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Acute Liver Failure in Children: Clinical Presentation and Management

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ABSTRACT

Introduction: *Acute liver failure (ALF) is an uncommon condition in which rapid deterioration of liver functions results in coagulopathy, usually with an international randomized ratio (INR) of greater than 1.5 which is not corrected by a single dose of vitamin K, the condition associated with encephalopathy or INR 2 or more and is not corrected by a single dose of vitamin K without encephalopathy. Acute liver failure (ALF) is a life-threatening condition characterized by jaundice, encephalopathy and coagulopathy leading to multi-organ failure in a patient with no prior history of liver disease and carries a very high mortality rate.*

Objective: *To study the clinical presentation and management of acute liver failure (ALF) among children admitted to Jaffer Ibn Oaf Teaching Hospital in Khartoum, Sudan during the year 2019.*

Methods: *A descriptive cross sectional and hospital-based study conducted in all children presented to Jaffer Ibn Oaf Teaching Hospital in Khartoum, Sudan with acute liver failure during January to December 2019. The study sample was calculated by total coverage of all patients. Study questionnaires captured mainly quantitative data. The data was reviewed and analyzed into descriptive and inferential statistics by using computerized software package for window statistical package for social science (SPSS) version 21.*

Results: *47 children had acute liver failure were included. The prevalence of pediatric ALF in the studied hospital was 8.95%. The majority of participants were males and were 2 months to 14 years of age. All patients (100%) presented with jaundice, 38 (80.9%) had weakness and fatigue, 23 (48.9%) developed encephalopathy, mainly grade-I, 19 (40.0%) had nausea, 16 (34%) had ascites and 7 (14.8%) had seizures. INR was prolonged in all patients. Most patients had abnormal liver function tests. Almost all patient received vitamin K injection. Many patients needed pressure and circulation support and special treatment based on the underline cause. The mortality rate was 34% and 29.8% of the patients were recovered without liver transplantation. Statistically significant best outcome associated with elder age and hepatic encephalopathy grade-1. Poor outcome was significantly frequent among patients with anemia, thrombocytopenia, leukocytosis, hypokalemia and high liver enzymes.*

Conclusion: *Pediatric acute liver failure mainly presented with jaundice, weakness and fatigue, grade-I encephalopathy, nausea, ascites and seizures. Treatment was mainly supportive with some patient needed treatment for the underlying causes. Poor outcome associated with anemia, thrombocytopenia, leukocytosis, hypokalemia and high liver enzymes.*

Keywords
Acute liver failure, Children, Clinical presentation, Management.

Introduction

Acute liver failure (ALF) is an uncommon condition in which rapid deterioration of liver functions results in coagulopathy, usually with an international randomized ratio (INR) of greater than 1.5 which is not corrected by a single dose of vitamin K, the condition associated with encephalopathy or INR 2 or more and is not corrected by a single dose of vitamin K without encephalopathy. Acute liver failure often affects children and carries a very high mortality. For an adult to be classified as having ALF, hepatic encephalopathy within 8 weeks of the development of clinical jaundice, in the absence of a pre-existing liver condition is required. However, hepatic encephalopathy is particularly difficult to assess in children and neonates [1,2].

ALF is the final common pathway of a variety of insults to the liver. There is considerable variation in the etiologies round the world, with acute viral hepatitis and drugs accounting for the majority of cases. In children, acute viral hepatitis is the most common identified cause in most of the series; but there is a lot of geographical variation. Hepatitis A virus (HAV) is the commonest cause of ALF in children from developing countries, being reported in 40%-60% cases, while hepatitis E virus (HEV) is seen only in 2%-4.6% cases [3]. In children younger than 7 months, metabolic and infectious diseases were the most commonly known etiologies. In another study; herpes simplex virus (HSV) was the most common infectious etiology for Paediatric Acute Liver Failure (PALF) [4]. Acetaminophen overdose was the most common cause of drug-induced ALF, accounting for more than three quarters of drug-induced cases [5].

Children who presented with features of ALF should undergo diagnostic evaluation to ascertain the cause of liver failure and extent of liver injury. All patients should undergo complete physical examination, including a thorough assessment of their neurological status. Laboratory evaluation of these patients should include assessment of liver synthetic function, a complete metabolic panel, serum ammonia and a complete blood count. To better define the etiology of acute liver failure, the evaluation should include age-appropriate testing for infectious causes, metabolic liver diseases, autoimmune diseases and Wilson disease [6]. The evaluation should include ultrasound of the abdomen with Doppler examination. Liver biopsy should be considered when the diagnosis is unclear and more information is needed regarding the extent of liver injury. Liver biopsy in the setting of ALF is generally done via trans-jugular approach. One needed to use caution in interpreting the degree of liver necrosis as the extent of liver injury may not be uniform. Adults ALF studies have suggested that liver biopsy showing more than 50% to 75% necrosis as a poor prognostic factor [7,8].

Criteria for the diagnosis of Acute Hepatic Failure are rapid deterioration from health to coma over a short time course (usually less than two weeks), coma with hyperammonemia, coagulopathy: prolonged prothrombin (PT) and partial thromboplastin times (PTT), other hepatic dysfunctions: decreased serum levels of albumin and cholesterol, elevation in both direct and indirect reacting bilirubin and signs of acute hepatic necrosis: elevations in serum transaminases [9].

Pediatric ALF is one of the most challenging medical emergencies due to the multi-organ system involvement, potential rapid neurological deterioration and the need for multidisciplinary supportive interventions. Pediatric patients with suspected ALF should be evaluated immediately. The immediate availability of hepatologist and the level of expertise provided with the initial evaluation are crucial. Early transfer to a center with liver transplant capabilities is of paramount importance. Close monitoring of stable patients in routine paediatric hospital units may be appropriate. Pediatric patients with altered mental status or worsening coagulopathy, however, should be in setting where frequent laboratory, physiological and neurological monitoring can be accomplished which is often in an intensive care unit, as children with ALF can rapidly decompensate. The intensive care unit plays a pivotal role in the management of patients with pediatric ALF by providing support for failing organs while simultaneously allowing time for hepatic regeneration as wall as the optimization of clinical status if liver transplantation is ultimately required. According to the US ALF study group, the mortality rate for adult patients with ALF has reduced and the improvement is partly secondary to advances in critical care medicine and management strategies. Such strategies should also be used to improve the outcomes of pediatric patients with ALF [10,11].

Close collaboration between gastroenterology/Hepatology, intensive care, neurology, neurosurgeon, metabolic disease specialist and transplant surgeon will afford the best opportunity to survive. The chaos surrounding the patient with ALF makes the initial assessment challenging, but detailed history and physical examination cannot be overlooked. Hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with hepatic dysfunction. Changes in behavior, cognition, neurological examination and electroencephalogram (EEG) are assessed to characterize the patient as having one of five clinical stages of encephalopathy, ranging from stage 0 with minimal or no evidence of neurological dysfunction to stage 4 coma [12].

Admission to intensive care unit ICU and laboratory monitoring should be important. Intravenous fluids should be restricted to 85-90% of maintenance fluids to avoid over hydration yet still provide sufficient glucose and phosphorus to achieve normal values. Identify and treat complications: hepatic encephalopathy is not always clinically apparent. Distinguish a hepatic-based encephalopathy from other causes of an altered mental status. Monitoring intracranial pressure remains controversial due to associated complications of the procedure and no evidence of improved survival for those who were monitored [13]. Treatment and management tools may include plasma-pheresis or exchange, steroids, molecular absorbents recycling system (MARS), liver/hepatocyte transplant and therapy for specific disorders.

Study Methodology and Results

Study Method

This was a cross-sectional hospital-based study in Jaffer Ibn Oaf Teaching Hospital. It is a tertiary pediatric hospital located in the Khartoum city center which serves as a referral hospital for children from all states of Sudan. It has 200 beds and works 24 hours/7 days. In 2019, the total admission to the hospital was 3045 patients. Gastrointestinal department is one of the hospital departments provided medical services specialized to patients with gastrointestinal disorders. It consists of 20 beds and the total admission in 2019 was 525 patients. This study was conducted during one year (January - December 2019). Study included all children presented to the study area with acute liver failure during 2019. Inclusion Criteria were both sexes, less than 16-yenrs old, had acute liver failure. Exclusion criteria were children known cases of chronic liver disease presented with acute liver failure.

Total coverage including all cases who fitted the inclusion criteria of the study presented to the hospital during the study period. Data was collected using data sheet which was obtained from hospital records. The data was reviewed and analyzed into descriptive and inferential statistics by using computerized software package for window statistical package for social science (SPSS) version 21. Statistically significant test was performed and the results obtained were presented in figures and tables. Ethical clearance was obtained from ethical committee in Sudan Medical Specialization Board and from Ministry of Health in Khartoum State as well as hospital administration. Informed consent was obtained from all guardians of children included in the study.

Study Results

The study investigated the clinical presentation and management of children presented with acute liver failure to Jaffer Ibn Oaf Teaching Hospital throughout the year 2019. A total of 47 patients presented to the study area. They represented 8.95% of total pediatric cases admitted to gastrointestinal department during the same period. The age of the patients was found to be 2 months – 14 years. Twenty patients (42.5%) were in age group of 12 months or less., sixteen patients (34%) were in age group 1-5 years, eight patients (17%) were 5-12 years and 3 patients (6.4%) were more than 12 years. Mean age was 1.7+2.5 years (Table 1). Males were 27 (57.4%) while females were 20 (42.6%). Male to female ratio was 1.4: I (Figure 1).

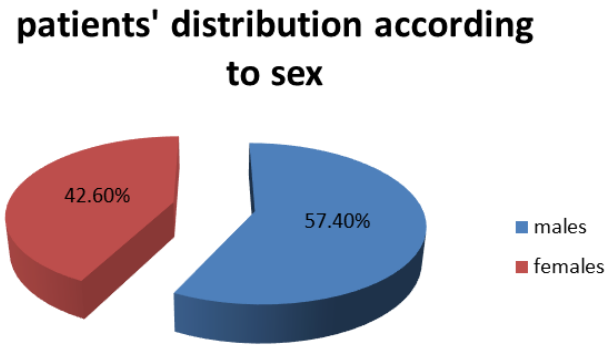

Figure 1: Patient distribution according to sex.

Age at admission	Frequency	Percentage
Less than 1 year	20	42.6%
1 year – 5 years	16	34%
5 years – 12 years	8	17%
More than 12 years	3	6.4%
Total	47	100%

Table 1: Age distribution of children with ALF [N=47].

All patients (100%) presented with jaundice, 38 (80.9%) patients with weakness and fatigue, 23 (48.9'%) patients with of encephalopathy, 19 (40.4%) with nausea, 16 (34%) with ascites and 7 (14.8%) patients presented with seizures (Figure 2). Regarding the stage of hepatic encephalopathy; 8 (34.8%) patients presented with e liver failure with hepatic encephalopathy grade-1, 4 (17.4%) patients presented with grade-2, 5 (21.7%) patients with grade-3 and 6 (26.1%) patients were with grade-4 (Table 2).

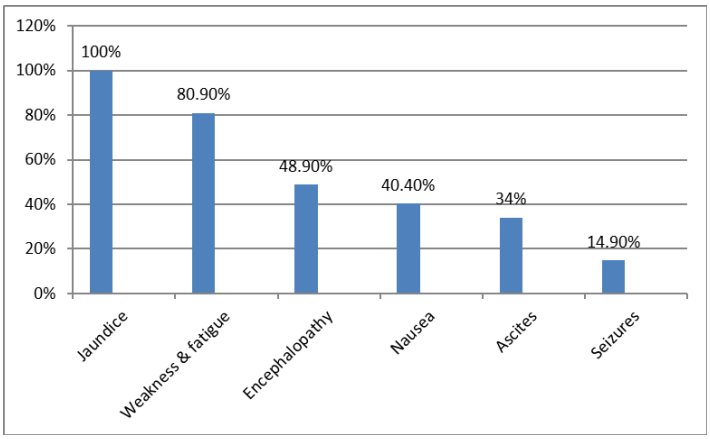

Figure 2: Symptoms and signs of ALF in the studied group.

Hepatic encephalopathy	Frequency	Percentage
Grade-1	8	34.8%
Grade-2	4	17.4%
Grade-3	5	21.7%
Grade-4	6	26.1%
Total	23	100%

Table 2: Distribution of children with ALF and hepatic encephalopathy [N=23].

Laboratory Results

Hemoglobin level was done to all patients and found abnormal in 32 (68.1%) and normal in 15 (31.9%). Platelet count was performed to 45 (95.8%) patients, while 2 (4.2%) patient's records were missing. In this study, total platelet count was normal in 22 (46.8%) and abnormal in 23 (49%) patients. Total white blood count (WBC) was performed to 45 (95.8%) patients, while 2 (4.2%) patients' records were missing. The study found platelets count normal in 20 (42.6%) and abnormal in 25 (53.2%). Serum sodium level was performed in 38 (80.9%) and found normal in

21 (44.7%) patient and abnormal in 17 (36.2%). Serum potassium was performed in 38 (80.9%) of studied patient. It was found normal in 27 (57.4%) patients and abnormal in 11 (23.5%) (Table 3). Serum urea level was performed in 35 (74.5%) patients and found normal in 33 (70.2%) and abnormal in 2 (4.3%). Creatinine level was performed to 35 patients (74.5%) and was normal in 32 (68.1%) and abnormal in 3 (6.4%).

Investigation	Abnormal	Increased	Decreased	Range	Mean ± SD
Hemoglobin	32 (68.1%)	0	32 (68.1%)	4.7 - 10	7.1 ± 1.7
Platelets count	23 (49%)	3 (6.3%)	20 (42.7%)	18 – 925	125 ± 2.3
White cell count	25 (53.2%)	23 (49%)	2 (4.2%)	3.5 71.8	17500 ± 4.5
Sodium Na+	17 (36.2%)	0	17 (36.2%)	107 – 130	11.5 ± 6.1
Potassium K+	11 (23.5%)	1 (2.1%)	10 (21.$%)	2.4 – 6.2	3.2 ± 1.7

Table 3: Laboratory results distribution of children with ALF.

Liver Function Test

Total protein level was estimated in 44 (93.6%) of participants: it was normal in 19 (40.4%) and abnormal 25 (53.2%). Serum albumin level was done in 46 (97.9%) of patients; it was normal in 13 (27.7%) and abnormal in 33 (70.2%). Total serum bilirubin (TSB) and direct serum bilirubin were found abnormal in all patients (100%). Liver enzymes; Alanin transaminase (ALT) was performed in 45 patients (95.7%); it was normal in 7 (14.8%) and abnormal in 38 (80.9%). Aspartate transaminase (AST) was performed in 45 patients (95.7%); it was normal in 4 (8.5%) and abnormal in 41 (87.2%). Alkaline phosphatase (ALP) was performed in 45 patients (95.7%); it was normal in 31 (66%) and abnormal in 14 (29.7%). PT was performed in 39 patients (83%); it was normal in 3 (6.3%) and abnormal in 36 (76.6%). PTT was performed in 31 patients (65.9%); it was normal in 1 (2.1%) and abnormal in 30 (63.8%). INR was performed in 45 (95.7%) and found abnormal in all patients (Table 4). (Some laboratory test results were missing from patients' records).

Investigation	Abnormal	Increased	Decreased	Range	Mean ± SD
Serum albumin	33 (70.2%)	0	33 (70.2%)	1 – 3.3	2.6 ± 2.1
TSB	43 (91.5%)	43 (91.5%)	0	4.5 – 33.4	17.1 ± 5.4
ALT	38 (80.9%)	38 (80.9%)	0	53 - 1338	504 ± 9.9
AST	41 (87.2%)	41 (87.2%)	0	32 – 1042	615 ± 9.7
ALP	31 (66%)	31 (66%)	0	92 – 1042	660 ± 7.9
PT	36 (76.6%)	36 (76.6%)	0	20 – 166.6	38 ± 7.9
INR	47 (100%)	47 (100%)	0	1.57 – 15	2.3 ± 1.6

Table 4: Liver function test results distribution of children with ALF.

Regarding the management of acute liver failure; it was found that forty-six (97.9%) patients received vitamin K injection, thirty-five (74.5%) patients needed pressure and circulation support, twenty-four (51.1%) received fresh frozen plasma, fifteen (31.9%) received packed red cell transfusion, twelve patients (25.5%) received special treatment based on the underline cause and 6 patients (12.8%) received N-acetylcysteine injection. None of the patients treated with hemofiltration, plasmapheresis, mechanical ventilation or liver transplant (Table 5). The study found that the cause of acute liver failure was infections in 25 patients (53.2%), 5 (10.6%) were duo to autoimmune disorders, one patient (2.1%) had metabolic cause and 16 (34.1%) had indeterminate acute liver failure. Regarding the outcome: 16 patients (34%) were died, 14 patients (29.8%) were alive and well without transplant, and one patient (2.1%) developed chronic liver disease and 16 patients (34%) with unknown outcome (Figure 3).

Management	Yes		No	
	No.	%	No	%
Vitamin K Injection	46	97.9	1	2.1
Pressure & circulation support	35	74.5	12	25.5
Fresh frozen plasma	24	51.1	23	48.9
Red cell transfusion	15	31.9	32	68.1
Treatment of underlying cause	12	25.5	35	74.5
N-acetylcystien	6	12.8	41	87.2
Ventilation support	0	0	47	100
Hemofiltration	0	0	47	100
Plasmapheresis	0	0	47	100
Liver transplant	0	0	47	100

Table 5: Management of children with ALF.

Discussion

This is a retrospective study to determine the clinical presentation and management of patients with paediatric ALF. As might be the expected, the aetiology of ALF in children was different from adult patients. The current study showed that the prevalence of acute liver failure was 8.95% of total cases admitted to gastrointestinal department during the same period in Jaffer Ibn Oaf Teaching Hospital. Our finding was high compared to other studies conducted in Thailand where they investigated the incidence rate of ALF and it was around 6.29% and in USA around 5.5% [14]. Therefore, it's important to determine the prognosis of ALF, because acute liver failure is a rapidly progressive, potentially fatal syndrome and because of the shortage of facilities of liver transplantation. The study focuses on the unique aspects of children presenting with evidence of ALF who should be considered separately in terms of medial decision making.

In the current study; 42.8% of the patients' age 12 months or less and 57.4% were males. Male to female ratio was 1.4: 1. Similarly; Sundaram (2011) found 57.4 % of the patients were males [15] whereas, Nunez-Ramos (2018) found 50% were males [16]. On the other hand; Squires (2006) found most of the patients were females [17]. This experience demonstrates age at presentation of acute liver failure is a clear predictor of outcome. In the current study; statistically significant increase age associated with the

best outcome; patient's age less than one year had the worse outcome while patients who were more than 6 years had the best outcomes. The study didn't find statistical association between gender and outcome. As ALF was more frequent in infant age, the study justified that this group may represent with congenital and inherited conditions such as hemochromatosis or other metabolic diseases.

In this study: all patients (100%) with acute liver failure presented with Jaundice as the commonest complain followed by weakness and fatigue (80.9%) and then encephalopathy (48.9%). The majority of the patients presented with hepatic encephalopathy grade-I. Additionally, the patients who presented with hepatic encephalopathy grade-I had a better prognosis than other grades. This study supports a definition of pediatric ALF that does not require hepatic encephalopathy HE. In contrast, Nunez-Ramos (2018) reported a high incidence of hepatic encephalopathy as 60% at presentation [16]. Death or transplant, however, occurred in a third of subjects even without encephalopathy. This emphasized that children particularly in infants, the presence of encephalopathy is unnecessary for the diagnosis of pediatric ALF and does not adequately predict survival. HE is difficult to asses in children and, in fact, may never become clinically apparent in the setting of ALF [18,19].

We found that all patients had abnormal INR and abnormal direct bilirubin levels. Most o the patients had abnormal complete blood count, serum proteins levels, high liver enzymes (ALT, AST & ALP), prothrombin time (PT) and partial thromboplastin time (PTT). Anemia is a frequent complication of liver disease and could be of multifactorial etiology. Similar multiple hematological abnormalities were reported by Gkamprela E. et al. [20]. Coagulopathy is another cardinal feature of ALF. The liver has the central role in the synthesis of almost all coagulation factors and some inhibitors of coagulation and fibrinolysis. Hepatocellular necrosis leads to impaired synthesis of many coagulation factors and their inhibitors [21].

In the current study; significantly high white cell count (WBC) was associated with poor ALF outcome. This may be due to that liver is an important component of the immune system. In ALF, rapid immune paralysis is well known and overt sepsis has been reported [22,23]. Similarly, a strong association between infection and course of ALF and encephalopathy has been clearly documented by: Choudhury A. et al. [22] and Cristina Sole et al. (2016) [23]. We find no association between serum sodium Na level and ALF, although Cardenas A. et al. (2014) and Liao H. et al. found different findings [24,25]. Hyponatremia is an almost universal finding due to water retention and a shift in intracellular sodium transport from inhibition of Na/K ATPase.

It clear that abnormal investigation results may indicate that those patients were susceptible to bleeding tendency, secondary infection, heart and renal failure and even multi-organ failure which may play a factor to worse their prognosis and burden the disease. Therefore, the study suggests that it is important to conduct rapid assessment and investigations of ALF patients and perform early and proper correction to improve the disease outcome.

A limitation of this study was that most of the practice regarding ALF investigations was extrapolated from adult literature and guidelines. This may lead to significant controversies in medical management of acute liver failure in children. Another limitation was missing information regarding investigations from the incomplete patients' records. Lastly, pediatric acute liver failure requires careful attention to unique characteristics of this age group. Because the study highlighted that hepatic encephalopathy is not an absolute requirement to establish the diagnosis of ALF in children; the etiologies of ALF in children differ from those in adults, with children having more infection and indeterminate cases and the outcome varies among diagnostic groups.

Conclusion

1. The prevalence of acute liver failure was 8.9% of total cases admitted to gastrointestinal department in Jaffer Ibn Oaf Teaching Hospital during the same study period.
2. Most of the patients were males with age group less than 5 years.
3. Jaundice was the commonest presentation of acute liver failure followed by weakness and fatigue then hepatic encephalopathy, the majority of whom were grade-1 encephalopathy.
4. The study highlighted that hepatic encephalopathy is not an absolute requirement to establish the diagnosis of ALF in children; the etiologies of ALF in children differ from those in adults, with children having more infection and indeterminate cases.
5. All patients had high INR, high total bilirubin levels, while most of them had abnormal complete blood count, serum proteins, ALT, AST, ALP, PT and PTT. ALF poor outcome significantly increases among patients with anemia, thrombocytopenia, leukocytosis, hypokalemia, high ALT, high AST and high INR.

Recommendations

1. To raise the awareness of doctors and other health care providers about pediatric ALF; presentation, causes, management and outcome.
2. To have special consideration to abnormal investigation results with related to poor prognosis during ALF management.
3. Conduct a cohort study in the same hospital and other health facilities for long period to generalize the findings and recommendation, create local guidelines and update available data about pediatric ALF.

Compliance with Ethical Standards

Ethical Consideration

Ethical clearance was obtained from ethical committee in Sudan Medical Specialization Board and from Ministry of Health in Khartoum State as well as hospital administration.

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