Original Article

A Case Report Of Acute Liver Disease

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Abstract

Acute liver failure is defined as a severe acute liver injury for lesser than 26 [3] weeks duration with encephalopathy and impaired synthetic function in a patient without cirrhosis or preexisting liver disease. It is associated with morbidity and mortality and its overall survival rate has improved through intensive care management and advancements [1,2] in liver transplants. Etiologies vary by age with metabolic and infectious diseases prominent in the first year of life and acetaminophen overdose and Wilson's disease occurring in adolescents.

IAP definition: liver dysfunction within 8 weeks of onset of symptoms (neonates may have deranged liver functions without overt symptoms) which is uncorrectable (6-8 hours after administration of one dose of parenteral vitamin K) coagulopathy with INR >1.5 with hepatic encephalopathy or INR >2.0 in patients without encephalopathy and no evidence of chronic liver disease either at presentation or in the past.

INTRODUCTION:

Acute liver failure (ALF) is not a diagnosis but a clinical syndrome. Acute liver failure is characterized with biochemical evidence of severe hepatic dysfunction (like coagulopathy and jaundice) complicated by hepatic encephalopathy that develops within 8 weeks of the onset of the signs and symptoms of liver disease. Recognition of hepatic encephalopathy in children is difficult and may not be clinically apparent until the terminal stages of the disease process.

The Pediatric Acute Liver Failure (PALF) Study Group was formed in 2000 as a multisite, multinational consortium to prospectively study ALF in children from birth up to 18 years of age. The criteria of the study include:

(1) no evidence of a known chronic liver disease

(2) hepatic-based coagulopathy that is not corrected by parenteral administration of vitamin K

(3) hepatic encephalopathy must be present if the uncorrected prothrombin time (PT) or international normalized ratio (INR) was between 15 and 19.9 seconds or 1.5 to 1.9, respectively

(4) hepatic encephalopathy was not required if the PT or INR was greater than or equal to

Classification:

O'grady and collegues classified acute liver failure into 3 categories based on interval between the development of jaundice and onset of encephalopathy.

1. HYPERACUTE LIVER FAILURE: The onset of encephalopathy less than 7 days after development of jaundice.
2. ACUTE LIVER FAILURE: The onset of encephalopathy 8 to 28 days after development of jaundice.
3. SUBACUTE LIVE RFAILURE: The onset of encephalopathy more than 5 weeks but less than 12 weeks after development of jaundice.

This classification may help in knowing the etiology of liver failure. For example hyperacute liver failure is usually from acetaminophen poisoning or viral infections, while subacute liver failure
is usually caused by an idiosyncratic drug induced live injury, autoimmune hepatitis or Wilson's disease, cancer [6,7]

ETIOLOGY

Acetaminophen-induced liver injury

Drug-induced Liver injury (non-acetaminophen)

- Antibiotics: amoxicillin-clavulanate, ciprofloxacin, nitrofurantoin, minocycline, dapsone, doxycycline, trimethoprim-sulfamethoxazole, efavirenz, didanosine, abacavir
- Anti-epileptics: valproic acid, phenytoin, carbamazepine
- Anti-tuberculosis drugs: isoniazid, rifampin-isoniazid, pyrizinamide
- Miscellaneous: propylthiouracil, amitryptiline, statins, amiodarone, methotrexate, methyldopa
- NSAID: Diclofenac, ibuprofen, indomethacin, naproxen
- Herbs: ma huang, kava kava, Herbalife

Viral hepatitis

- Hepatitis A, B, C and E
- CMV, EBV, herpes virus, varicella zoster virus

Pregnancy specific liver diseases

- Acute fatty liver of pregnancy
- HELLP syndrome
- Preeclampsia-associated liver diseases

Ischemic hepatitis

- Systemic hypotension
- Cardiomyopathy
- severe asphyxia
- obstructive lesions of the aorta
- Autoimmune hepatitis
- Budd-Chiari syndrome

Reversible causes

- Autoimmune hepatitis
- Leptospirosis, hepatic amoebiasis, malaria, rickettsial diseases

Metabolic causes

- Wilson's disease
- Galactosemia,
- tyrosinemia,
- hereditary fructose intolerance
- fatty acid oxidation disorders
- mitochondrial disorder
- iron storage disease
- Niemann-Pick disease

MISCELLANEOUS

- Malignant infiltration
- Mushroom poisoning

Drug-induced acute liver injury

Many over-the-counter medications, dietary supplements, weight loss medications, and prescription medications can lead to acute liver injury. Liver injury from drugs are dose- dependent (acetaminophen toxicity, valproate toxicity. Obtaining a detailed medication history is important and should include the dosage, therapy start, duration of treatment, and last dose. History regarding usage of herbal products should be noted.

Acetaminophen hepatotoxicity

Acetaminophen hepatotoxicity is the most common cause of acute liver failure in developed countries. It results from excessive ingestion of acetaminophen either from inadvertent use of supratherapeutic doses for pain control. Hepatic toxicity from acetaminophen is due to increased production of the toxic metabolite N-acetyl-p-benzoquinone imine. Acetaminophen has become the first-line analgesic/ antipyretic medication for children. The usual pediatric dose ranges from 10 to 15 mg/kg/dose administered every 4 hours to a maximum of 80 mg/kg/day. The clinical presentation includes a profound uncorrectable coagulopathy and elevated serum aminotransferase levels elevated till 10,000 IU/mL coupled with highly elevated bilirubin. ALF following ingestion of a single overdose of APAP is preventable with prompt patient identification and early intervention with either oral or intravenous N acetylcysteine (NAC).19

Mushroom poisoning

Mushroom poisoning, though rarely seen, is an important cause of ALF. Amanita phalloides is the most common mushroom to cause hepatotoxicity. The diagnosis should be suspected in patients with a history of recent mushroom ingestion and in those who present with severe gastrointestinal (GI) symptoms such as nausea, vomiting, abdominal

cramping, and diarrhea. Symptoms usually start within 6 to 12 hours of mushroom ingestion and AFL occurs in a subset of patients.

Reversible causes of ALF

Autoimmune hepatitis can present as ALF. Prompt identification and early institution of immunosuppressive therapy may decrease the need for liver transplantation in patients who respond to medical treatment. Patients with hematological malignancies such as lymphoma rarely present with ALF. Severe liver involvement may be seen in some systemic infections such as leptospirosis, rickettsial infections, hepatic amoebiasis, dengue, malaria, and typhoid. In these situations, early administration of targeted antimicrobial medication may reverse ALF and restore normal functioning.

Miscellaneous

Wilson's disease can rarely present as ALF

Malignancy may also lead to ALF, either due to the presence of multiple hepatic metastases, or as a result of diffuse infiltration of the liver by malignant cells, usually in hematologic malignancies. Primary hepatic malignancies such as fibrolamellar carcinoma and multifocal hepatocellular carcinoma are rarely reported causes of ALF.

Any condition that results in acute ischemic injury to the liver can lead to ALF. Budd Chiari syndrome, prolonged systemic hypotension and sepsis are some of the clinical conditions that can cause hepatic ischemia, hepatocyte injury and necrosis, and subsequent ALF.

INFECTIOUS:

An infectious etiology is often considered when children presents with nonspecific symptoms such as myalgia, fever, decreased appetite, and listlessness and ALF. Infections are identified more frequently in the younger population. The infectious agents found in young infants include herpes simplex, adenovirus, enterovirus, and paramyxovirus, while Epstein-Barr virus (EBV) occurred more frequently in older patients. Viral hepatitis is the most common cause of ALF worldwide and is the predominant cause of ALF in developing countries. Hepatitis A, B, and E infections have been implicated, as well as other rare viral causes including herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and parvoviruses.

Hepatitis A and E viruses are transmitted through the fecal-oral route mainly through consumption of contaminated food or water and are associated with poor hygiene and sanitation. Hepatitis A viral infection occurs in about 1.5 million people a year worldwide; however, less than 1% of patients affected by hepatitis A virus develop ALF. Hepatitis A infection follows a more severe course in adults compared with children and results in a hyperacute or acute pattern of liver failure. In developed countries, improved sanitary conditions as well as effective use of hepatitis A vaccination has led to a lower incidence of acute hepatitis A.

Hepatitis B is the most common cause of ALF in Asia and parts of Europe. It is transmitted through exposure to blood or other bodily fluids of infected persons. Less than 1% of patients infected with hepatitis B will develop ALF; however the mortality from hepatitis B-induced ALF is higher than in those with hepatitis A or E infection. Particularly important clinical scenario is patients with previously stable, subclinical hepatitis B virus infection with without established chronic liver disease. Reactivation of hepatitis B infection in these patients may lead to ALF.

Hepatitis C virus is not believed to cause ALF in the absence of a coexisting etiology. However, rare cases of ALF from hepatitis C have been reported.

Hepatitis A virus is a common cause in areas where it is endemic or referral centers for endemic areas,[8] While hepatitis B is a reported cause of ALF in infants[9].Hepatitis C virus is a very rare primary cause of ALF. Hepatitis E occurs within endemic areas such as India, Africa, and
Mexico. Echo virus is described primarily in newborns or neonates and is usually associated with systemic viral sepsis.[10] Parvovirus B19 has been proposed as a cause for ALF, but whether it is a primary cause or a confounding factor in the setting of other viral diseases (e.g., hepatitis A, EBV) is not clear.[11] Parvovirus has been implicated in those patients with ALF who subsequently develop aplastic anemia,[12] . Epstein-Barr virus is known to be a cause of ALF and can be associated with hemolytic anemia[13] and hemophagocytic syndrome.[14] It is more commonly an issue in children with immunodeficiencies. Herpes simplex occurs most commonly in the first 2 weeks of life and is almost always associated with systemic disease.

CASE REPORT

A 13 year old female child born out of non consanguineous marriage was brought in emergency room with complaint of fever high grade continuous and anorexia 3 days, vomiting frequent for initial 2 days, yellow urine, abdominal pain and drowsiness - 1 day and not responding to any stimuli- 3 hours. No history of convulsion. No history of rash, joint pain, itching, edema of legs, bleeding or hepatotoxic drug ingestion. No history of jaundice in the past. She was Immunized completely till date in government hospital. All the developmental milestones were normal. No relevant family history of liver disease, infant death or autoimmune conditions.

Physical examination: Euthermic, Weight 32.00 kg, height 148 cm,

Pulse 128/min, RR 18/minute (Kussmaul breathing), SpO2 98, BP 110/70 mm Hg

Jaundice ++, Dehydration ++, active bleeding per oral and per nasal
PA: Soft, liver 6 cm, spleen 1cm, there were no free fluids or dilated abdominal wall veins. CNS: Respond to pain, hypertonia, DTR Brisk, No signs of meningeal irritability, pupils semi dilated and sluggishly reacting to light, plantars extensors bilateral.
Ophthalmological examination didn't reveal Kayser-Fleischer Ring Other systems clinically normal

Investigations:

COMPLETE HEMOGRAM

Hb 11.3 gm%
RBC 4.1 million/cmm
PCV 33.05%
MCV 80.6 fL (83-101)
MCH 27.6 pg (27-32)
MCHC 34.2 g/dL (31-37)
RDW 13.9% (11.6-18)
WBC 930/cmm P
42
L 53
E 1
M 4
Platelet count 107000/cmm Blood
sugar 76 mg/dl

LFT:

S. Bilirubin 12.9 mg/dl
Bilirubin Conjugated 10.5 mg/dl
Bilirubin Unconjugated 2.4 mg/dl SGPT
(ALT) 2276U/L
SGOT (AST) 2000 U/L
S. Alkaline Phosphatase 1000 IU/L
Proteins 5.64 gm/dl
Albumin 3.49 gm/dl
Globulin 2.15 gm/dl
A/G Ratio 1.6
PT 47.3 seconds
INR 3.58 (0.85-1.15)

S.Ammonia 176.7 micromol/L (11-51)

Blood urea 26.59 mg/dl S. Creatinine 0.8 mg/dl

S. Electrolytes were within normal limits.

Anti-HAV IgM Positive
Anti-HCV IgM Negative
Anti-HBC IgM Negative
HBsAg Negative
Blood culture was sent.

Final diagnosis: Acute liver failure- Hepatic encephalopathy grade IV in a case of acute viral hepatitis A with probable sepsis

Child has to be treated with oxygen support, head elevation, **hepatic drip (D10 400 ml + normal saline 100 ml + KCL 5 ml + Calcium gluconate 5 ml + MVI 2 ml)**, Injection vitamin K 5 mg, antibiotics –(cefuroxime + ampicillin Cloxacillin), injection ranitidine, 3% normal saline (150 ml in 30 minutes followed by 32 ml/hour) and ryles tube aspiration. Relatives were counselled regarding prognosis, need of assisted ventilation and liver transplant in detail. After 6 hours child developed massive hematemesis, was pulseless and expired after failed resuscitation.

DISCUSSION:

Increasing bilirubin and prolonged international normalized ratio (INR) greater than 1.5 are pointers toward impending acute liver failure. Hepatitis A is the most common cause of acute viral hepatitis in children which runs a benign course in the majority and complications are very rare. Nevertheless, hepatitis A can sometimes cause acute liver failure. The need for early identification of possible acute liver failure among hepatitis A patients, Even though there is evidence of specific genetic features in viruses found in hepatitis A patients, the reason why some hepatitis A patients present acute liver failure, whereas most of them present a self- limited picture, remains unknown.

Viral and toxin induced bone marrow suppression can lead to abnormal haematological indices. Viral infections such as hepatitis, HIV, cytomegalovirus, Epstein –Barr virus (cause infectious mononucleosis), sepsis and malaria can cause pancytopenia.

Majority of pediatric acute failures have unknown etiology.

Pathogenesis - There is extensive necrosis of peripheral hepatocytes with little or no regeneration leading to loss of liver cells or microvesicular fatty changes of hepatocytes seen in inborn errors of metabolism and Reye's syndrome

Cerebral edema and raised ICT can be due to ammonia, osmotic disturbances, metabolic disturbances, cerebrovascular dysregulation and infections.

Clinical features:

Jaundice is most common presentation.

Encephalopathy - Poor feeding, reversal of sleep cycles and irritability in infants and alteration in mood and excessive sleepiness or confused state in older children.

The child may have raised intracranial pressure (increased muscle tone, hyperventilation, unequal or dilated pupils with sluggish response to light, focal seizures, papilloedema, trismus, posturing or loss of brainstem reflexes), cerebral edema, seizures, tremors, asterixis (loss of motor control of certain areas of the body-muscles often in the wrist and fingers).

Foetur hepaticus may be found. Liver may or may not be palpable. An enlarged liver is generally associated with a better prognosis than a shrunken liver. Assessment of liver span, mental status and stigmata of chronic liver disease must be evaluated

Coagulopathy - Bleeding manifestations like petechiae, purpura, hematemesis, bleeding per rectum or bleeding from any other site.

Hepatic encephalopathy can be staged as follows:

Grade I: Altered mood or behaviour, sleep disturbances, irritability, minimal change in level of consciousness

Grade II: Drowsy, gross disorientation, inappropriate behaviour, some confusion

Grade III: Stuporose but talking and obeying simple commands, speech may be inarticulate,marked confusion.

Grade IV: Coma, unresponsive to pain, decorticate/decerebrate posturing

Complications of AHF include cerebral edema, coagulopathy, hypoglycemia, electrolyte disturbances, acidosis, sepsis and renal failure.

Laboratory parameters:

CBC

Blood cultures both bacterial and fungal

Hepatic profile – LFT, CPK, LDH, total protein and albumin

Viral markers - IgM anti HAV, IgM anti HCV, HBsAg, IgM anti HEV, anti HBcAg Coagulation profile

Biochemistry – RFT, blood sugar, electrolytes. Continuous monitoring of vital signs, heart rate, respiratory rate, blood pressure, continuous oxygen saturation and end-tidal ($ETCO_2$) monitoring should be done. Frequent neurological assessment for worsening hepatic encephalopathy is important.

Do elective Intubation in grade III or IV encephalopathy.

Fluids 50-75 % of maintenance fluids should be given. Give dextrose (monitor glucose frequently), minimum sodium with aggressive potassium maintenance (hypokalemia aggravates hepatocyte injury).

Vasoactive drugs (dopamine, epinephrine, norepinephrine, vasopressin) may be required in hypotension.

Avoid NSAIDs. Use paracetamol/ibuprofen as antipyretic.

Sepsis: Combination of third generation cephalosporin with Cloxacillin/Vancomycin/Teicoplanin is used to cover for any secondary sepsis. Antifungal (fluconazole) may be required in patients with longer ICU stay.

Bleeding: H2 blockers (Ranitidine 2-4 mg/kg/day div 8 hourly 50 mg maximum dose), PPI (Pantoprazole) or sucralfate should be used for prevention of gastritis induced bleeding.

Anticonvulsant: Preferred drugs are phenytoin, levetiracetam.Avoid valproate, phenobarbitone, long acting benzodiazepienes.

ABG

USG abdomen/X-Ray chest

Paracetamol and valproate drug levels in suspected poisoning

Serum ammonia and lactate - It has no correlation with severity of encephalopathy and may be very high in inborn errors of metabolism

Investigations for Wilson's disease and inborn errors of metabolism should be done if required. Amylase, lipase

Autoantibody serology - ANA, SMA, LKM, IgG

Sedation should be avoided.

Syrup Lactulose 2 ml/kg/dose 4 hourly (usually 15 ml TDS) through the nasogastric tube if there is no active bleeding.

The dose can be titrated so that the patient passes two semisolid stools per day.

Lactulose is a synthetic disaccharide that consists of fructose and galactose. As there is no corresponding disaccharide in the human intestinal mucosal cells, lactulose is not split in the small intestine and therefore it is not absorbed. In the colon, lactulose is broken down to organic acids (acetic acid and lactic acid) by the action of colonic bacteria. This fermentation acidifies the content of intestine and it exerts an osmotic effect, which is believed to be responsible for the increase in stool volume and frequency observed during lactulose administration. Higher the lactulose dose, higher is the osmotic effect. Acidification of the colon contents inhibits the non-ionic diffusion of ammonia from the colon into blood. This action is thought to be responsible for the beneficial effects of lactulose in hepatic encephalopathy. Ammonia level > 200 mg/dl is associated with worsening encephalopathy and herniation. The accelerated intestinal transit and the acidified content are the explanation for the reduced levels of ammonia observed under lactulose. It can be used as enema in patients with gastrointestinal bleeding.

Avoid nephrotoxic drugs and monitor renal functions as the development of hepatorenal syndrome is not uncommon. Urine output should be closely monitored as the incidence of concomitant acute kidney injury is high. If there is oliguria, it will lead to increasing positive fluid balance, which is detrimental. In such a scenario, early continuous renal replacement therapy (CRRT) should be considered.

L-Ornithine-Asparate (Hepamarz), dose in children above 5 years is, 5 ml twice a day after meals. It is a combination of two aminoacids. After administration, it breaks down into L- ornithine and L-asparate to provide critical substrates for urea cycle in the liver where harmful toxicammonia is converted into non-toxic urea, which is eliminated via kidneys. Therefore, it improves the detoxification capacity of ammonia in the blood. Hyperammonemia is the potential complication of most of the liver diseases and can lead to subclinical hepatic encephalopathy.

Ampicillin/neomycin can be used which decreases the concentration of urease producing bacteria, thus decreasing production of ammonia.

Rifaximin - a synthetic derivative of Rifamycin is a minimally absorbed antibiotic which has been documented in the treatment of ALF.

Coagulopathy is universal (platelet dysfunction, hypofibrinogenimia and vitamin K deficiency) but all deranged INR and thrombocytopenia do not need correction. Blood products can cause fluid and protein overload which may worsen cerebral edema and encephalopathy and hamper in usage of King's college criteria for liver transplantation. Platelets are indicated only in the setting of bleeding or for doing a procedure where platelet count should be

>50000/cmm. FFP 15-20 ml/kg 6 hourly or 3-5 ml/kg/hr as continuous infusion is indicated when INR>7 or with significant bleeding requiring invasive procedure. Cryoprecipitate is helpful in significant hypofibrinogenemia (<100 mg/dl). Single dose of 5-10 mg Vitamin K1 is recommended empirically in all patients.

Cerebral edema has universal poor outcome. It should be managed with 30–45-degree head elevation, 20% mannitol 0.5-1 g/kg over 20 minutes or 3% Normal saline 5 ml/kg in 30 minutes followed by 1 ml/kg/hour (prophylactic

infusion to maintain sodium at 145-155 mol/L is justified in severe encephalopathy) and sodium thiopental in resistant cerebral edema in bolus dose of 2-4 mg/kg over 15 minutes followed by a slow intravenous infusion of 1-2 mg/kg/hour. Assisted ventilation is of great help. Hyperventilation is recommended as an emergency option.

Barbiture and selective head cooling can be used. Bleeding, dehydration and electrolyte imbalance should be aggressively managed as they can worsen the encephalopathy.

In paracetamol poisoning, N-acetyl cysteine is the drug of choice. It is given as 150 mg/kg in dextrose 5% or dextrose 10% or normal saline over 15 minutes, followed by 50 mg/kg over 4 hours followed by 100 mg/kg in 24 hours as separate infusion. It is contraindicated in patients with sulfa allergy.

In hepatic encephalopathy beyond stage II, protein restriction of 0.5-1 gram/kg per day is recommended; normal intake is recommended in early stages. Enteral route is preferred whenever feasible. Calorie dense feeding is useful to restrict volumes.

According to recent reports, Lactulose, L-orthinine, L-asparate and other non absorbable antibiotics are not useful. They recommend N-acetyl cysteine 100 mg/kg/day in all cases of ALF irrespective of the etiology and prophylactic proton pump inhibitors.

Liver transplantation when done for acute liver failure has survival rates of more than 95% at 5 years. King's College criteria should be used in predicting prognosis and liver transplantation.

King's college criteria for liver transplantation in acute liver failure

APAG* - associated AHF pH < 7.3 or INR > 6.5, serum creatinine > 3.4 mg/dl and grade III –IV Encephalopathy *APAP- Acetaminophen Paracetamol	All other causes of AHF INR > 6.5 Or Three of following variables: 1. Age < 10 or > 40 years 2. Cause is non A, non B hepatitis or Idiosyncratic drug reaction 3. Duration of jaundice before encephalopathy > 7 days 4. INR >3.5 5. Serum billirubin > 17.5 mg/dl

APAG* - associated AHF pH < 7.3 or INR > 6.5, serum creatinine > 3.4 mg/dl	All other causes of AHF INR > 6.5 Or

and grade III –IV Encephalopathy *APAP- Acetaminophen Paracetamol	Three of following variables: 6. Age < 10 or > 40 years 7. Cause is non A, non B hepatitis or Idiosyncratic drug reaction 8. Duration of jaundice before encephalopathy > 7 days 9. INR >3.5 10. Serum billirubin > 17.5 mg/dl

Serum bilirubin >10 mg/dl (indirect bilirubin > direct bilirubin also bad for prognosis), blood glucose<45 mg/dl, pH<7.35 or > 7.45,increasing grade of encephalopathy, more than 7 days interval between the onset of prodromal symptoms and encephalopathy are associated with increased mortality. Paracetamol induced ALF has better prognosis than metabolic disease induced ALF.

In spite of the best supportive measures, AHF has very high mortality in the range of 80-90% in the absence of liver transplantation so early consultation with liver transplant team is emphasized over and above multi-disciplinary approach of management. Liver transplantation is the only lifesaving option when spontaneous recovery is unlikely.

Considering the availability of safe and effective vaccines, cases of acute liver failure due to viral hepatitis A should not occur any longer. In spite of such availability, in many parts of the world viral hepatitis A is still the major cause of acute liver failure in children.

We stress the importance of high level of suspicion of acute liver failure in the management of an atypical clinical and laboratory picture, and in patients who, during the course of viral hepatitis A, develop any disturbance in sleeping pattern or present signs of encephalopathy or coagulopathy, fluid and electrolyte imbalance and sudden reduction of hepatometry.

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