Acute Liver Failure Caused by Hepatitis-E Virus and Paracetamol

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ABSTRACT:
Acute liver failure is characterized by severe and sudden liver cell dysfunction leading to hepatic encephalopathy and hepatic coagulopathy in a person without history of liver disease in the past. This catastrophic illness can rapidly progress to coma and death from cerebral edema and multi organ dysfunction. It carries a high mortality rate if liver transplantation is not carried out. In West, paracetamol is the main cause of hepatotoxicity whereas in the East viral hepatitis tops the list. This report describes a case of acute liver failure in which probably both the agents were involved. The patient recovered with antidote therapy and maximum supportive care.

Key words: Acute liver failure, paracetamol, hepatitis E

INTRODUCTION
Acute liver failure (ALF), also sometimes known as fulminant hepatic failure, is a multisystem illness that evolves quickly after catastrophic insult to the liver leading to hepatic encephalopathy and coagulopathy in a person without prior history of liver disease. Acute liver failure occurs when the rate of extent of liver damage is inadequately balanced by liver regeneration. The natural history of this illness is variable and survival without transplantation ranges from 10% to 90%. Brain edema, intracranial hypertension and multiorgan dysfunction are the three major factors responsible for death in this disease. The etiology of ALF is different depending upon the region. In the West, paracetamol tops the list while in Asia viral hepatitis is still the major cause of ALF. In India and Nepal hepatitis E virus (HEV) is the major culprit. Drug-induced hepatitis, mainly due to anti-tubercular drugs, leading to ALF is reported in India. However, herbal medications during acute HEV hepatitis along with septicemia are major causes of ALF in Nepal (unpublished data). Among developed Asian countries, hepatitis B virus (HBV) is one of the key causes. Liver transplant has changed the gloomy outlook of the disease, and post-transplant survival rates of 60%-70% have been reported from most centers. However, liver transplant is expensive, necessitates lifelong immunosuppression, and is limited by donors.

Though uncommon, paracetamol overdose is slowly becoming more common in the East. This author has had a case where paracetamol was the causative agent of liver failure. However, HEV hepatitis was co-existent and must have accelerated the liver failure. This type of case has not yet been reported in the literature and, to best of my knowledge, this is the first case to be reported so far.

CASE REPORT
A 45-years-old male patient with no history of significant illness in the past was brought unconscious to the
emergency room. As stated by the patient party he had been all right five days back. He then complained of headache, malaise, generalized body aches and loss of appetite. He took paracetamol tablets (500 mg each) at eight different times on the same day for fever, headache and body aches. Next day he again took eight more tablets in 24 hours. He noticed yellowish discoloration of the eyes on the third day of his illness and contacted a local Ayurvedic practitioner. He was advised to apply some medicines (composition not known) over the umbilical region. Subsequently his condition became worse and he went to the local hospital in a drowsy state. During the course of the treatment, he lost consciousness and his condition gradually worsened. For better management, he was referred to our center. At the emergency, he was in grade IV hepatic encephalopathy with decerebrate rigidity. Respiration was spontaneous but labored. There was profuse sweating, pupils were unequal but reacting to light. There was deep icterus and pedal edema. Abdominal findings were normal except for a yellowish tint in the skin. Ultrasound examination in the ER showed a small liver, splenomegaly, and partially-collapsed gall bladder with pericholecystic edema. There was free fluid in the rectovesical pouch and Morrison’s space. Doppler examination of the portal system showed decreased portal flow and portal venous velocity. His liver function and liver biochemistry were deranged. Prothrombin time was over 58 seconds. A provisional diagnosis of acute liver failure probably due to paracetamol overdose was made. The patient was given 200 ml of Mannitol over 10 minutes before transferring him to the ICU. As hypoglycemia was present, 50% dextrose was given as IV bolus. The central line could not be opened due to an anatomical abnormality in the right clavicular region. Two peripheral lines were opened. Subsequently, the patient was managed conservatively with intravenous N-acetyl cysteine, 20% mannitol, vitamin K, fresh frozen plasma, antibiotics (Imipenem), vitamin B complex, IV proton pump inhibitor and IV dextrose. Blood for viral markers and paracetamol level were sent. All viral markers were negative except for hepatitis E virus. Anti HEV IgM was positive. Paracetamol level was high (174 mg/dL) as anticipated. Tests for septicemia and disseminated intravascular coagulation were negative. Other lab parameters at admission are given in Table 1. After six hours of treatment, signs of cerebral edema started to subside. Rigidity slowly disappeared and the patient started showing movements. After 20 hours he started making incomprehensible sounds. But patient’s renal function started deteriorating. Mannitol was stopped and a dose of IV antibiotics adjusted. Recovery was slower probably due to persistent cerebral edema and inability to administer mannitol. After dose adjustment, renal function improved to normal the next day. Mannitol was restarted. Paracetamol level was rechecked after 24 hours. It was still high and N-acetyl cysteine was given at a dose of 100 mg/kg for the next 16 hours. The next day paracetamol level dropped to normal. On
the fourth day, the patient was little drowsy but conscious and was given sips of liquid. On the fifth day, the nasogastric tube was removed and liquid diet by mouth started. On the seventh day all IV medication were changed to oral and the patient was finally discharged on the ninth day of admission. His lab parameters had be come to normal after one month of illness.

DISCUSSIONS
There is little information on the epidemiology of ALF in various regions of the world. Paracetamol poisoning accounts for 40% of cases of ALF in the UK but it is falling since the legislation limited the amount that can be purchased over the counter. Similar is the data from USA where it was 39% as shown by a data from 17 tertiary centers. Drug as a common etiological factor of ALF is not yet established in the East. In the Far East, paracetamol overdose is a less common cause of ALF. However, in India anti-tubercular therapy is one of the important causes among drug-induced ALF. Hepatitis E virus is significant cause of fulminant hepatic failure in India. In one study from India, HEV was responsible for 40% of cases of acute liver failure. Hepatitis E is common in parts of Asia and Africa and the risk of developing ALF increases to 25% in pregnancy, especially in the third trimester. Unlike reported earlier, paracetamol overdose for suicide is slowly increasing in developing countries.

Paracetamol can cause liver failure by both idiosyncrasy and dose-related toxicity. It causes ALF in a dose more than 4 gm per day and mortality is highest at a dose over 48 gms. The dose of paracetamol in this case is just below the accepted lethal dose, that is > 4 gm day. It was an unintentional overdose and the patient had ingested the same amount for two consecutive days. As incubation period of HEV hepatitis is 2-9 weeks, there was ongoing hepatitis while he ingested the drug. Excretion of paracetamol must have been hampered and earlier depletion of glutathione must have taken place. Thus, two etiological factors must have played role in bringing about the ALF. Investigation for acute hepatitis, hence, is required in those cases where features of acute liver failure appear even after a low dose of paracetamol intake, especially in geographical areas where HEV hepatitis is endemic.

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