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), Epstein-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, <i>Salmonella typhi</i> , Yersinia, Gonococci, Legionella, Brucella Chlamydia: Fitz-Hugh-Curtis Syndrome Spirochetes: Syphilis, Leptospira, Lyme disease Rickettsia: Scrub typhus <i>Mycobacterium tuberculosis</i>
Metabolic causes: Wilson's disease	Parasites: <i>Plasmodium falciparum</i> Amoebic liver abscess <i>Schistosoma</i> species
Ischemic injury: acute ischemic hepatitis, hepatic artery thrombosis	Fungi: Candida species <i>Histoplasma capsulatum</i>
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,

Table 2 Summary of Common Causes Presenting as Jaundice and Encephalopathy in Tropics. Causative Organism, Mode of Infection, Presentation, Diagnostic Tests and Specific Management has been Outlined Especially for Infective Causes.

Diseases	Causative agent	Mode of infection/disease	Distinctive features apart from jaundice and encephalopathy	Diagnostic tests	Specific treatment
Acute Liver failure	Hepatitis A, B, and E virus (HAV, HBV, HEV) or drug-induced	Feco-oral for HAV, HEV, parenteral for HBV	History of viral prodrome may be present. Clinically liver size may be noted to be shrinking and significant coagulopathy is present	Serological diagnosis with IgM anti HAV, IgM anti HEV. For hepatitis B, HBsAg and IgM anti HBc Coagulopathy as indicated by raised INR Imaging can demonstrate shrinking liver	No specific treatment is available for HAV and HEV infection. In severe hepatitis B infection, one may give entecavir or tenofovir. ALF is managed by intensive supportive treatment and by liver transplantation in selected cases
Malarial hepatopathy	<i>Plasmodium</i> protozoa (<i>P. falciparum</i> , rarely <i>plasmodium vivax</i>)	Bite of <i>anopheles</i> mosquito	a. Paroxysm of fever, shaking chills and sweats occur every 48 or 72 h, depending on species. Hepatosplenomegaly common b. Features of severe malaria include cerebral malaria often presenting as coma, severe anemia, hypoglycemia, metabolic acidosis, acute renal failure (serum creatinine > 3 mg/dl), ARDS, shock or "algid malaria", DIC and Hemoglobinuria	a. Microscopy: thick smears—parasite detection; thin smears—species identification. b. Quantitative buffy coat test c. Rapid diagnostic tests (RDTs)—histidine rich protein, lactate dehydrogenase antigen based immune-chromatography. Sensitivity and specificity >95%. Malaria ruled out if two negative RDTs	Drug of choice: artesunate 2.4 mg/kg i.v. bolus at admission, 12 h and 24 h; followed by once a day for 7 days + Doxycycline 100 mg p.o. 12 hourly Alternative: quinine 20 mg/kg loading dose, followed by 10 mg/kg i.v. infusion 8 hourly + Doxycycline 100 mg p.o. 12 hourly Clindamycin is recommended in place of doxycycline in pregnant women and children. Exchange transfusion is a treatment option for parasitemia >10%
Dengue fever	Dengue virus (flavivirus) serotypes 1–4	Bite of <i>Aedes</i> mosquitoes	a. Dengue fever: headache, retro-orbital pain, myalgia, arthralgia, rash b. Dengue hemorrhagic fever (DHF) thrombocytopenia, skin, mucosal and gastrointestinal bleeds, rise in hematocrit. Hepatomegaly is common c. Dengue shock syndrome. Weak pulse, cold clammy extremities, pulse pressure < 20 mmHg, hypotension d. Complications: encephalitis, myocarditis, hepatitis, renal failure, ARDS, ?hemophagocytosis	a. Nonstructural protein 1 antigen detection (Rapid card test)—Sensitivity 76–93%, Specificity >98% b. IgM, IgG serology (IgG titer > 1:1280 is 90% sensitive and 98% specific)	a. Isotonic fluid infusion just sufficient to maintain effective circulation during the period of plasma leakage; guided by serial hematocrit determinations b. Blood transfusion is done only with overt bleeding/rapid fall in hematocrit

Typhoid fever	<i>Salmonella typhi</i> , serovar paratyphi A, B or C	Oral, through contaminated food and water	IP: 1–14 days Week 1: fever, headache, relative bradycardia followed in week 2 by abdominal pain, diarrhea, constipation, hepatosplenomegaly, jaundice and encephalopathy. Week 3: complications such as intestinal bleeding, perforation, MODS	Typhidot—sensitivity 95–97%, specificity >89%, (Widal test is non-specific) Blood culture is gold standard, positive in 40–80% of patients usually during first week Bone marrow cultures—sensitivity 80–95%; may remain positive even after 5 days of pre-treatment	Ceftriaxone i.v. 50–75 mg/kg/day for 10–14 days to cover MDR <i>S. typhi</i> . Azithromycin and ciprofloxacin Consider dexamethasone 3 mg/kg followed by 1 mg/kg 6 hourly for 48 h in selected cases with encephalopathy, hypotension or DIC
Leptospirosis	<i>Leptospira interrogans</i>	Direct contact of skin or mucosa with water contaminated with urine or body fluid of an infected animal.	IP: 5–14 days. Biphasic illness, (a) Anicteric leptospirosis: abrupt onset of fever, chills, headache, myalgia, abdominal pain, conjunctival suffusion, transient skin rash. blcteric leptospirosis (Weil's disease) occurs in 5–15%—Jaundice, proteinuria, hematuria, oliguria and/or anuria, pulmonary hemorrhages, ARDS, myocarditis. Hepatomegaly is common	(a) Raised creatinine phosphokinase levels, (b) Culture (blood, cerebrospinal fluid, urine) (c) Positive serology (d) Microscopic agglutination test (Sensitivity 30–63%, specificity > 97%) (e) IgM ELISA (Sensitivity 52–89%, specificity > 94%)	Penicillin G 1.5 MU 6 hourly for 7 days Alternative: Third generation cephalosporin. Oral Doxycycline in uncomplicated infections. Plasma exchange, corticosteroids and intravenous Ig in selected patients in whom conventional therapy does not elicit a response.
HIV cholangiopathy	Human immunodeficiency virus and superadded opportunistic infections	Sexual or parenteral transmission	History suggestive of HIV infection. Usually in patients with low CD4 counts. Presentation as cholangitis often associated with diarrhea	Imaging by MRCP or ERCP shows picture like sclerosing cholangitis	Retroviral therapy and antimicrobials
Hepatobiliary tuberculosis	<i>Mycobacterium tuberculosis</i>	Droplet infection or oral ingestion	History of prolonged ill health, with low grade fever, night sweats and weight loss	Biopsy showing typical caseating granuloma, with or without acid fast bacilli	Antituberculosis treatment regimen with rifampicin, isoniazid, ethambutol and pyrazinamide
Scrub typhus	<i>Orientia tsutsugamushi</i>	Bite of chiggers (larva of trombiculid mite)	IP: 1–3 weeks. Fever, headache and myalgia, breathing difficulty, delirium, vomiting, cough, jaundice. Hepatomegaly common. Characteristic rash: eschar early in disease	1. Weil-Felix: poor sensitivity and specificity 2. Indirect fluorescent antibody: “Gold standard” 3. Enzyme-linked immunosorbent assay (ELISA) for immunoglobulin G (IgG) and IgM antibodies: sensitivity and specificity > 90%	First line: Doxycycline 100 mg BD for 7 days (Level IA) Azithromycin or Rifampicin or chloramphenicol as alternatives in children and pregnant women

(Continued on next page)

Table 2 (Continued)

Diseases	Causative agent	Mode of infection/disease	Distinctive features apart from jaundice and encephalopathy	Diagnostic tests	Specific treatment
Amoebic liver abscess	Entameba histolytica	Feco–oral transmission	Pain right upper abdomen, right lower chest, fever, tender hepatomegaly and right lung base signs. In untreated cases by severe sepsis follows. Encephalopathy and jaundice can also occur	Ultrasound and computed tomography scans for anatomical diagnosis. Serologic tests (ELISA or IHA) are about 90% sensitive for amoebic liver abscess	Metronidazole 500 mg thrice a day intravenously or 800 mg thrice a day orally. Alternatively, Chloroquine phosphate 600 mg (base) stat followed by 300 mg base daily for 2–3 weeks
Sepsis syndrome	Gram negative or gram positive organisms, fungi	Community acquired or hospital acquired	Fever, localizing symptoms of infection such as cough, dysuria etc. Later MOF. More common in immunocompromised host	Blood culture and features of sepsis syndrome	Fluids and appropriate antimicrobials
Pregnancy related liver disease	–	Mechanism not fully understood	Illness in a pregnant lady presenting with acute fatty liver disease of pregnancy (AFLP), preeclamptic liver dysfunction or hemolysis elevated liver enzyme and low platelet (HELLP) syndrome	Clinical diagnosis supported by imaging and laboratory evidence of liver failure	Early delivery, supportive treatment
Hemophagocytic lymphohistiocytosis	Infections such as Epstein–Barr virus, immunodeficiency, rheumatologic syndromes and immunodeficiency	Genetic predisposition may be present	Fever, hepatosplenomegaly, lymphadenopathy, neurological manifestations	Cytopenias, elevated LDH, Serum ferritin, triglycerides and FDPs. Histologically evidence of hemophagocytosis	High-dose dexamethasone, etoposide, and cyclosporine A, together with intrathecal methotrexate (IT MTX) for patients in whom CNS-HLH did not remit after 2 weeks of dexamethasone
Bilirubin encephalopathy	–	Hemolytic anemia caused by Rh or ABO incompatibility or bilirubin metabolism disorders	Illness in new born especially those with low birth weight, hypothermia, anoxia, acidosis, sepsis, hypoalbuminemia, and meningitis	Bilirubin toxicity	Phototherapy, exchange transfusions

Note: Abbreviations used in table (IP—Incubation period, ARDS—acute respiratory distress syndrome, MODS—multi-organ dysfunction syndrome, MRCP—magnetic resonance cholangiopancreatography, ERCP—endoscopic retrograde cholangiopancreatography, LDH—lactic dehydrogenase, FDPs—fibrin degradation products, IHA—Indirect hemagglutination assay).

coagulopathy and renal failure during the course of prolonged hepatitis. Patients often develop spontaneous bacterial peritonitis and gastrointestinal bleeding. Encephalopathy is usually a preterminal event. Liver biopsy reveals extensive bridging, submassive necrosis, cholestasis and failure of regenerating activity. HBV and HEV are the common causes in most patients.

Acute-on-chronic liver failure (ACLF) has been recently recognized as an entity and can be defined as an acute hepatic insult superimposed on established stable chronic liver disease leading to decompensation of liver disease.¹⁴ Alcoholic cirrhosis constitutes 50–70% of the underlying liver diseases in ACLF in Western countries, whereas in most of tropical countries proportion of HBV is much higher. Among the precipitating causes of ACLF, HEV superinfection has remained a very important acute insult in the Indian subcontinent and is an important cause of jaundice, encephalopathy and mortality in patients with cirrhosis.¹⁵ Reactivation of HBV infections leading to hepatitis “flares” are the other major causes of ACLF in the Asian region.¹⁶ In contrast to this, sepsis and variceal bleeding play important roles in the sudden decompensation of established chronic liver disease in the West.

A study from AIIMS, New Delhi including more than 1000 patients with ALF, have reported that approximately 80% of patients develop encephalopathy within 2 weeks of onset of icterus and all patients present within 4 weeks of onset of jaundice.¹⁷ None of the patients who were diagnosed as ALF on the basis of clinical presentation with jaundice, encephalopathy and coagulopathy, on postmortem liver biopsies showed evidence of underlying chronic liver disease.

ALF is seen with equal frequencies among males and females in Japan but elsewhere in world, it is more common in females.¹⁶ Pregnant women with ALF are widely regarded as having more severe disease with higher complication rates and mortality compared with non-pregnant females. Among the females, ALF seems to be more common during pregnancy. Of the females presenting with ALF, majority (up to 60%) in the child-bearing age are pregnant. Indian epidemics of hepatitis E virus have shown that pregnant women especially in their second and third trimesters get infected more frequently (12–20%) than men and non-pregnant women (2–4%) for unclear reasons.¹⁸ Even the mortality rate is significantly higher among pregnant women who develop hepatitis during epidemics (10–39%) than in the general population affected with hepatitis (0.06–12%). In the sporadic setting, evidence of HEV infection has been detected in 30–45% of patients with ALF. One study found that progesterone receptor gene mutations (PROGINS) occur more frequently among pregnant female patients with ALF and these patients also had high viral load leading to poor pregnancy outcomes in hepatitis E.¹⁹ Once the pregnant females develop ALF, mortality is similar to that of non-pregnant women and

men with ALF, and is independent of the cause or trimester.¹⁸ Acute Fatty Liver of Pregnancy is related to genetic predisposition, and may also have geographical variation in prevalence.

The etiological profile of ALF seen in Western countries has been different than what is seen in South Asia. One major difference between regions is due to high prevalence of hepatitis E in the Indian subcontinent. In contrast to the heterogeneous natural course reported from the UK, France, the USA and Japan, Indian patients have a more uniform clinical presentation and natural course, although current evidence now supports the view that the virus genotypes may determine differences in presentation. The survival frequency in hepatitis E virus-induced ALF was reported to be more than 60% and this is similar to that observed for hepatitis A. Differences in genotype and in presence of previously silent underlying chronic liver disease in some patients may be an explanation for reports of ALF with differing nomenclature, definitions and natural course, resulting in sub-classification of this entity.

Most cases of ALF in the West are due to drugs and toxins with paracetamol (acetaminophen) being the major culprit in many countries including the USA, the UK, other European countries and Australia. The common etiologies of ALF in different parts of the world are highlighted in Figures 1 and 2 (Modified from Shalimar et al 2013).²⁰ Published reports from the Indian subcontinent reveal that hepatitis viruses are the commonest etiological agent in more than 90% of patients with ALF. Non-A, non-E hepatitis account for 38% (although this group could also be classified as indeterminate cause). Hepatitis E virus was

Figure 1 Prevalence of different causes of acute liver failure in different countries. Paracetamol overdose is hardly if ever seen in India, while it is the commonest etiology in UK and USA. Viral hepatitis is the commonest etiology in India.

Figure 2 Prevalence of different hepatotropic viruses as etiology amongst acute liver failure cases in different countries. Hepatitis B is common in Europe and Japan while hepatitis E is the commonest virus causing acute liver failure in India.

responsible for 31% of cases. There are relatively few drug-induced cases except those caused by ATTs.¹⁷ In Australia, Paracetamol (Acetaminophen) overdose was seen in 36% cases while Viral hepatitis was seen in only 14%. Additional 34% were classified as non-A, non-B viral hepatitis.²¹ In Japan, Hepatitis B appears to be a common cause.²² In the UK,²³ paracetamol overdose was the commonest etiology (57%) ALF, as was in the USA,²⁴ and Europe.^{25,26} One exception is Spain, where the incidence of acetaminophen overdose is relatively low.²⁷ Other drugs responsible include NSAIDs, antiepileptics, antimicrobial agents such as antituberculosis therapy (ATT; isoniazid, usually in combination with other medications such as rifampicin and pyrazinamide), antibiotics and antifungals. Phenprocoumon, an oral anticoagulant accounts for 23% of non-paracetamol drug-induced ALF in Germany. Numerous other drugs also have been implicated as the cause of ALF, predominantly in the West. In one series of 133 US cases of ALF, the commonest drug-induced liver injury cause was ATT (19%), followed by all other antibiotics combined (23%). Complementary and alternative medications were observed in 11%, antiseizure medications in 9% and NSAIDs in 5%. Amanita poisoning (Amanita phalloides) is sometimes seen as a cause of ALF in US and European ALF. It occurs and is when amateur mushroom hunters fail to differentiate between the edible and the poisonous variety.²⁸ However, this condition is rarely seen in eastern Asian countries including the Indian subcontinent.

As with etiology, the spectrum of complications also differs between various geographical areas. Renal failure has been described in 40–80% of patients from Western series depending upon the etiology and is associated with a

poor prognosis. This complication often accompanies Paracetamol overdose (70%) and is less commonly seen with other causes in western series. The other causes associated with increased incidence of renal failure include amanita poisoning and trimethoprim-sulfamethoxazole toxicity.¹⁸ In Indian subcontinent, where viral hepatitis is the common etiology, renal failure has been reported in 10% of patients.²⁰ In India, 58% of ALF patients have cerebral edema at the time of hospitalization. This complication suggests poor prognosis and high mortality rate.²⁹ Sepsis is common sequel of ALF across the globe though type of infection varies as per local conditions. In recent reports, the predominant organisms reported are Gram negative.^{18,30}

There are several non-hepatotropic viruses that can also lead to similar syndrome. One example is Yellow fever, which is caused by a virus carried by mosquitoes. It is common in South America and in sub-Saharan Africa. Symptoms usually develop 3–6 days after a mosquito bite and may be severe in elderly. In initial stage of disease presents as headache, muscle and joint aches, fever, flushing, loss of appetite, vomiting, and jaundice are common. Symptoms often go away briefly after about 3–4 days. Most people will recover but some may get worse within 24 h. Complications include heart, liver, and kidney failure, bleeding disorders, seizures, coma, and delirium.^{31,32}

MALARIAL HEPATOPATHY

Hepatic dysfunction in malaria has been recognized since many years^{33,34} but it is doubtful if acute liver failure can be caused by Malaria.³⁵ However, coexistence of malarial hepatopathy and cerebral malaria is not uncommon and can sometimes be confused with syndrome of acute liver failure.³⁶ The majority of the cases have either isolated infection with *Plasmodium falciparum*³⁷ or a mixed infection with both *P. falciparum* and *Plasmodium vivax*³⁸ and rarely with *P. vivax* alone.³⁹ The incidence of jaundice is reported to be 2.58% only.⁴⁰ In a study of the 732 adult patients with falciparum malaria, only 39 (5.3%) were noted to have jaundice and only 18 (2.45%) had evidence of malarial hepatitis.³⁴ In severe malaria incidence of jaundice may vary from 8 to 37% both in adults as well as children.^{41,42}

Jaundice in Malaria is multifactorial in origin.⁴³ The rupture of hepatocytes during the primary schizogony results in cellular damage but this does not result in significant hepatic dysfunction.⁴⁴ Severe infestation of the red blood cells by *P. falciparum* and resultant hemolysis results in the rising bilirubin. *P. falciparum*, during development inside RBC induces formation of sticky knobs on the surface of the erythrocytes.⁴⁵ These knobs bind to receptors on endothelial cells in capillaries and venules. Infected red cells also stick to uninfected red cells and form rosettes which clog the microcirculation. The cytoadherence and sequestration of red cells within these small vessels leads

to microvascular obstruction to blood flow with resultant ischemia leading to various organ dysfunctions, including hepatic dysfunction.

Other mechanisms suggested are occlusion of portal venous branches by parasitized red blood cells,⁴⁶ endotoxemia due to severe systemic infection,⁴⁷ intrahepatic cholestasis due to reticuloendothelial blockage and hepatic microvillus dysfunction⁴⁸ and apoptosis and oxidative stress.⁴⁹ There can also be, as mentioned earlier a coinfection with viral hepatitis E or A which are common in this country.^{50–52} Underlying chronic hepatitis B infection can be a risk factor for severe malarial infection and coexistence of two may result in exaggerated hepatocyte dysfunction.⁴³ Some cases of severe malaria also have disseminated intravascular coagulation which can contribute to hepatocellular dysfunction seen in severe malarial infection.⁵³ Hepatitis may also be a result of drug-induced liver injury caused by a variety of drugs used in Malaria such as mefloquine, chloroguanide, amodiaquine and pyrimethamine sulfadoxine combination.⁴³

“Malarial hepatitis” was the term initially used to describe hepatocytic dysfunction in severe and complicated malaria; however, actual inflammation of the liver parenchyma is almost never seen. It is characterized by a rise in serum bilirubin along with the rise in serum glutamate pyruvate transaminase levels to more than three times the upper limit of normal.⁵⁴ This in the absence of evidence of exposure to hepatotoxic drugs and absence of clinical or serological evidence of viral hepatitis makes malarial hepatopathy a unique entity. Rarely in endemic areas, malaria can coexist with viral hepatitis.⁴³

Clinical presentation that is confused with liver failure has been described as type B presentation.³⁴ These patients usually present with acute onset fever along with jaundice which is usually severe and is associated with coma, renal failure and DIC. Severe hemolysis can lead to significant anemia but in the presence of jaundice, clinical examination may be misleading and one can miss significant pallor. Systemic examination reveals hepatomegaly and often significant splenomegaly. According to WHO, clinical signs of liver failure such as asterixis are almost never seen unless there is concomitant viral hepatitis.⁵⁵ Severe impairment of the sensorium is not unusual in severe malaria, however this may be multifactorial. Cerebral malaria, hypoglycemia, hypoxia and/or uremia due to renal involvement may also contribute to the altered mental status or encephalopathy in severe falciparum infection.

True hepatic encephalopathy is considered rare in malaria. However, one study of 86 adult patients with malarial hepatopathy (with serum bilirubin >3 mg%), reported hypersomnia, inversion of the sleep rhythm and delirium in 15 patients. Arterial blood ammonia levels were raised in all the patients (range 120–427 mEq/l) but asterixis were observed in only nine patients. However, psychometric

tests were abnormal in 12 and altered mental state was seen in 13 patients.³⁵

Electroencephalogram (EEG) in these patients may reveal delta waves, pseudo periodic burst suppression and triphasic waves.⁴⁵ In one study, triphasic waves, which are considered characteristic of hepatic encephalopathy, were seen in three out of 15 patients having malarial hepatitis³⁵

Most of these patients have elevated Serum bilirubin with conjugated fraction crossing 50% mark.⁵⁶ Liver enzymes are elevated 3–5 times the normal but may be elevated much beyond this. INR is usually normal, even in patients with marked elevation of enzymes and is elevated only with DIC.^{43,44} This is one of the major differences from ALF. Ultrasonography will find hepatomegaly with or without splenic enlargement again differentiating it from ALF.

Histological findings in malarial hepatopathy include deposition of “Malarial (hemozoin) pigment”, inflammatory infiltrates, reticuloendothelial cell hyperplasia, congestion of hepatocytes, cholestasis and associated centrilobular necrosis.^{43,57} The last finding may be the result of associated ischemia due to preterminal hypotension. On electron microscopy hepatocyte swelling, Kupffer's cell hypertrophy, sinusoidal macrophage hypertrophy along with changes in endoplasmic reticulum/mitochondria, loss of microvilli and damage to canalicular membranes is seen.⁵⁸

In endemic and hyperendemic areas, malarial hepatitis must be excluded in all cases diagnosed to have ALF, because it is an eminently treatable condition. Presence of persistent fever, disproportionate anemia, oligo/anuria, firm splenomegaly and normal increased liver span are some of clinical findings that will point towards Malarial hepatopathy. On investigations, ALT is mildly elevated and INR prolongation is conspicuous by its absence. There may be no difference in duration of jaundice, altered consciousness and the interval between onset of jaundice and altered consciousness in two groups.³⁴

DENGUE FEVER

Dengue Hemorrhagic Fever (DHF) is a common seasonal arthropod-borne viral fever in South-East Asia.⁵⁹ It has been estimated that over 50 million cases of severe dengue fever occur in Asian countries with a mortality of upto 5%.⁶⁰ By definition, Dengue virus is a non-hepatotropic virus, but a wide spectrum of liver dysfunction is frequently seen along with this infection which includes liver failure.⁶¹ Jaundice in dengue infection has been associated with fulminant liver failure and by itself is a poor prognostic factor.⁶²

Liver involvement in dengue is usually manifested by hepatomegaly (clinically) or increase in liver enzymes

(biochemically). Presentation with jaundice can simulate acute hepatitis. Severe dengue can manifest with fulminant hepatic failure and has been the cause of death in many children with dengue infection.⁶³ Other gastrointestinal manifestations include acalculous cholecystitis, acute pancreatitis, acute parotitis and diarrhea.⁶⁴ Hepatitis is common and can be found in 60–90% of dengue-infected patients.⁶⁵ Most of cases with hepatitis have mild disease with less than 11% cases developing a rise in transaminases above ten times the upper limits of normal.⁶⁶ Usually the SGOT levels are more than SGPT levels probably due to skeletal muscle injury.⁶⁷ Jaundice has been reported in 2–25% of cases by several authors.⁶⁸ In a study of 120 cases, 80.8% had hepatomegaly, (more common in severe dengue (93.1%) and dengue with warning signs (84.4%) group). Jaundice was observed in 72 (60%), most common again in severe dengue (94.5%); thus, making jaundice an important predictor of severe dengue.⁶⁹ Acute liver failure (ALF) occurs less frequently and is seen mainly in children with upto 50% mortality, though it can also occur in adults.^{70–73} Hepatic failure following DHF has been described earlier too.^{74,75} Nonfatal Reye's syndrome confirmed by liver biopsy has also been described as a complication of DHF.⁷⁶ Altered sensorium in these cases is due to hepatic encephalopathy or shock and multiple organ involvement.⁶¹

The usual cause of liver injury in Dengue fever is thought to be due to (i) Direct cytopathic effect of the virus; (ii) Killing of virus-infected cells by the host immune response; and (iii) a non-specific effect of shock and hypotension (iv) Hepatic sinusoidal obstruction coupled with shock might be the underlying mechanism of liver failure in this disease⁷⁷ (v) Drug-induced liver injury due to antipyretics and herbal drugs are other possible contributors (vi) Rarely one may come across coinfection with other hepatitis viruses, which are endemic in our region.⁷⁸

Liver histology shows hepatocytes necrosis at zone two and councilman bodies.⁷⁹ The presence of dengue virus antigens and nucleic acid has been shown in liver tissue using immunohistochemistry, in situ hybridization and in situ polymerase chain reaction techniques.⁸⁰ It is unclear if the virus multiplies in the hepatocytes. In recent years, dengue-specific CD4+ and CD8+ T-cells have been shown to play a part in the pathogenesis of severe forms of Dengue fever⁸¹ and higher incidence of severe liver injury in patients with complicated dengue may suggest a role for host immune responses in the causation of liver injury as well.⁸²

Thus, the diagnosis of acute liver failure due to dengue should be considered in patients with fever who develop jaundice and altered sensorium with associated hemorrhagic manifestations, thrombocytopenia, AST levels higher than ALT levels, plasma leak syndrome character-

ized by increasing hematocrit, gall bladder wall edema and ascites.⁸³

TYPHOID FEVER

Enteric or Typhoid fevers are commonly seen in India in epidemic⁸⁴ as well as sporadic forms. Hepatitis and jaundice have been frequently reported in typhoid fevers.⁸⁵ Osler reported jaundice in 8 out of 1500 cases,⁸⁶ though subsequently its incidence has been noted to vary from 0.5 to 7.6% of all cases.⁸⁷ Presence of Jaundice in typhoid fever may cause diagnostic problems, especially in the tropics where malaria and viral hepatitis are also common. Similarly, the high incidence of sickle cell disease in tropical Africa further complicates the picture as a combination of fever and jaundice is also a common form of presentation.⁸⁸ Fulminant hepatitis has been described in typhoid fever due to coinfection with hepatitis A.⁸⁹ Hepatic involvement in typhoid is thought to be due to damage to hepatocytes by endotoxins as histologically only reticuloendothelial cell hyperplasia has been recorded.⁸⁷ Liver involvement in Typhoid fever is usually accompanied by hepatomegaly and biochemical abnormalities which include raised transaminases as well as raised alkaline phosphatase & 5' nucleosidase.⁹⁰ Hepatic encephalopathy can also occur in Typhoid fever, though is less common.⁹¹ A wide variety of neuropsychiatric abnormalities including coma have been described due to Typhoid fever.^{92,93} So it is not unusual to have a case with jaundice and altered sensorium unrelated to hepatic encephalopathy in Typhoid fever.

Jaundice usually appears in second week of the fever and improves slowly with recovery of the patient.⁹⁴ In one study, 87% patients hepatomegaly and this sign can alert a physician while considering the diagnosis of ALF.⁹⁵ Neuropsychiatric manifestations are usually seen in the third week of fever and may range from psychosis to coma. Liver function test may show evidence of hepatic dysfunction even in the absence of jaundice. This occurs in 21–60% of cases.⁸⁷ It has been suggested that a significant rise in transaminase levels may occur due to either invasion of liver by Salmonella or high concentration of endotoxins which damage the hepatocytes.⁹⁵ The bacteria may also proliferate in the hepatocytes and produce hepatic damage by stimulating the synthesis and release of cytokines.⁹⁴ Histopathologic study of the liver reveals typhoid nodules, cloudy swelling, ballooning degeneration, moderate fatty change and mononuclear cell infiltrate in few focal areas.⁹⁶ Intact bacilli have also been demonstrated in the parenchyma of the liver by immunohistochemistry and have been cultured from liver biopsy.^{87,97} Conjugated bilirubin constituted more than 80% of the total serum bilirubin. This is less due to hemolysis and more due to canalicular occlusion by swollen hepatocytes. This may

be followed by focal hepatocellular necrosis which can promote rupture of bile canaliculi leading to direct reflux of bile into the hepatic sinusoids, hence the predominant elevation of conjugated bilirubin.⁹⁵ A & B. The presence of comorbid state such as malnutrition and anemia results in a disease with fulminant course because of impaired immune response. The incidence of complications such as gastrointestinal hemorrhage and ileal perforation is also higher in icteric patients as compared to non-icteric typhoid patients. Mortality is also significantly higher in the jaundiced typhoid patients.

Leptospirosis

Weil's disease or leptospirosis is a spirochetal infection caused by *Leptospira interrogans*. These spirochetes also infect rats, dogs, cattle, sheep and swine. Infection occurs to those who work in contaminated water, especially during rainy season. The disease has an incubation period of 2–26 days with an average of 10 days. Classically it is a biphasic illness with mild first phase and severe second phase. Common initial presentation is with a nonspecific febrile illness, but in some it takes a serious turn in second phase with development of hepatorenal dysfunction often with pulmonary hemorrhage, (also known as Weil's syndrome).⁹⁸ These severe manifestations usually develops 4–9 days into the illness. The organisms can damage blood vessels, either directly or through immune mediated injury and lead to centrilobular necrosis of the liver and renal tubular dysfunction (interstitial nephritis and acute tubular necrosis).

Liver involvement may present with tender hepatomegaly and jaundice. In icteric patients, jaundice usually appears on days 4–6, up to 9 days after onset. Apart from liver damage, an additional hemolytic component of jaundice results hemolysis and breakdown of erythrocytes in areas of hemorrhage. Serum bilirubin levels may be very high. Serum aminotransferase (AST, aspartate aminotransferase, glutamate oxaloacetate transaminase; GGT, gamma glutamyl transpeptidase; and ALT, alanine aminotransferase, glutamate pyruvate transaminase) levels are frequently normal, but sometimes raised to 2–3 times normal levels. A raised serum bilirubin level with normal aminotransferases is highly suggestive of leptospirosis rather than hepatitis.

Besides severe hepatorenal dysfunction, patients can present with ARDS, myocarditis, rhabdomyolysis, thrombocytopenia, DIC, hemorrhage into the skin and internal organs, uveitis, and digital gangrene. Clinically, patients have characteristic conjunctival suffusion or hemorrhages often with uveitis, severe muscle tenderness and non-oliguric renal failure with hypokalemia.

An outbreak in Mumbai in 2000 revealed that 35% of patients had pulmonary manifestations. 80% of patients who died had pulmonary hemorrhages and 70% had renal

failure. Patients with conjunctival suffusion and pulmonary or renal failure were more likely to be MAT positive.⁹⁹ Later part of illness may be associated with Aseptic meningitis and in some patients mental confusion, hallucination and psychosis complicate the physical illness.¹⁰⁰ Occasional patient may develop encephalitis, in which the patients may lose memory and hallucinate, be delirious, confused, disorientated, or semi-comatose, or develop extrapyramidal symptoms. Convalescence from meningitis or encephalitis may be prolonged and involve periods of physical, muscular weakness and mental exhaustion for months. Latter may give a false suggestion of hepatic encephalopathy. Diagnosis is made with serology with the microscopic agglutination test (MAT) as the gold standard with either a four fold rise in titers or a single titer of >1:800 being diagnostic.¹⁰¹

HIV CHOLANGIOPATHY

A number of opportunist infections can involve the biliary tree in patients with HIV infection and lead to jaundice, HIV cholangiopathy and acute cholecystitis. Among these are included *Cryptosporidium parvum*, Microsporidia, *Cyclospora cayetanensis*, and *Isospora belli*. Most patients with cholangiopathy have severe immunosuppression, with CD4⁺ counts of <200/mm³. HIV cholangiopathy can also be caused by infection with cytomegalovirus (CMV), *Mycobacterium avium-intracellulare* complex infection, and *Candida albicans*.¹⁰²

Typical symptoms are RUQ pain, fever, and elevated serum ALP. Jaundice is uncommon. Diarrhea is common because many of the pathogens infect the small bowel as well. On physical examination RUQ or epigastric tenderness is characteristic. ERCP shows characteristic picture like that of sclerosing cholangitis. While it will not cause ALF, concomitant CNS involvement is not uncommon in view of marked immunosuppression and may lead to varied manifestations including coma. Therefore HIV associated cholangiopathy must be considered in syndrome of jaundice and encephalopathy.

Hepatobiliary Tuberculosis

Tuberculosis primarily is a lung disease but is known to involve several other organs of body. Liver involvement is seen at autopsy in 25–50% of patients dying from active pulmonary tuberculosis. Miliary tuberculosis, due to hematogenous spread of tubercle bacilli, causes multiple granulomas within the liver leading to Granulomatous hepatitis. Patients present with unexplained fever, jaundice, hepatomegaly, elevated ALP, and abnormalities of other liver function tests. Laparoscopy may be diagnostic as it shows cheesy white irregular nodules on the liver surface. Biopsy from such lesions reveals caseating granulomas. Granulomatous hepatitis with multiple

granulomas in the liver may also be seen following vaccination with BCG (bacillus Calmette–Guérin), especially in persons with impaired immune response. Less commonly, patients may develop tuberculous liver abscess. Rarely tuberculosis can also involve biliary system leading to obstructive jaundice. Bile duct involvements may be due to enlarged tuberculous lymph node compressing the bile duct or diffuse involvement of the intrahepatic ducts by tubercle bacilli. ERCP reveals multiple intrahepatic biliary strictures, areas of dilatation, beading and ectasia, resembling sclerosing cholangitis or cholangiocarcinoma. Biliary stricture may occur at the hilar region or distal common bile duct with dilatation of the intrahepatic ducts.¹⁰³ Liver failure is not a presentation of hepatobiliary tuberculosis but concomitant CNS involvement in tuberculosis can produce varied clinical picture with a variety of neuro-psychiatric presentations including Coma.

JAUNDICE AND ENCEPHALOPATHY CAUSED BY TROPICAL INFECTIONS AS A PART OF MULTIORGAN INVOLVEMENT

Several tropical diseases including bacterial sepsis can produce the syndrome of jaundice and encephalopathy as a part of multi-organ involvement in critically ill patients in ICU. List of such infections will include all causes of cholangitis, pyogenic or amoebic liver abscesses, septicemia from any systemic bacterial infection, Toxic shock syndrome, malaria, typhoid, leptospirosis and so on.^{104–106} Acute jaundice can be a harbinger or marker of sepsis, multisystem organ failure (MSOF), or a reflection of transient hypotension (shock liver), right-sided heart failure, the metabolic breakdown of red blood cells, or pharmacologic toxicity. The persistence of jaundice is associated with a significant increase in patient morbidity and mortality. These patients are often encephalopathic due to associated hypoxia, electrolyte disturbance or even hypoglycemia. Hemolysis, Massive transfusion, Hypotension/"shock liver", Disseminated intravascular coagulation, Soft tissue trauma and hematoma resorption, Sepsis, Liver trauma/biloma, Liver failure/MSOF and Medications/hepatotoxins may contribute to varying degree in causation of jaundice.¹⁰⁷ Special mention must be made of amoebic liver abscesses where presence of jaundice with serum bilirubin above 3.5 mg/dl and presence of encephalopathy are risk factors that point to a poor prognosis.¹⁰⁸

PREGNANCY RELATED LIVER DISEASE

The relationship of hepatitis E related ALF with pregnancy has been described above. Apart from that, pregnancy is associated sometimes with several specific syndromes, which are not seen in non-pregnant females or males. These include acute fatty liver disease of pregnancy (AFLP), preeclamptic liver dysfunction and, hemolysis

elevated liver enzyme and low platelet (HELLP) syndrome, which can present in similar manner. It has been reported that Pregnancy-related liver disorders accounted for 8% of all maternal deaths at one center from 1999 to 2011.¹⁰⁹ Risk of maternal death can be minimized by timely recognition and early/aggressive multi-specialty management of these conditions. Urgent termination of pregnancy remains the cornerstone of therapy for some of these life-threatening disorders, but recent advancements in our understanding help us in better overall management of these patients. One study found that Presence of ascites and hypertension differentiates pregnancy associated acute liver disease (PAALD) from ALF caused by viral hepatitis and should prompt early delivery.¹¹⁰ In one study, ascites was observed in 35 of 46 patients with PAALD (76%). In 25 patients tested (71.4%), the ascites fluid had low levels of albumin (<0.2 g/dL) and protein (<1 g/dL) and high serum ascites albumin gradients, indicating portal hypertension. Spontaneous bacterial peritonitis was observed in 48% of patients tested and was not associated with mortality. Patients with ascites had significantly low serum levels of protein and albumin ($P < .001$). Model for end-stage liver disease scores did not differ between patients with or without ascites (32 vs 27; $P = .1$).¹¹¹ Authors have described a new prognostic score that can predict mortality by using only two variables i.e. bilirubin and INR.¹¹²

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

HLH is a potentially fatal syndrome characterized by fever, splenomegaly, jaundice, and the pathologic finding of hemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors) in bone marrow and other tissues.¹¹³ It may be primary (genetic), or secondary (acquired) to viral infections, autoimmune diseases or malignancy such as lymphoma. It is caused by excessive inflammation and tissue destruction due to abnormal immune activation and excessive inflammation caused by a lack of normal downregulation of activated macrophages and lymphocytes.¹¹⁴ As a result most patients with HLH exhibit impaired cytotoxic function of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), coupled with excessive activation of macrophages. Excessive cytokine production (cytokine storm) by macrophages, NK cells, and CTLs is thought to be a primary mediator of tissue damage and ultimately leads to multiorgan failure and the high mortality of the syndrome.

The initiating trigger for an acute episode is often an infection or an alteration in immune homeostasis. Immune activation is commonly initiated by an infection both in those with a genetic predisposition and in sporadic cases. The most common infectious trigger for HLH is viral infection, especially with Epstein–Barr virus (EBV). Many other infectious organisms are also implicated. Other

triggers include inherited immunodeficiency syndromes, malignancy, rheumatologic disorders, or HIV infection. What distinguishes HLH from other syndromes of immune activation, immunodeficiencies, and inflammatory states is the coexistence of immune dysregulation with unchecked inflammation.¹¹⁵

Clinically patients will present with fever, hepatosplenomegaly, lymphadenopathy, jaundice (in more than 2/3 cases), and often maculopapular rash. Of central nervous system manifestations (seen in nearly half the cases), encephalopathy, meningismus, and seizures are the most commonly reported.¹¹⁶ The most prominent laboratory abnormalities noted are cytopenias, which may be profound. Serum chemistry findings may suggest hemolysis, with hyperbilirubinemia, hypertriglyceridemia and marked elevation of ferritin and lactate dehydrogenase. Serum fibrinogen is typically low, and there may be disseminated intravascular coagulation. Typical hemophagocytosis is seen in bone marrow, spleen, and lymph nodes and occasionally the central nervous system and skin. Hemophagocytosis may be present in the liver, but infiltration of the hepatic portal tracts with lymphocytes is also common.¹¹⁷

Diagnosis can be made if five of following eight findings are present (a) Fever $\geq 38.5^{\circ}\text{C}$ (b) Splenomegaly (c) Peripheral blood cytopenia, with at least two of the following: hemoglobin $<9\text{ g/dL}$ (for infants <4 weeks, hemoglobin $<10\text{ g/dL}$); platelets $<100,000/\text{microL}$; absolute neutrophil count $<1000/\text{microL}$ (d) Hypertriglyceridemia (fasting triglycerides $>265\text{ mg/dL}$) and/or hypofibrinogenemia (fibrinogen $<150\text{ mg/dL}$) (e) Hemophagocytosis in bone marrow, spleen, lymph node, or liver (f) Low or absent NK cell activity (g) Ferritin $>500\text{ ng/mL}$ (often $>3000\text{ ng/mL}$) and (g) Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms. Alternatively Molecular identification of an HLH-associated gene mutation such as *PRF1*, *UNC13D*, *STX11*, *STXBP2*, *Rab27A*, *SH2D1A*, or *BIRC4* (homozygosity in children; or heterozygosity in adults with suggestive clinical findings) also is enough for diagnosis.

BILIRUBIN ENCEPHALOPATHY

Jaundice and encephalopathy in infants has been called bilirubin encephalopathy. In 1903, Dr. Christian Schmorl used the term *kernicterus* to describe the neuropathologic yellow staining (secondary to unconjugated bilirubin) of the basal ganglia of infants who died with neonatal jaundice. The terms *kernicterus* and *bilirubin encephalopathy* are commonly used interchangeably.¹¹⁸

Bilirubin encephalopathy is a disease of infants. The most common cause is any type of hemolytic anemia, usually due to Rh or ABO incompatibility. Other causes include congenital or acquired disorders of bilirubin metabolism. Factors implicated in potentiating the risk of developing bilirubin encephalopathy include low birth weight,

Figure 3 Clinical approach to patients presenting with jaundice and encephalopathy. If the patient is pregnant, she can have acute liver failure but one must also consider pregnancy related liver diseases. In neonates, possibility of bilirubin encephalopathy needs to be ruled out due to hemolytic anemia. Acute liver failure is characterized by, among other things, rising or prolonged prothrombin time/INR and shrinking liver size. Patients who have persistent fever, hepatomegaly and absence of coagulopathy are candidates where miscellaneous causes of jaundice and encephalopathy should be considered.

hypothermia, anoxia, acidosis, sepsis, hypoalbuminemia, and meningitis.¹¹⁹

Neurologically in early phase, which is seen in the first few days of life, infants present with somnolence, hypotonia, and loss of the Moro reflex. This is then followed several days later by an irreversible stage characterized by hypertonia of the extensor muscle groups. Patients who survive the neonatal period demonstrate the chronic manifestations of bilirubin encephalopathy i.e. choreoathetosis, sensorineural hearing loss, dental dysplasia, gaze abnormalities (particularly vertical gaze palsy) and mild mental retardation.¹²⁰

CONCLUSIONS

A Patient presenting with jaundice and encephalopathy is normally considered to have ALF or SAHF. And commonest cause of ALF in most Western countries is drug-induced. In tropical country like India, not only the etiological profile.

Of ALF is different, but several additional etiologies need to be seriously considered. Hepatitis E is the commonest single cause of ALF as well as the precipitating factor for ACLF. Several non-hepatotropic viruses such as Dengue fever, may also present with similar syndrome. Apart from viruses, several other etiologies will need to be considered such as bacterial infections, malaria, leptospirosis, typhoid fever and so on. A careful clinical assessment with detection of hepatomegaly and lack of significant coagulopathy may rule out ALF as the obvious cause of this syndrome. Approach to such patients has

been outlined in Figure 3 and Table 2 and details of diagnosis and treatment are described elsewhere.¹²¹

CONFLICTS OF INTEREST

All authors have none to declare.

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