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Fulminant Hepatic Failure: Clinical Spectrum & Outcome

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Abstract:
Introduction: *Present study was conducted to assess the demographic characteristics, risk factors, causative spectrum, clinical features, natural course and outcome in patients of fulminant hepatic failure. We also tried to study the outcome in relation to risk factors, etiology, clinical and biochemical parameters and derive prognostic indicators that would be relevant to fulminant hepatic failure patients.*
Materials & Methods: *A total of 36 diagnosed cases of Fulminant hepatic failure, fulfilling our inclusion and exclusion criteria were selected for the study. The detailed clinical history, complete general, systemic examination, central nervous system examination and investigation findings was noted in a predesigned proforma. The baseline functional status (motor, sensory, autonomous) was assessed and severity of disease was classified using Modified Parsons-Smith scale of hepatic encephalopathy Classification. Patient's progress was observed on the basis of parameters in classification and addition laboratory investigations. Patients was followed till the time of discharge or death, if happens. During hospital stay, patients were monitored for occurrence of complications, if any. The outcome of fulminant hepatic failure was measured in terms of duration of recovery and discharge or death.*
Results: *Most of the patients were less than 30 years (52.8%) slight female predominance (55.6% vs 44.4%). Most common cause of fulminant hepatic failure was HEV (36.1%) followed by HBV, Indeterminate Hepatitis, AKT induced, AFLP and Auto-immune Hepatitis. Most of the patients were in encepahalopathy grade III (52.8%), followed by grade II (25%). Out of the total 36 patients, 22 patients died (61.1%), while 14 patients (38.9%) survived. Most common cause of death was cerebral edema (72.7%) while sepsis was the cause in 27.3% patients. Presence of sepsis, high total billirubin and cerebral oedema were significantly associated with poor outcome.*
Conclusion*: Most common cause of fulminant hepatic failure was HEV followed by HBV. The mortality rate with fulminant hepatic failure was high at 61.1% with most common causes being cerebral oedema and sepsis. Presence of cerebral oedema and high total bilirubin levels were significantly associated with poor outcome.*
Keywords: *Clinical Spectrum, Fulminant Hepatic Failure, Mortality, Sepsis, Viral Hepatitis*

I. Introduction

Fulminant hepatic failure (FHF) of Fulminant Hepatitis (FH) is defined by the sudden onset of hepatic encephalopathy in an otherwise healthy individual, often in association with coagulopathy, jaundice and multisystem organ failure. It is one of the most challenging gastrointestinal emergencies encountered in clinical practice and encompasses a pattern of clinical symptoms and pathophysiological responses associated with the rapid arrest of normal hepatic function [1].

The main causes of FH are viral infections, drugs, and indeterminate causes. Early elucidation of the cause of acute liver failure (ALF) is one reason to refer patients to a specialist center as quickly as possible so that its consequences can be established promptly and the appropriate treatment can be initiated.

At present there are no universally accepted criteria for the diagnosis of Fulminant hepatic failure. It carries high mortality rate with short-term transplant-free survival rate of 43% [2]. Moreover, it accounts for about 7% of liver transplants among adults [3]. The condition is potentially lethal and has poor survival rates worldwide. The condition is particularly distressing as it occurs acutely in previously 'healthy' individuals and progresses rapidly in spite of all modern treatment.

Most reports on Fulminant hepatic failure have been from the west, and particularly from three countries: the UK, France and also Japan. Recent studies conducted in north and central India found striking differences in the causative spectrum, disease pattern and prognostic factors as compared with the available data from the west [4,5]. Present work was thus conducted to study the disease features and derive prognostic indicators that would be relevant to outcome of patients of Fulminant hepatic failure.

II. Materials And Methods

Study Area and Study Period: Study was conducted at department of Medicine of Dr. V.P. Medical College and Hospital. The study duration was from August 2013 to December 2015. (21/2 years). The study was commenced after due approval from the hospital ethics committee.

Study Design: Hospital Based Prospective Observational Study

Sampling Technique & Sample Size: Consecutive type of non-probability sampling was followed for selection of study subjects. A total of 36 diagnosed cases of Fulminant hepatic failure, fulfilling our inclusion and exclusion criteria were selected for the study after taking informed consent.

Inclusion criteria

First time diagnosed cases of Fulminant hepatic failure, of age >18 yrs, irrespective of gender, based on following symptoms:

a. Onset of hepatic encephalopathy within 8 weeks of appearance of symptoms of jaundice.

And/or;

b. Elevated levels of :

i. Liver function tests: ALT, AST, alkalinephosphatase, GGT, total bilirubin, albumin

ii. Prothrombin time > 30 sec.

And/or;

c. Viral hepatitis serologies: anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV reactive.

OR

d. Non-reactive in viral hepatitis serologies.

Exclusion Criteria

1. Known case of liver cirrhosis presenting with fulminant hepatic failure.
2. Physical trauma to liver.
3. Diagnosed case of Hepatocellular carcinoma presenting with fulminant hepatic failure.
4. Patients not willing to give written informed consent.

III. Methodology

The detailed clinical history, complete general, systemic examination, central nervous system examination and investigation findings was noted in a predesigned proforma. The baseline functional status (motor, sensory, autonomous) was assessed and severity of disease was classified using Modified Parsons-Smith scale of hepatic encephalopathy Classification [6]. Patient's progress was observed on the basis of parameters in classification and addition laboratory investigations. Patients was followed till the time of discharge or death, if happens. During hospital stay, patients were monitored for occurrence of complications, if any. The outcome of fulminant hepatic failure was measured in terms of duration of recovery and discharge or death.

Statistical analysis

The data was analyzed using SPSS ver. 21 using appropriate statistical tests.

IV. Results

Most of the patients were less than 30 years (52.8%) while 22.2% were above 50 years of age. Female patients were more as compared to males (55.6% vs 44.4%). Most common cause of fulminant hepatic failure was HEV (36.1%) followed by HBV (22.2%), Indeterminate Hepatitis (22.2%), AKT induced (8.3%), Acute fatty liver of Pregnancy (AFLP) (8.3%) and Auto-immune Hepatitis (2.8%) (Table 1). Anorexia, nausea, fever, malaise and vomiting were the most common clinical features in the patients. Most of the patients were in encepahalopathy grade III (52.8%), followed by grade II (25%) (Table 2). On PA examination, ascites was seen in one third of the patients, while liver percussion > 2 was observed in 44.4% patients. Raised echo and free fluid was observed in 27.8% and 33.3% patients. Sepsis was present in 13.9% patients and cerebral Oedema was present in 52.8% patients (table 3). Out of the total 36 patients, 22 patients died (61.1%), while 14 patients (38.9%) survived (Table 4). Most common cause of death was cerebral edema (72.7%) while sepsis was the cause in 27.3% patients. Presence of sepsis, high total billirubin and cerebral oedema were significantly associated with poor outcome ($p<0.05$) (Table 5). No significant difference was observed between outcome of patients and varied etiology of hepatic failure ($p> 0.05$) (table 6).

V. Discussion

Most common cause of fulminant hepatic failure was HEV (36.1%) followed by HBV (22.2%). Hepatitis E is an important cause of acute clinical hepatitis in adults throughout Asia [7]. It is also the most common cause of acute viral hepatitis in the adult population in India [8]. In men and non-pregnant women, the disease is usually self-limited and has a case-fatality rate of < 0.1%. However, in pregnant women, particularly

from certain geographical areas in India, HEV infection is more severe, often leading to fulminant hepatic failure and death in a significant proportion of patients [9].

The disease was first recognized as a distinct clinical entity in the 1980s when sera from persons affected during a large water-borne epidemic of viral hepatitis during 1955-56 in Delhi [8] and another epidemic in Kashmir were found to lack serological markers of acute hepatitis A and B [9]. It is an enterically transmitted disease that spreads through fecal contamination of drinking water. HEV infection, a common cause of water-borne epidemics, is endemic and frequently responsible for acute viral hepatitis in developing countries [10,11]. According to the South-East Asia Regional Office of the World Health Organization (WHO), hepatitis E is widespread in developing countries, accounting for upto 30-70% of all sporadic cases of acute viral hepatitis [8,12]. HEV causes high mortality in pregnant women, 20-30% as compared to 0.2-1% in general population [13,14]. It has been implicated as an important etiological agent for sporadic fulminant hepatic failure (FHF) in developing countries. The classic epidemiological studies by Viswanathan [10] and recent serological studies by Wong et al. [15] and Khuroo et al. [8] have convincingly demonstrated that HEV is an important cause of non-A non-B viral hepatitis. Our data correspond with the existing epidemiological features of HEV.

In our study, patients with HEV (29.7 years) were relatively younger than the mean age of study subjects (35.2 years). The youngest patient was a child of 12 years age and the oldest patient was a 67-year-old male. Thus, we found that all age groups were susceptible to hepatitis E infection, which was comparable to Khuroo et al. [8]. In a study by Tejas et al. the most common age group affected was 21-30 years [16].

Jaundice was present in all patients. Anorexia, nausea, fever, malaise and vomiting were the most common clinical features in the patients of our study. In a study by Tejas et al. most common presenting symptom was jaundice (100%) followed by nausea/ vomiting (87%) [16]. In a similar study by Khuroo MS et al. [17] female to male ration was observed as 1.6:1 with mean age of patients as 31.1 +/- 14.7 years. Hepatitis E virus was the aetiological cause in 79 (43.9%) patients, while hepatitis A virus, hepatitis B virus, hepatitis C virus and non-A, non-E agent/'s could be incriminated in four (2.1%), 25 (13.9%), 13 (7.2%) and 56 (31.1%) patients respectively.

A study was done by Jaiswal AB et al. [18] to establish the aetiology and prognostic factors of Fulminant Hepatic failure (FHF) in central India. Hepatitis E virus (HEV) and hepatitis B virus (HBV) were aetiological agents amongst 41% and 37% patients with FHF respectively. Mixed infection among such cases even though observed was infrequent and 15% (n = 14) of FHF did not have any serological markers. They were presumed to be due to non A-E viral infection. Thirty-one (33%) of the FHF patients were pregnant and 29 (94%) of them were due to HEV. In present study only 8.8% females were found to be pregnanat.

In present study, out of the total 36 patients in present study, 22 patients died (61.1%), while 14 patients (38.9%) survived. Most common cause of death was cerebral edema (72.7%) while sepsis was the cause in 27.3% patients. No significant difference was observed between outcome of patients and varied etiology of hepatic failure ($p > 0.05$). Presence of cerebral oedema was significantly associated with poor outcome ($p<0.05$). Total billirubin was significantly higher in patients who died compared to survived patients (14.98 vs 11.04 mg%; $p< 0.05$). The static prognostic risk factors noted in the study by Jaiswal et al. [18] were age above 40 years, presence of identifiable viral aetiology (A to E), alcoholic status in males and pregnancy particularly in the third trimester or postpartum state. Among the dynamic factors, bilirubin level above 20 mg/dl and prothrombin time over 20 seconds appeared to be the risk factors. In a study by Acharya SK et al. [19] approximately one-third of AHF patients survive with aggressive conservative therapy, whereas two-thirds (65.6%) of deaths occur within 72 h of hospitalization. Cerebral oedema and sepsis are the major fatal complications observed. In a similar study by Kuroo et al. [17] mortality rate was observed as 72.8% and early predictors of a poor outcome are non-E aetiology, prothrombin time >30 s, grade of coma >2 and age >40 years. In a study of early indicators of prognosis in fulminant Hepatic failure by Radha KD et al. [20] mortality rate was 63.9%. Multivariate logistic regression identified 6 independent CPI of adverse outcome on admission: age >50 yr, JEI-7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, prothrombin time >35 seconds, and creatinine >1.5 mg/dL.

VI. Conclusion

Most common cause of fulminant hepatic failure was HEV followed by HBV. The mortality rate with fulminant hepatic failure was high at 61.1% with most common causes being cerebral oedema and sepsis. Presence of cerebral oedema and high total billirubin levels were significantly associated with poor outcome.

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TABLES

Table 1. Distribution of patients as per etiology of Fulminant Hematic Failure

Etiology	N	%
HEV	13	36.1%
HBV	8	22.2%
Indeterminate	8	22.2%
AKT Induced	3	8.3%
Acute fatty Liver of Pregnancy	3	8.3%
Auto-immune Hepatitis	1	2.8%
Total	36	100.0%

Table 2. Distribution of patients as per presenting symptoms

Presenting Symptoms	N	%
Fever	17	47.2%
Vomiting	10	27.8%
Pain In Abdomen	9	25.0%
Malaise	11	30.6%
Anorexia	21	58.3%
Nausea	20	55.6%
None	6	16.7%

Table 3. Distribution of patients as per Encephalopathy Grade

Encephalopathy Grade	N	%
I	4	11.1%
II	9	25.0%
III	19	52.8%
IV	4	11.1%
Total	36	100.0%

Table 4. Distribution of patients as per Outcome

Outcome	N	%
Death	22	61.1%
Survived	14	38.9%
Total	36	100.0%

Table 5a and 5b. Association of various parameters with outcome in patients of Fulminant Hepatitis

Variables	Outcome		Total	p- value
	Died (n-22)	Survived (n-14)		
Sepsis	5	0	5	**0.054**
	100.0%	0.0%	100.0%	
Cerebral edema	15	4	19	**0.02**
	78.9%	21.1%	100.0%	

Variables	Outcome	N	Mean	SD	p- value
Age	**Alive**	14	30.86	10.95	**0.12**
	Died	22	37.91	13.93	
Total bilirubin	**Alive**	14	11.04	4.39	**0.009**
	Died	22	14.98	3.96	
SGPT	**Alive**	14	411.57	294.76	**0.36**
	Died	22	533.55	435.63	
SGOT	**Alive**	14	490.29	339.61	**0.43**
	Died	22	617.55	523.64	
AP	**Alive**	14	237.07	185.03	**0.54**
	Died	22	321.09	482.13	
PT	**Alive**	14	32.21	13.43	**0.28**
	Died	22	36.59	10.40	
BUN	**Alive**	14	37.86	10.38	**0.69**
	Died	22	39.68	14.79	
Creatinine	**Alive**	14	1.65	1.16	**0.47**
	Died	22	1.41	0.83	
Hospital stay	**Alive**	14	15.00	5.38	**< 0.001**
	Died	22	7.73	3.52	

Table 6. Association of various etiologies with outcome in patients of fulminant hepatitis

Etiology	Outcome		Total
	Died	Survived	
AFLP	1	2	3
AIH	0	1	1
AKT	2	1	3
HBV	4	4	8
HEV	7	6	13
Indeterminate	8	0	8
Total	22	14	36
p- value: 0.137			