Etiology & Prognostic Factors of Fulminant Hepatic Failure In Children (A Hospital –Based Study)

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ABSTRACT:

BACKGROUND:

Fulminant hepatic failure (FHF) is one of the most challenging pediatric emergencies encountered in clinical practice and encompasses a pattern of clinical symptoms and pathophysiological responses associated with the rapid arrest of normal hepatic function. Major differences exist in etiology of FHF between western & eastern countries.

OBJECTIVE:

To study etiologies, prognostic factors and the outcome of Fulminant Hepatic Failure in a sample of Iraqi children.

PATIENTS AND METHODS:

A prospective study was done on (31) patients with (FHF) admitted to the Gastroenterology and Hepatology unit in Children Welfare Teaching Hospital (During the period from January 2010-January 2011). The patients referred to our center from all over Iraq.The diagnosis of FHF was based on the presence of biochemical evidence of acute liver injury (elevated plasma transaminases), associated with PT > 15 seconds, not corrected by vitamin K, in the presence of clinical hepatic encephalopathy, or PT > 20 seconds with or without clinical hepatic encephalopathy in a patient previously healthy or have well compensated liver disease. Detailed history, clinical examination, routine biochemical parameters, and relevant diagnostic test carried out to all patients.

RESULTS:

During the study period, (31) patients admitted with the diagnosis of FHF. Eighteen males (58.1%) and 13 females (41.9%), the most common affected age group was toddlers. The mean age of the study population was (2.93± 1.06).The most common etiology was viral in 15(48.3%) cases. {10(32.2%) had HAV}, 3(18%) had HBV, and 2(6.5%) had HEV} viruses, 2(6.5%) had CMV & 1(3.2%) had herpes virus hepatitis. Two (6.5%) had Galactosemia, 2(6.5%) had Wilson's disease and 2(6.5%) had autoimmune hepatitis. Etiology could not be established in 5(16.1%) of cases .Twenty patients died with death rate of (64.5%).

CONCLUSION:

The study indicates that Hepatitis A was the most common cause of FHF with high mortality rate. Those who died were younger, suffered GI bleeding, a higher grade of encephalopathy, longer duration of illness before onset of encephalopathy, prothrombin time > 41seconds, had higher bilirubin & lower SGPT, lower albumin, & lower blood sugar.

KEY WORDS: fulminant hepatic failure.

INTRODUCTION:

Fulminant hepatic failure (FHF) is rare but devastating syndrome that results in the death of most children affected. The broadest definition of fulminant hepatic failure is the failure of vital function of the liver occurring within weeks or a few months of onset of clinical liver disease.[1] Terms; such as subacute hepatic failure, subacute hepatic necrosis, and late onset hepatic failure used to describe cases in which encephalopathy develop 8-24 weeks after the onset of liver disease. Unlike in adult, encephalopathy is not regarded essential for FHF diagnosis in children because it is difficult to detect in infants. [2]

In developing countries, infectious hepatitis especially HAV is the most common cause, while in endemic areas, hepatitis B is the most common cause. Using HBV vaccine in the last few years lead to decrement of its incidence but with

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concomitant increase in the proportion of non A-non G hepatitis which has poor prognosis and associated with aplastic anemia .Other causes include drugs and toxins,ischemia,autoimmune,malignancy,and idiopathic .[3]

Approximately 250 children are affected each year in USA ,mortality rate 75-80% of the affected children which greatly improved after introduction of liver transplantation.FHF cause approximately 0.1% of all deaths and 6% of liver related deaths .[4]

Regional and geographic differences in etiologies also influence the clinical course and nature of the disease. In developed countries, metabolic disease such as hereditary Tyrosinemia ,Galactosemia, inborn errors of fatty acid oxidation , mitochondrial respiratory chain disease, inborn error of bile acid metabolism ,hemophagocyticlymphohistiocytosis with or without HBV is the most common cause of FHF.[5]

At the time of presentation 80-90% function of liver cells is lost, outcome in children is better than adult because of ability of liver cells to regenerate and complete recovery is possible. [6]

Mechanism that leads to FHF are poorly understood, it is unknown why only 1-2% of patients with viral hepatitis experience liver failure. [7]

Liver transplantation is the only therapeutic option for FHF, but the shortage of available donor organs is the major limiting factor in liver transplantation .Other surgical but less effective method are hepatocyte transplantation and bioartificial liver.[8]

This study was done to find out the etiology, prognostic factors, and outcome of Fulminant Hepatic Failure in Children.

PATIENT AND METHODS:

A prospective study was done on (31) patients with diagnosis of FHF admitted to the Gastroenterology and Hepatology unit in Children Welfare Teaching Hospital (During the period from January 2010-January 2011), The patients were referred to our center from all over Iraq.

The diagnosis of FHF was based on the presence of biochemical evidence of acute liver injury (elevated plasma transaminases), associated with PT > 15 seconds, not corrected by vitamin K, in the presence of clinical hepatic encephalopathy, or PT > 20 seconds with or without clinical hepatic encephalopathy in a patient previously healthy or have well compensated liver disease.[9]

The age of the study group was between (birth-16 years), divided into:-

- Neonates (0-30days).
- Infants (>30 days- 1 year).
- Toddlers (>1year-6 years).
- School age (>6 years-16 years).

Regarding staging of encephalopathy (stage I ,lethargy and difficulty in performing mental tasks, stage II ,drowsiness and asterixis, stage III, stupor and hyper-reflexia ,stage IV ,coma). [7]

Patients with malignant diseases &all cases of acute liver failure associated with liver disease more than 24 weeks history were excluded from the study.

All patients were evaluated with a detailed history and clinical examination on admission; In addition to routine investigations, patients sera were screened for serological markers of hepatitis A, B, C, & E using ELISA. Special investigations include serum ceruloplasmin & Serum copper & 24 hours urine copper, immune markers and metabolic studies as needed. Radiological investigation include (chest X ray, ultrasound, CT or MRI), liver biopsy could not be done because of the critical situation of all patients in the study group.

The patients were nursed in Gastroenterology and Hepatology unit with standard supportive treatment & close monitoring. Liver transplantation is not available in our center.The result were analyzed using Chi square, with P-value of less than 0.05 was considered significant.

RESULTS:

Out of 31 patients with the diagnosis of FHF enrolled in this study there was 18 males (58.1%) and 13 females (41.9%) with ratio of 1.4:1.The mean age of the study population was toddlers(2.93± 1.06).

Table (1) showed that viral hepatitis was the most common etiology in 18patients, hepatotropic viruses in 15(48.4%),CMV in 2 infants(6.5%), Herpes virus in 1 infant(3.2%).No causes found in 5(16.1%) from the available investigations in our unit.

Table 1: Etiology of the FHF cases of the study Groups.

etiology	Age groups									
	Neonates		Infants		Toddlers		School ages		Total	
	Count	%	Count	%	Count	%	count	%	count	%
Hepatitis(Hepatotropic viruses)	0.0	0.0	2	6.5	10	32.3	3	9.7	15	48.3
CMV	0.0	0.0	2	6.5	0.0	0.0	0.0	0.0	2	6.5
Herpes	0.0	0.0	1	3.2	0.0	0.0	0.0	0.0	1	3.2
Galactosemia	1	3.2	1	3.2	0.0	0.0	0.0	0.0	2	6.5
Autoimmune hepatitis	0.0	0.0	0.0	0.0	1	3.2	1	3.2	2	6.5
Wilson's disease	0.0	0.0	0.0	0.0	1	3.2	1	3.2	2	6.5
septic shock	0.0	0.0	2	6.5	0.0	0.0	0.0	0.0	2	6.5
Unknown	0.0	0.0	2	6.5	3	9.7	0.0	0.0	5	16
Total	1	3.2	10	32.4	15	48.4	5	16	31	100

The association of hepatotropic viral hepatitis infection with fatalities reveals 7/10of hepatitis A & 2/3 of HB infection as shown in table 2.

Table 2: The association of hepatotropic viral infections with the outcome of the FHF in this study.

	Total		Survived(n=5)		Non survived(n=10)	
	n	%	n	%	n	%
HAV	10	32.2	3	9.7	7	22.5
HBV	3	9.7	1	3.2	2	6.5
HEV	2	6.5	1	3.2	1	3.2
Total	15	48.4	5	16.1	10	32.2

Correlating the different prognostic factors to the rate of mortality, it was found that poor prognosis was found in all factors except two factors (SGOT& ALP) as shown in table 3.

Table 3: Correlation of the different prognostic factors to the outcome in 31 child with fulminant hepatic failure.

	All patient (mean±SD)	Survived (mean±SD)	Non survived (mean±SD)	p.value
Age (year)	2.63±2.72	3.94±2.72	1.92±2.51	0.04
Time from jaundice to encephalopathy (days)	20.83±14.71	9.72±6.1	26.95±14.54	0.001
GI bleeding	1.77±0.42	2.0±0.00	1.65±0.48	0.02
TSB (mg/dl)	18.23±5.27	14.33±4.11	20.37±4.63	0.001
S.albumin (g/l)	30.35±4.24	33.18±3.78	28.8±3.70	0.004
S.SGPT(U/l)	377.64±70.6	428.6±63.7	349.6±58.45	0.002
S.GOT(U/l)	288.7±103.8	325.18±93.78	268.7±105.92	0.15
S.ALP(U/l)	261.4±36.02	269.54±29.97	257.0±38.95	0.36
PT(seconds)	36.35±12.9	27.09±9.59	41.45±11.74	0.002
RBS(mg/dl)	79.9±38.54	104.72±26.3	66.30±37.81	0.006

The grades of encephalopathy were correlated with survival (as shown in figure 2). The higher mortality were associated with higher grades 3& 4(84.6 % & 100 % respectively), in contrast to patient present with grade 1 (0%) & in grade 2 (25%). Patients without encephalopathy had greater mortality (50%) than those with grade 1& 2 encephalopathy.

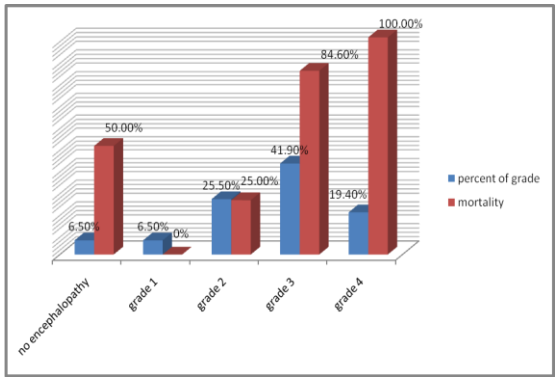

Figure 2: Grade of encephalopathy and outcome in FHF.

DISCUSSION:

In this study, the most common etiology was viral hepatitis in 15(48.4%) of cases including HAV 32.3 %,HBV 9.7% ,& HEV 6.5% .In study from India by Poddar et al , viral hepatitis was also the major cause of FHF, which constituted 94% of cases, HAV was 51% ,HEV in 25%, HAV + HEV in 10% and HBV in 7.5%.[10] Another study from karatchi also noted that viral hepatitis is the major cause of FHF, which constituted 74% of cases, including HAV in 56% and HBV in 18%.[11] whereas, hepatitis B is predominant in the far East and hepatitis C in Japan.[12,13] Squire et al found 1% Hepatitis A, and no cases of Hepatitis B &6% of patients had herpes simplex virus and Epstein Barr virus. [14]In this study CMV was found in 2 (6.5%) patients, and Herpes Simplex virus in 1 (3.2%) patient. Children are more prone to acquire hepatitis A virus in our population due to its high prevalence in the community, poor socioeconomic condition & no HAV vaccine in our national vaccination program.

In this study, 2(6.5%) patients had Wilson's disease, 2 patients had Galactosemia (6.5%), & 2 with autoimmune hepatitis (6.5%). Bendre et al also found Wilson's disease in 5.5% of his cases. [15]Another Study from Karatchireported 8% of their patients had Wilson's disease and 2% had autoimmune hepatitis. [11] Squires et al observed Wilson disease and defects or deficiencies in mitochondrial function and metabolism (i.e., mitochondrial hepatopathies) in 18% of cases, and autoimmune hepatitis in 6% cases among 348 children with FHF. [14] Durand et al. noted Neonatal Hemochromatosis and Mitochondrial Cytopathy as important causes of neonatal FHF [3]; whereas Mieli-Vergani et al. noted hemophagocyticlymphohistiocytosis as the most important cause [16].

Although drug induced fulminant hepatitis is a major cause of FHF in western world, none was detected in this study. Septic shock with liver failure was observed in 6.5% in the current study, it was not identified by Bendre et al [15], Squires et al [14], or by Poddar et al [10].

We could not find any definite cause of FHF in (16.1%) of our patients. The only availableviral studies in our setting were for A, B, C, E. No cause could be identified in 22% of cases by Bendre et al [15], 6% by Poddar et al [10], and 49% by Squires et al [14]. Obviously, some unknown environmental toxins, metabolic disorder, non A - non G viruses or other infectious agent have to be investigated as causative agents. [17]

Mortality of patients in this study was 20 patients (64.5%), (60%) inKaratchi study[11], (39 %) inBendre et al[14], (25%) inPoddar et al[10]andin Squires et al study mortality was (20.8%) among patient who were not transplanted[14] .Way lee et al observed that overall survival without liver transplantation was (33%) , which is not significantly different from the (29%) reported from King's College Hospital published 20 years ago, indicating that there has been no improvement in supportive management for this fatal disease[18].But in the last 2 decades, liver transplantation has significantly advanced the management of FHF, improving the survival rate to (60%)[19].

In this study Patients' outcome was influenced by number of factors and mortality was highest among children with mean age 1.9±2.5 year ,Poddar et al also found mean age of the death was

4.4 ± 2.9 years [10], Squires et al showed higher mortality among children less than 3 years of age [14], O'Grady et al. noted that children younger than 10 years with FHF had a worse prognosis than older age groups [20].

Grading of hepatic encephalopathy remains an important predictor of the outcome. Grade III and grade IV has poor outcome because these stages are commonly associated with cerebral edema [10]. In this study mortality with grade III was (84.6%), and (100%) with grade IV as compared to none of patients with grade 1 and (25%) with grade II, Other studies also reported higher mortality in higher grade of encephalopathy such as Bandre et al who showed (85.7%) with grade III and grade IV and (9%) with grade I & II [15] , Similarly Poddar et al observed that all patients with grade I or II and (53%) with grade III or IV recovered while (47%) with grade III or IV died [10]. Squires et al observed that only (25%) of grade III or IV had a spontaneous recovery [14].

In this study, it was found that better survival of the patients was associated with the shorter time to onset of encephalopathy; also Rivera-Penera et al noted that children with a shorter duration of encephalopathy after the onset of clinical disease were more likely to survive without liver transplantation. [21]

Poor outcome is also related to the severity of coagulopathy as evidenced by the current study (PT 41.4 seconds in non-survived as compared to 27 seconds in survived). Similarly, Bandre et al observed PT 32 seconds in dead patients as compared to 18.8seconds in recovered patients [15]. Squires et al identified INR > 2.55as risk factor to predict death [14].In this study GI bleeding was associated with high mortality, also observed by bender et al [15]. A study by Srivastava and colleagues on 41 children with FHF, showed the presence of GI bleeding to be independent predictors of mortality. [22]

Total bilirubin and SGPT are also predictive factors of mortality because high serum bilirubin with lower SGPT reflects the severity of liver dysfunction and liver injury[7]. The current study showed higher bilirubin i.e. (20.37±4.63) and lower SGPT levels i.e. (349.6±58.45) in non-survived group as compared with survivors (14.33±4.11, 428.6±63.7 respectively). Similarly Bandre et al observed higher bilirubin in non-survival i.e. (13.9) versus (10.9mg/dl) in recovered patients and lower SGPT in non-survived i.e. (530.6) versus (1385IU/L) in recovered patients [15]. However Poddar et al reported a higher serum bilirubin in non-survival i.e. (25.5 mg/L) versus (12.8 mg/L) in recovered patients &the SGPT level didn't affect the outcome [10]. Squires et al identified serum bilirubin (> 5mg/dl) as a risk factor to predict death [14].

It was noted from this study that children with worse hepatic synthetic function (low albumin) were less likely to recover spontaneously which was observed also by Way lee et al [17].

Interestingly, it was found in this study that low random blood sugar at presentation is another indicator of mortality especially if associated with seizures, as 4 patients presented with hypoglycemia & seizure, 3 of them died, a finding which could not be seen in other literatures. In this study, gender of the patient, serum ALP & SGOT didn't show any significance regarding outcome. Way lee et al found also the sex of child and S. ALP level were not significant factors affecting the outcome [18].

CONCLUSION:

From this study it was concluded that Hepatitis A was the most common cause of FHF (32.3%) with high mortality rate. Those who died were younger, suffered GI bleeding, with a higher grade of encephalopathy, longer duration of illness before onset of encephalopathy, prothrombin time > 41seconds, had higher bilirubin & lower SGPT, lower albumin, & lower blood sugar.

Recommendations

1-Take all measures to lower the risk of HAV infections (thorough cleaning and hand washing, good sanitations and sewage disposal systems and vaccination).

2- Prompt and comprehensive medical intervention in patients with hepatic encephalopathy and GIT bleeding.

3- Precise metabolic investigations as soon as possible to treat the patients and prevent the complications.

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