that the original disease may have been autoimmune in nature. In some of these groups, as well as in those of a known etiology, the potential for paracetamol-induced co-toxicity may be raised by the presence of paracetamol adducts.[16] Equally, studies have suggested that some cases of presumed seronegative etiologies may have HEV infection, and appropriate tests regarding sensitivity and specificity should always be undertaken.[17]

Mortality related to ALF can be attributed to three complications in particular: cerebral edema, multiorgan 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; Orthotropic 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.[18,19] N- Acetylcysteine (NAC) has emerged as a beneficial treatment for both paracetamol and non-paracetamol ALF.[20-23]

Not much is known about the indeterminate ALF, so in this prospective study, we aimed to determine the clinical features, biochemical parameters and outcome of indeterminate ALF.

METHODS

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

Study subjects

Total of 30 patients with diagnoses of Indeterminate ALF who fulfilled eligibility criteria were recruited in the study. This study was conducted over a period of three years from May 2011 to May 2014. Information regarding various demographic 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) and coagulogram of subjects were carried out.

Eligibility criteria

Inclusion criteria include patients having age >18years 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 no established etiology of ALF. Exclusion criteria include patients having viral-ALF, drug-induced ALF, autoimmune ALF, acute on chronic liver failure, ALF during pregnancy and hepatic shock.

Detailed study design

After ALF was diagnosed, a detailed history was taken for any hepatotoxic drug intake, including homeopathic, herbal medications and intravenous drug abuse. Indeterminate cause was diagnosed in a patient with clinical and biochemical features of FHF, absence of acute viral markers of known hepatitis viruses (A–E), no exposure to drugs, hepatotoxins, systemic infections, biliary obstruction or infection and metabolic liver diseases.

Blood samples of all the patients were taken for the etiological diagnoses, which included hepatitis B surface antigen (HBsAg), hepatitis B core IgM (HBc-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 a study when indicated.

Supportive treatment

All patients were managed with the standard supportive care treatment.24 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, hypertonia 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 1.5 mg/dl. Response to treatment was monitored clinically (grade of encephalopathy) and biochemically (bilirubin, PT, INR, etc.).

Statistical analyses

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 $\chi 2$ 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 30 patients of indeterminate ALF in total. Table 1 shows the clinical profile of patients with indeterminate ALF when categorized as survived and died. There were 12 patients in the survived group and 18 patients in died group. Mortality was 60%. Majority of the patients were females (56.7%). Coma grade at the time of admission showed that the majority of patients (60%) had grade III and IV encephalopathy.

The patients in both the groups were comparable for the different grade of encephalopathy (p=0.368) despite more patients in died group having a higher grade of encephalopathy.

Table 1: Baseline characteristics of indeterminate ALF on the basis of survival.

Characteristics	Total (n=30)	Survived (n=12)	Died (n=18)	P value*
Categorical variables [N (%)]				
Female gender	17 (56.7)	7 (58.3)	10 (55.6)	0.885
Hepatic- encephalopathy				0.368
Grade I-II	12 (40)	6 (50)	6 (33.3)	
Grade III-IV	18 (60)	6 (50)	12 (66.7)	
Fever	12 (40)	6 (50)	6 (33.3)	0.368
Vomiting	10 (33.3)	4 (33.3)	6 (33.3)	1.000
Continuous variables [mean±SD]				
Age (in years)	32.6±12.5	30.6±11.6	42.6±10.2	0.005
INR	2.8±1.3	2.3±1.1	3.2±1.0	0.027
Bilirubin (mg/dl)	22.9±7.9	16.4±8.5	26.3±8.4	0.004
AST (mg/dl)	1034 ±678	768 ±694	1196±440	0.047
ALT (mg/dl)	894±723	690±756	1150±466	0.048
Albumin (g/dl)	2.8±0.7	2.9±0.4	2.6±0.5	0.093
Creatinine (mg/dl)	1.4±0.8	1.2±0.7	1.5±0.8	0.300
Interval between jaundice and encephalopathy (days)	44±16.4	38±18.3	52±11.4	0.015
Grade of coma	2.4±0.9	2.0±1.1	2.9±0.7	0.010
MELD score	33.4±5.6	27.5±5.8	35.8±6.7	0.001

P value <0.05 is considered statistically significant, N=Number; SD=Standard deviation

The two groups did not differ significantly with respect to fever and vomiting. The mean age in survived group was 30.6±11.6 years and in died group was 42.6±10.2 years (p=0.005). INR, bilirubin AST, ALT and creatinine were

significantly higher in died group than survived group while Albumin was similar between two groups. Mean grade of coma was significantly higher in died group than survived group (p=0.010).

Interval between jaundice and encephalopathy was more in died group than survived group. MELD score was 35.8±6.7 in died group and 27.5±5.8 in survived group and the difference was statistically significant (p=0.001).

A total of 12 patients developed renal failure during the hospital course with 2 (16.7%) in survived group versus 10 (55.6%) in died group (p=0.036). The other complication noted during hospital course included development of ascites and hypotension did not differ significantly between two groups.

Sepsis occurred in 3 (25%) patients in survived group versus 12 (66.7%) patients in died group (p=0.029). Mannitol use and need for mechanical ventilation were similar between the two groups (p=ns) (Table 2).

Table 2: Hospital course of indeterminate acute liver failure.

Characteristics	Survived (n=12)	Died (n=18)	P value*
	N (%)	N (%)	
Renal failure	2 (16.7)	10 (55.6)	0.036
Development of ascites	2 (16.7)	4 (22.2)	0.716
Sepsis	3 (25)	12 (66.7)	0.031
Mannitol	3 (25)	5 (27.8)	0.904
Hypotension	2 (16.7)	5 (27.8)	0.518
Mechanical ventilation	2 (16.7)	3 (16.7)	1.000

*P<0.05 is considered statistically significant

The mean number of days of admission in hospital in the survived group was 7.9±3.6 versus 12.1±3.3 in died group. The difference between the two groups was statistically significant (p=0.003) (Table 3).

Table 3: Length of hospital stay in survived group and died group.

	Survived Mean±SD (Range)	Died Mean±SD (Range)	P value*
Duration of hospital stay (days)	7.9±3.6 (5-12)	12.1±3.3 (8-15)	0.003

*P<0.05 is considered statistically significant

DISCUSSION

Despite major advances in hepatology, ALF remains a major challenge. ALF is a rare syndrome characterized by an acute abnormality of liver function tests in an individual without underlying chronic liver disease. Thus, the term ALF is appropriately used to describe patients who develop both coagulopathy and altered mentation.[25] 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.[21] Clinical and etiological profile varies with geographical area and time.[26] Each different etiology leads to a similar final common pathway. Trying to determine etiology is essential, however, as outcomes, prognosis and the use of antidotes depend on the identification of the causative process. So, the prospective study was carried out to determine the clinical features, biochemical parameters and outcome of indeterminate ALF.

In our study there were 30 patients of indeterminate ALF, which constituted around 35% of cases of 84 ALF patients, an endemic zone for HEV.[10,27,28] Similar percentage of indeterminate cause of ALF was shown by Khuroo et al while western studies reported less percentage and other studies even reported higher percentage.[7,25,27] Whether some of these patients were related to exposure to some unidentified herbal agents or toxins could not be ascertained with certainty.[29] The increase in indeterminate etiology from western could be because of unexpected acetaminophen toxicity, a novel or unrecognized virus, metabolic or xenobiotic injury. Also, undiagnosed immune dysregulation may result in ALF.[30,31]

In this study overall mortality was 60% which is reported to be higher than other etiology (viral, drug, etc.) of ALF. This is because indeterminate ALF has a poor prognosis as studied previously.[11,12] Majority of the patients were females (56.7%). Coma grade at the time of admission showed that the majority of patients (60%) had grade III and IV encephalopathy. The mean age in survived group was 30.6±11.6 years and in died group was 42.6±10.2 years (p=0.005). INR, bilirubin AST, ALT, creatinine, mean grade of coma and interval between jaundice and encephalopathy were significantly higher in died group than survived group. MELD score was significantly higher in died group (35.8±6.7) versus survived group (27.5±5.8) (p=0.001). Sepsis and renal failure occurred more frequently in died group than survived group. Duration of hospital stay was also significantly more in died group 12.1±3.3 days versus survived group 7.9±3.6 days (p=0.003). Significantly longer hospital stay in the died group could be because of frequent complications of ALF.

Coilly et al in his study revealed that majority of patients were males (61%) with a mean age of 32±14 years.[32] Wei et al in his study also revealed that indeterminate ALF patients have significantly higher bilirubin and creatinine than other etiology.[12]

CONCLUSION

Indeterminate ALF disproportionately affected young males. Mortality was as high as 60%. The marked

difference in spontaneous survival can be explained by the severity of hepatic dysfunction on admission and more frequent complications. Duration of hospital stay was also significantly more in died group than survived group.

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