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ORIGINAL PAPER

Fulminant Hepatic Failure in an African Setting: Etiology, Clinical Course, and Predictors of Mortality

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Abstract This is prospective cross-sectional study on 37 patients presenting to different hospitals in Khartoum state, Sudan, sought to determine the etiology, clinical course, and predictors of mortality in patients presenting with fulminant hepatic failure (FHF). Patients were subclassified into hyperacute, acute, and subacute FHF; all sera were tested for hepatitis A, B, C, and E; negative samples were tested for antinuclear antibodies and anti-smooth muscle antibodies. The commonest etiologic factors included seronegative hepatitis (38%), hepatitis B virus (22%), severe *Plasmodium falciparum* malaria (8%), autoimmune hepatitis (8%), hepatitis E virus (5%), anti-tuberculous drugs (5%), and lymphomatous infiltration of the liver (5%). The mortality rate was high at 84%. Poor prognostic factors included presentation with grade III/IV encephalopathy, evidence of bacterial infection, and a prolonged prothrombin time of >25 seconds over the controls.

Keywords Fulminant hepatic failure · Encephalopathy · Predictors of mortality

Introduction

Fulminant hepatic failure (FHF) is a clinical syndrome developing as a result of massive liver cell necrosis occurring in patients without preexisting liver disease with a high mortality rate in the absence of orthotopic liver transplantation (OLT) [1]. The majority of studies on FHF were conducted in Europe [1], India [2], the United States [3], and Japan [4]; there are no reported studies from Africa. Common etiologic factors include paracetamol overdose, idiosyncratic drug reactions, hepatitis B virus infection, and seronegative hepatitis [5]. Poor prognostic features as suggested by O'Grady et al. [1] included non-A, non-B viral hepatitis, drug reactions, age >40 years, duration of jaundice before onset of encephalopathy of >7 days, serum bilirubin >300 μmol/L, and prolongation of prothrombin time >50 seconds over controls. Another study from India by Acharya et al. [2] suggested poor prognostic features to include age >40 years, presence of clinical features of cerebral edema, serum bilirubin >15 mg/dL (170 μmol/L), and prolongation of prothrombin time >25 seconds over controls.

The aims of this study were to determine the etiology, clinical course, and predictors of mortality in Sudanese patients with FHF.

Patients and methods

This cross-sectional prospective study was carried out from July 2003 to October 2004 in 4 large teaching hospitals in Khartoum state.

All patients admitted to these hospitals with a diagnosis of FHF were included in the study. FHF was defined as onset of encephalopathy occurring within 12 weeks of the onset of jaundice. FHF was further subclassified according to the criteria set by O'Grady et al. [6] into hyperacute, acute, and subacute, with an icterus–encephalopathy interval of 0–7 days, 8–28 days, and >28 days, respectively. Patients with a previous history of jaundice, alcohol consumption,

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or clinical features or ultrasound evidence of chronic liver disease were excluded from the study.

Full clinical examination was carried out on admission. Static and dynamic variables were recorded. The static variables included age, gender, and onset of jaundice prior to encephalopathy. Dynamic variables included grade of encephalopathy; clinical features of possible cerebral edema such as presence of systemic hypertension, bradycardia, hyperventilation, abnormal pupillary reflexes, and muscle rigidity; evidence of bacterial infection which included either a pyrexia $>37.5^{\circ}$C; clinical signs of pneumonia; a total white blood cell count of $>11{,}000$ cells/mm^3; or evidence of urinary tract infection.

Laboratory investigations included prothrombin time, serum bilirubin, AST/ALT levels, and serum creatinine. All patients were screened for evidence of acute viral hepatitis with hepatitis A virus (HAV) IgM antibodies (ETI-HA-IgMK Plus, DiaSorin, Saluggia, Italy), hepatitis B surface antigen (HBsAg), hepatitis B core IgM antibodies (Kehua, Biotech. Co. Ltd, Shanghai, China), hepatitis C virus (HCV) antibodies (HCV Ab, Dia. Pro Diagnostic Bioprobes, Milan, Italy), and hepatitis E virus (HEV) IgM antibodies (Genlabs, Singapore).

Samples negative for viral serology were further tested for antinuclear antibodies and anti-smooth muscle antibodies. The international autoimmune hepatitis group score was used for diagnosis of autoimmune hepatitis [7]. All patients had a blood film for malaria and abdominal ultrasound to exclude evidence of chronic liver disease or obstructive jaundice. All patients received standard management of FHF, including prophylactic antibiotics, and all were managed on general medical ward.

The study was approved by the medical research board, faculty of medicine, University of Khartoum. Consent was obtained from a close relative at the time of admission and the consultant directly in charge of the patient to put together a case series. Consent could not be obtained for post mortem examination on diseased patients.

Statistical analysis

Statistical analysis was done using SPSS software program to calculate frequencies, χ^2 and t-tests. P value was taken at a significant level of $<.05$. Multiple regression analysis was used where appropriate to define strength of associations between mortality and the different risk factors.

Results

Thirty-seven patients presenting with FHF were included in the study; 57% were males. Mean age of the study group was 38 years (range, 19–75 years). Twenty-two patients (59%) were <40 years old. Fourteen patients (38%) presented with hyperacute FHF, 12 (32%) presented with acute FHF, and 11 (30%) presented with sub acute FHF (Table 1).

Table 1 Demographic and clinical profiles of 37 patients presenting with FHF

Variable	Survivors, *n* (%)	Total *N* (%)
Number	6 (16)	37 (100)
Gender		
M	4 (19)	21 (57)
F	2 (13)	16 (43)
Age (y)		
≤40	5 (23)	22 (59)
>40	1 (7)	15 (41)
Icterus–encephalopathy interval (days)		
0–7	4 (29)	14 (38)
8–28	2 (17)	12 (32)
29–84	—	11 (30)
Grade of encephalopathy		
I	2 (40)	5 (13)
II	4 (50)	8 (22)
III	—	17 (46)
IV	—	7 (19)
Cerebral edema		
Yes	1 (7)	15(41)
No	5 (23)	22 (59)

The majority of cases were due to seronegative hepatitis (38%), HBV (22%), autoimmune hepatitis (8%), or severe *Plasmodium falciparum* malaria (8%). Other diagnoses included HEV (5%), anti-tuberculous drugs (5%), lymphomatous infiltration of the liver (5%), acute fatty liver of pregnancy (3%), acute Budd–Chiari syndrome (3%), and ketoconazole toxicity (3%; Table 2). None of our patients used over the counter drugs or herbal medicines and none used intravenous drugs.

Table 2 Etiology of FHF in 37 patients

Etiology	Survivors (*n*)	Nonsurvivors (*n*)	Total *N* (%)
Number	6 (16)	31 (84)	37 (100)
Seronegative hepatitis	1	13	14 (38)
HBV	2	6	8 (22)
Severe *falciparum* malaria	1	2	3 (8)
Autoimmune hepatitis	1	2	3 (8)
HEV	1	1	2 (5)
Anti-tuberculous drugs	—	2	2 (5)
Lymphomatous infiltration	—	2	2 (5)
Acute fatty liver of pregnancy	—	1	1 (3)
Budd–Chiari syndrome	—	1	1 (3)
Ketoconazole toxicity	—	1	1 (3)

Table 3 Multiple logistic regression analysis of poor prognostic factors

Factor on admission	*P* value
Evidence of infection*	<.021*
Grade III/IV encephalopathy*	<.031*
Prothrombin time >25 seconds*	<.041*
Evidence of cerebral edema	<.054
Jaundice–encephalopathy interval >28 days	<.058
Bilirubin level >18 mg/dL	<.059
Age >40 years	<.068
Serum creatinine >1.2 mg/dL	<.585

*Significant; $P < .05$.

Poor prognostic factors included a prolonged prothrombin time >25 seconds over control, evidence of bacterial infection and grade III/IV encephalopathy on admission (Table 3). The mortality rate was a high at 84%.

Discussion

This is one of the few studies on FHF in Africa; most of the studies have been reported from Europe [1], Asia [2], the United States [3], and Japan [4].

HBV constituted 22% of our cases; this is likely due to the fact that HBV is endemic in Sudan with seroprevalence of HBsAg reaching >18% in some areas [8]. None of our patients presented with paracetamol overdose, reflecting the fact that hair-dye poisoning [9] and not paracetamol is commonly used in suicidal intent in our population, and none had HAV infection, which may be explained by the fact that HAV continues to be endemic in Sudan with a high prevalence of infection during childhood [10, 11]. In the Kings College Hospital series [1] in the United Kingdom, paracetamol overdose constituted >50% of cases and HAV infection 6% of cases. In India [2] non-A, non-B hepatitis constituted 62% of cases followed by HBV infection in 27% of cases.

HCV antibodies were detected in 1 case; unfortunately, we were unable to test for HCV RNA in our patients, so it would be difficult to relate the cause of acute liver failure to HCV. Although we did not include HCV as a cause of FHF in our series, it is interesting to note that cases of HCV infection causing FHF were reported in Japan [4] and India [2] but not Europe [1].

Severe *Plasmodium falciparum* malaria infection constituted 8% of our study group. Although it is still debated whether severe *Plasmodium falciparum* malaria is a cause of FHF, in recent years isolated cases have been reported from various parts of the world [12, 13]. One patient presented with generalized lymphadenopathy, hepatosplenomegaly, jaundice, and encephalopathy. Lymph node biopsy revealed non-Hodgkin's lymphoma.

Of our patients, 30% presented with subacute FHF with encephalopathy occurring 4 weeks after onset of jaundice (45% had seronegative hepatitis, 36% had HBV, and the rest were due to drug reaction and autoimmune hepatitis). None of these patients survived, and although this was not a statistically significant predictive factor for mortality in our study, duration of jaundice before onset of encephalopathy of >7 days was a poor prognostic factor in the Kings' College Hospital series [6], where 22% (after exclusion of cases due to paracetamol overdose) presented with subacute FHF (83% were due to non-A, non-B hepatitis, the rest due to HAV, HBV, and drug reaction). This is different from studies from India [2], where none of the patients presented with subacute FHF.

Of our survivors, 80% were <40 years old and all presented with hyperacute or acute FHF similar to other studies [1]; they mostly had HBV, HEV, and seronegative hepatitis. Although age was not a statistically significant prognostic factor in our study, age <40 years was noted to be a good prognostic factor by O'Grady et al. [1].

None of those presenting with drug toxicity secondary to anti-tuberculous drugs or ketoconazole survived, similar to the study from Kings College Hospital in London [1].

Evidence of bacterial infection, a prolonged prothrombin time >25 seconds over controls, and presentation with grade III/IV encephalopathy were identified as poor prognostic factors in our patients; they were also noted as poor prognostic factors in India [2].

Our mortality was higher than other studies [1, 2], at 84%. We believe that the high prevalence of seronegative hepatitis in our study group and the fact that all of our patients could only be managed in general medical wards owing to lack of facilities to manage such patients in intensive care units and lack of facilities for OLT may have all been confounding factors that contributed to our high mortality.

Conclusion

We conclude that in our country seronegative hepatitis together with HBV constitute the major etiologic factors leading to FHF resulting in a high mortality rate. We believe there is a need to investigate for the role of other viruses in the etiology of seronegative hepatitis in patients with FHF in this country.

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