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Etiological and Clinical Spectrum of Acute Liver Failure of Infancy in Pakistan

Hussan Ali Sarwar, Huma Arshad Cheema, Aftab Anwar*, Sara Batool, Anjum Saeed, Nadeem Anjum

Children's Hospital Lahore, Lahore Pakistan, *Lahore General Hospital, Lahore, Pakistan

ABSTRACT

***Objective*:** To describe the aetiology and clinical spectrum of acute liver failure of infancy at a tertiary care hospital

***Study Design*:** Cross-sectional study.

***Place and Duration of Study*:** Department of Paediatric Gastroenterology, Hepatology & Nutrition, Children Hospital and Institute of Child Health, Lahore, from Nov 2020 to May 2021.

***Methodology*:** Infants under 12 months of age were enrolled having liver-based coagulopathy (not corrected after two doses of parenteral vitamin K, 10 mg) with INR > 2, whether encephalopathy was present or not. Encephalo-pathy is difficult to identify in infants, so it was not essential for the diagnosis of ALFI in our study. Infants diagnosed with chronic liver disease at presentation or those without final etiological diagnosis were excluded.

***Results*:** A total of 31 infants were enrolled fulfilling the criteria of acute liver failure of infancy and were studied about aetiology and clinical presentation. The mean age of presentation was 4.64±3.16 months, and males predominated in the study group (64.5%). Common clinical features were in descending order ascites in 29 (93.5%), jaundice in 28 (90.3%), pallor in 24 (77.4%) and peripheral oedema in 21 (67.7%). Metabolic liver diseases were the common cause of ALFI, constituting around (18, 58%) followed by sepsis (9, 29%). Galactosemia (11, 35.5%) stands out among the metabolic causes.

***Conclusion*:** Metabolic disorders followed by sepsis are the most common cause of ALFI.

Keywords: Acute liver failure of infancy, Aetiology, Clinical spectrum, Metabolic liver diseases.

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INTRODUCTION

Acute liver failure in infancy (ALFI) is a life-threatening condition that progresses quickly, leading to hepatic dysfunction, and has a high mortality, reaching 80 -100%.[1] Severe liver dysfunction occurs due to liver necrosis in an infant with no history of previous chronic liver disease.[2] Pediatric Acute Liver Failure (PALF) study group defined ALFI as infants with no known underlying liver disease who had evidence of a severe liver-based coagulopathy without encephalopathy.[3,4]

ALFI has several etiologies that vary according to the age of the patient and geographical areas. The wide spectrum of causes includes liver-based metabolic disorders, viral infections (herpes simplex, enteroviruses, and others), hematologic disorders, hypoxia, drugs, congenital heart diseases, vascular disorders and hemophagocytic lymphohistiocytosis (HLH).[5] Causes in infants usually are cryptogenic, HLH, metabolic diseases (neonatal hemochromatosis, tyrosinemia type 1, ornithine transcarbamylase deficiency, fatty acid oxidation defect, mitochondrial defect), toxic (Amanita phalloides, paracetamol, isoniazid, copper), infective (post septic shock, Hepatitis B, Herpes simplex Type I & II), autoimmune (liver-kidney microsomal positive).[6,7] In older children common causes are autoimmune hepatitis, drugs induced hepatotoxicity and enteroviruses.[8] Inherited metabolic disorders constitute 13-43% of causes of ALFI and include galactosemia, tyrosinemia, urea cycle defects, fatty acid oxidation defect, hereditary fructose intolerance, mitochondrial cytopathy and congenital disorders of glycosylation.[9] Early recognition of aetiology is essential as some diseases might require specific treatment or may constitute a contraindication to liver transplant (LT), an option that can improve outcomes in cases with advanced disease.[8] We described the aetiology and clinical spectrum of ALFI in our population to facilitate early recognition of disease by paediatricians and timely referral to pediatric liver centres in the country for prompt diagnosis and managemen t.

METHODOLOGY

The cross-sectional study was performed at the Department of Pediatric Gastroenterology, Hepatology and Nutrition, Children Hospital and the Institute of Child Health, Lahore, Pakistan, including 31 subjects through consecutive sampling, from November 2020 to May 2021, after taking IRB approval (Reference No. 2020-168-CHICH dated 12-11-2020) from Ethical

Correspondence: Dr Hussan Ali Sarwar, Department of Medicine, the Children Hospital Lahore, Lahore-Pakistan

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Committee. The incidence of ALFI accounts for 10-15% of all pediatric liver transplants.[9] Therefore, the sample size of 31 has been calculated with a 95% confidence level and estimated prevalence of risk factors within the target population as 10%.[9]

Inclusion Criteria: Infants of age less than 12 months with ALFI, having liver-based coagulopathy not corrected after two doses of parenteral Vitamin K, 10mg 24 hours apart with INR >2 whether encephalopathy was present or not, were included in the study.

Exclusion Criteria: Infants already diagnosed as having the chronic liver disease at presentation, infants in which diagnosis cannot be established or those with any other cause of bleeding other than liver disease were excluded from the study.

Non-probability consecutive sampling was employed. Encephalopathy was difficult to identify in infants, so it was not considered essential for the diagnosis of ALFI in our study. However, neurological distress was defined as inappropriate agitation or inconsolable crying, irritability, poor feeding or altered sleep-wake pattern according to age.[10,11]

The initial investigations of an infant with ALFI included: complete blood picture with peripheral smear and reticulocyte count, detailed liver function tests (LFTs) including PT, INR and albumin, blood glucose, urea, creatinine, electrolytes, ammonia, lactate, arterial blood gases, urine for the presence of reducing substances, and abdominal ultrasound. In general, liver biopsy is not required to identify the aetiology of patients with ALF, and it is usually contraindicated due to severe coagulopathy. However, in selected cases, when the aetiology of ALF is uncertain (e.g., autoimmune hepatitis) or a malignant infiltration is suspected, a liver biopsy may add helpful diagnostic information. To establish the aetiology of ALFI: advanced investigations (urine for succinyl acetone, alpha-fetoprotein, autoimmune markers, chromatography etc.) were advised on an infant-to-infant basis as guided by clinical history, examination and the diagnostic algorithm used in the department.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 24.0. Mean±SD were calculated for the continuous variable. In addition, frequency and percentage were calculated for categorical variables.

RESULTS

Thirty One infants met the inclusion criteria during the study period, which were included in the study. Ascites 29(93.5%) was the most common physical finding followed by jaundice 28(90.3%) and pallor 24(90.3%). 14(45.2%) infants in our study were expired (Table-I). A standard diagnostic evaluation revealed elevated aminotransferases levels, cholestasis and synthetic dysfunction consistent with diagnosis of ALFI. Laboratory parameters were shown in Table-II and advanced investigations shown in Table-III. Metabolic causes were most common among which galactosemia (GALT gene) was most prevalent (Table-IV). It was followed by sepsis (infant having documented fever >1000F + CRP >10 mg/L+ positive blood culture). Organisms isolated in this group were Klebsiella (3), Coagulase negative staphylococcus (2), Escherichia Coli (2), and Enterobacter (1).

Table-I: Clinical Features of Patients with Acute Liver Failure of Infancy

Parameters	Mean±SD	Parameters	Mean±SD
Age (months)	4.64±3.16	Length(cm)	58.5±7.06
OFC(cm)	37.80±3.68	Weight(kg)	4.77±1.74
Liver size(cm)	8.70±1.55	Spleen span(cm)	1.93±1.89
Parameters	n(%)	Parameters	n(%)
Gender			
Male Female	20(64.5%) 11(35.5%)	Family History	6(19.4%)
Encephalopathy	07(22.6%)	Acholic Stools	08(25.8%)
Jaundice	28(90.3%)	Bruises	09(29%)
Pallor	24(77.4%)	Pruritic Marks	02(6.5%)
Eye Findings	02(6.5%)	Edema	21(67.7%)
Ascites	29(93.5%)	Hypoglycemia	16(51.6%)

Table-II: Biochemical Features of Infants with Acute Liver Failure of Infancy (n=31)

Biochemical Features	Mean±SD	Biochemical Features	Mean±SD
Hb(g/dl)	9.1±1.60	INR	3.1±1.5
TLC(×109/L)	13.2±6.6	Albumin(g/L)	2.61±0.71
Platelets(×109/L)	203±121	GGT(IU/L)	123±159.6
Bilirubin(mg/dl)	12.1±8.04	Ammonia(mol/L)	143.5±118.2
ALT(IU/L)	392±1054	Blood Sugar (mg/dl)	99.69±47.21
AST(IU/L)	434±891	CRP(mg/L)	59.4±25.9
GGT (IU/L)	123±159.6	Base Excess	-3.55±1.26

Table-III:- Advanced Investigations (n=31)

Investigations	n	Mean±SD
Ferritin(ng/ml)	26	548.4±730.5
Triglycerides(mg/dl)	26	203±160.5
Lactate(mmol/L)	04	3.1±0.89
Alpha Fetoprotein	14	1.25±30913.51
Succinylacetone(µmol/L)	09	327.3±125.8

DISCUSSION

In our study, male preponderance was 64.5%, while females were 35.5%. Wands et al. conducted a similar study in which females (54.2%) were predo-

minant while males were 45.8%.[12] Family history of ALFI in siblings was present in 19.4%, which is quite high when compared with only 7.5% of participants of Durand *et al*.[10] Common clinical features in our study were ascites (93.5%), jaundice (90.3%), pallor (77.4%), oedema (67.7%) and hypoglycemia (51.6%). Bitar and colleagues did a similar study on young infants. They recorded jaundice (76%), hypoglycemia (54%), ascites (46%), renal failure (33%) and bleeding (28%) as the most common manifestations, which are in contrast to our findings.1 Encephalopathy was seen in 22.6% of subjects in our case series, which was similar to 22% of cases of infants with ALFI in Durand *et al*.[10]

Table-IV: Etiology of Acute Liver Failure of Infancy (n=31)

Causes of ALFI	n(%)
Galactosemia (GALT gene)	11(35.5%)
Sepsis	09(29%)
Familial Tyrosinemia Type I	02(6.5%)
CMV Hepatitis	02(6.5%)
Hereditary Fructose Intolerance (ALDOB gene)	01(3.2%)
Urea Cycle Disorder	01(3.2%)
Mitochondrial Cytopathy (DGUOK gene)	01(3.2%)
Neonatal Hemochromatosis	01(3.2%)
Progressive familial intrahepatic cholestasis type 2 (ABCB 11 gene)	01(3.2%)
Biliary Atresia	01(3.2%)
Niemann pick type C (NPC 1 gene)	01(3.2%)

A standard departmental diagnostic evaluation revealed elevated aminotransferases, cholestasis and deranged synthesis markers, consistent with ALFI. The mean bilirubin level in our study was 12.1mg, higher than Lu *et al*., who recorded bilirubin as 3.5mg.[13] Similarly, the mean ALT was 392 IU/L. At the same time, AST was 434 IU/L, which is almost double in value compared with the findings of Sundaram *et al*., who recorded median ALT as 156 IU/L and median AST as 215 IU/L.[3] However, the mean INR of our patients turned out to be lower (3.1) compared to others.[14] In the present study, metabolic etiologies were the most prevalent cause of liver failure, among which galactosemia (35.5%) was the most common. Various studies have concluded similar results by mentioning metabolic causes as the most common aetiology of ALFI with similar frequencies, i.e., 36% and 46.5%.[15,16] Though Bitar *et al*., commonly saw galactosemia, Durand *et al*., reported mitochondrial cytopathy as the most prevalent metabolic cause.[1,10] In contrast to our findings, Wands *et al*., found ischemic insult (54%) and perinatal hypoxic injury (33%) as the most common causes of ALFI. Liver-based IEM are a frequent cause of ALFI and might present with jaundice, hypoglycemia and liver failure in <12 months old. Therefore, IEM must always be considered a cause of ALFI in infants as eliminating a particular dietary agent and focused treatment proves lifesaving.

Sepsis was the second most common entity in our cohort, amounting to 29%. LU *et al*., have mentioned sepsis (46.7%) as the most common cause in their cohort.[13] Wands *et al*., propose perinatal hypoxic injury (33%), and Durand *et al*., mentioned neonatal hemochromatosis (16.2%) as second most causes. These findings are in contrast to our results.[10,12] Common viral infections, which can lead to ALFI in infants, are EBV, CMV, HSV type 1, HBV or echovirus. Common bacterial agents isolated in this age group are enterococcus and Gram-negative bacilli like Escherichia Coli, Proteus or Klebsiella.[17] In developing countries, infections are high, causing morbidity and mortality, sometimes leading to ALFI in some regions.[18] The outcome might be fatal in 22.2% of cases, so appropriate therapeutic measures should be taken. 45.2% of our subjects expired an outcome similar to 48.14% of participants in the infants' group of Grama *et al*.[11]

Early recognition and prompt therapeutic interventions can improve outcomes in most infants except for a few causes with multisystemic involvement, like mitochodriopathy. Niemann picks disease type c and advanced metabolic liver disease where the outcome may be guarded.

CONCLUSION

Acute liver failure in infancy is uncommon in developing countries like Pakistan. Instead, metabolic disorders followed by sepsis are the most common cause of ALFI in the present study.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

HAS: Conception, interpretation of data, drafting the manuscript, approval of the final version to be published.

HAC: Study design, data analysis, drafting the manuscript, cri-tical review, approval of the final version to be published.

AA: Critical review, approval of the final version to be published.

SB: Data acquisition, interpretation of data, approval of the final version to be published.

AS: Study design, Drafting the manuscript, interpretation of data, approval of the final version to be published.

NA: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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