Approach to Clinical Syndrome of Jaundice and Encephalopathy in Tropics

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A large number of patients present with jaundice and encephalopathy in tropical country like India and acute liver failure is the usual cause. Clinical presentation like ALF is also a complication of many tropical infections, and these conditions may mimic ALF but may have subtle differences from ALF. Moreover, what hepatologists see as acute liver failure in tropics is different from what is commonly described in Western Textbooks. Paracetamol overdose, which is possibly the commonest cause of ALF in UK and USA, is hardly ever seen in India. Most common etiology here is viral hepatitis (hepatitis E > hepatitis B> hepatitis A). Apart from ALF, one may also come across subacute hepatic failure (SAHF) as well as acute-on-chronic liver failure (ACLF) due to viral hepatitis. Interestingly, a host of other conditions can mimic ALF because clinical presentation in these conditions can be dominated by jaundice and encephalopathy. Malarial hepatopathy is possibly the best-known condition out of these and is not an uncommon manifestation of severe malaria. A similar presentation can also be seen in other common infections in tropics such as dengue fever, typhoid fever, leptospirosis, scrub typhus, amoebic liver abscesses, tuberculosis and other bacterial and fungal infections with or without human immunodeficiency virus (HIV) related disease. In many of these conditions, liver failure may not be underlying pathophysiology. Some pregnancy related liver diseases could also present with jaundice and encephalopathy. This review summarizes the commonly seen presentations in tropical country like India, where jaundice and encephalopathy dominate the clinical picture. (J Clin Exp Hepatol 2015;5:S116–S130)

Jaundice and encephalopathy are major components of the syndrome of liver failure,[1] which can be acute, subacute or chronic. Subacute[2–4] and chronic liver failure[5,6] are well-recognized syndromes with known causes of liver disease. While viral hepatitis and acetaminophen overdose are major causes of acute liver failure,[7] there are many other infections and non-infectious causes that can mimic this presentation especially in a tropical country like India.[8] In many of these situations, liver failure may not be the main problem. Medical personnel working in tropics and those dealing with patients traveling from these parts of the world should be aware of such differences in etiological profile of patients presenting with jaundice and encephalopathy.

Apart from hepatotropic (Hepatitis A–E) viruses that can cause acute liver failure, a variety of non-hepatotropic viruses, bacteria, protozoa and fungal infections can affect the liver leading to a clinical picture dominated by jaundice and encephalopathy. In tropical countries like India, infections such as malaria, typhoid fever, leptospira, dengue and so on are common, and are known to present with altered sensorium and jaundice and thus can mimic acute liver failure. Jaundice can also complicate systemic sepsis caused by Gram negative and Gram positive organisms. Exotoxins and endotoxins liberated by overwhelming infections can inhibit the transport of bile acids and other organic anions across the hepatic sinusoidal and canalicular membranes, thereby leading to intrahepatic cholestasis.

CLINICAL APPROACH

The approach to a patient with jaundice/deranged liver functions starts with a careful history and physical examination to evaluate for other features like pain right upper abdomen, persistent fever and other systemic manifestations. Presence of hepatomegaly or splenomegaly is another important point that makes diagnosis of ALF less likely. The liver functions may show a dominant cholestatic or hepatocellular jaundice, which may dictate further evaluation. Coagulopathy, which is invariably seen with ALF, may not be present in many other conditions. This review will outline the etiological profile of patients presenting with syndrome of jaundice and encephalopathy.

Keywords: jaundice, encephalopathy, acute liver failure, malaria, dengue fever

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Abbreviations: SAHF: subacute hepatic failure; ACLF: acute-on-chronic liver failure; HIV: human immunodeficiency virus; ALF: acute liver failure; EEG: electroencephalogram; DHF: dengue hemorrhagic fever; CMV: cytomegalovirus; MSOF: multisystem organ failure; HLH: hemophagocytic lymphohistiocytosis

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The syndrome of jaundice and encephalopathy can be caused by two groups of conditions. Firstly, all common diseases that lead to acute liver failure and secondly, uncommon diseases that may either cause or mimic acute liver failure (Table 1) Commonest among all causes remain hepatotropic viruses such as hepatitis A, B, E and others.

Table 1 The Syndrome of Jaundice and Encephalopathy can be Caused by a Multitude of Etiologies, Some Which are Summarized in this Table. Common Causes of ALF are Outlined in the First Column While Less Common Etiologies that can Present with Jaundice and Encephalopathy are Outlined in Second Column.

Common causes of acute liver failure (ALF)	Uncommon causes of jaundice and encephalopathy that may present with or without liver failure
Hepatotropic viruses: Hepatitis E, A, and B	Viruses: dengue (viral hemorrhagic fever), Ebstein–Barr virus, herpes simplex virus, herpes simplex virus types 1 and 2, human herpes virus 6, varicella zoster virus, cytomegalovirus, and parvovirus B19 Yellow fever and human immunodeficiency virus (HIV) Some reports also suggest a role for hepatitis TT (transfusion transmitted), or hepatitis G viruses and unknown viruses
Drugs: antituberculosis drugs, acetaminophen (Paracetamol), anti-infectives, anticonvulsants, and anti-inflammatory drugs most commonly implicated; herbal or adulterated traditional or complementary medications	Bacteria and Mycobacteria: Gram positive and Gram negative bacteria: toxic shock syndrome (Staphylococcal aureus or Group A Streptococci), Clostridia, Actinomyces, *Salmonella typhi*, Yersinia, Gonococci, Legionella, Brucella Chlamydia: Fitz–Hugh–Curtis Syndrome Spirochetes: Syphilis, Leptospira, Lyme disease Rickettsia: Scrub typhus *Mycobacterium tuberculosis*
Metabolic causes: Wilson's disease	Parasites: *Plasmodium falciparum* Amoebic liver abscess Schistosoma species
Ischemic injury: acute ischemic hepatitis, hepatic artery thrombosis	Fungi: Candida species *Histoplasma capsulatum*
Miscellaneous causes: autoimmune hepatitis, Acute Budd–Chiari syndrome and Malignant infiltration of the liver	Hyperthermic injury from heat shock, Amanita spp (mushroom) poisoning, Pregnancy-related disease, Hemophagocytic lymphohistiocytosis (HLH) syndrome, kernicterus

They can present with a variety of syndromes such as Acute Sporadic Viral Hepatitis, Epidemic Hepatitis, Acute liver failure, Subacute Hepatic Failure, Chronic Hepatitis and cirrhosis and Acute-on-chronic liver failure. Of these only ALF will be considered in little more details as the underlying liver disease is absent in this condition. Approach to uncommon causes of this syndrome seen especially in tropics is outlined in Table 2.

ACUTE AND SUBACUTE LIVER FAILURE

Jaundice and encephalopathy immediately brings to mind the diagnosis of liver failure. Acute Liver Failure (ALF) seen in Tropics is different from that seen in the Western Countries. ALF remains the commonest cause of patients presenting with jaundice and encephalopathy. There is no unanimity about the definition of acute liver failure. A recent review of 1233 published articles on ALF reported 41 different definitions using varying characteristics to define ALF.[9] In 1969, Trey and Davidson had defined ALF as occurrence of encephalopathy within 8 weeks of the onset of Jaundice due to hepatitis in an individual without pre-existing liver disease.[1,10] However, in subsequent years, reports on ALF emanating globally from various tertiary care centers, used varying criteria to define ALF though the presence of encephalopathy has been an essential criterion. The interval between onset of acute hepatitis illness (or Jaundice) and occurrence of encephalopathy has varied from 2 to 26 weeks in various papers.

O'Grady has differentiated between the terms 'hyperacute' and 'acute' by drawing a line at 7 days of interval between jaundice and encephalopathy but it may have different implications in terms of etiology. Most patients with paracetamol-induced ALF demonstrate a hyperacute presentation (encephalopathy), with peak of illness being approximately 72 h after ingestion of a toxic amount of acetaminophen. The spontaneous survival frequency of 40–67% is in contrast to acute or subacute groups such as drug-induced liver injury with much poorer survival of 7–28%.[11]

The subcommittee of the International Association for the Study of the Liver,[12] which included several regional experts associated with ALF in 1999, tried to provide nomenclature and defining criteria for ALF and SHF in an effort to universalize these conditions, which are being widely used in this country. Uniform definitions, diagnostic criteria and sub-classification to categorize ALF patients would allow better comparison of various reports from different regions.

Subacute hepatic failure (SAHF) may rarely enter the differential diagnosis and this entity has been reported mainly from the Indian subcontinent.[13] It is characterized by development of persistent or progressive jaundice, followed 6–24 weeks later by appearance of ascites,

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