HEPATIC MANIFESTATIONS OF TROPICAL DISEASES

‘Tropical diseases’ are the diseases that are prevalent in or are unique to tropical and subtropical regions. The tropical areas, which lie in the zone between the Tropic of Cancer and the Tropic of Capricorn, have a hot climate all the year and have larger volume of rains, which forms an ideal breeding ground for a large number of insect vectors and infective organisms. Insects such as mosquitoes and flies are by far the most common disease carriers. These insects may carry a parasite, bacterium or virus that is infectious to humans and animals. Human exploration of tropical rainforests, deforestation, rising immigration and increased international air travel and other tourism to tropical regions has led to an increased incidence of such diseases.

Diseases most prevalent in the tropics are malaria, giardiasis, schistosomiasis, chagas disease, leprosy, viral hepatitis, filariasis, hydatid disease, trypanosomiasis, leishmaniasis, leptospirosis, cholera, yellow fever, yaws, amoebiasis, tuberculosis and viral hemorrhagic fevers (Dengue, Lassa, Ebola, Marburg, Bunya, and Chikungunya fevers)

The tropical diseases which may commonly involve the liver include dengue, malaria, hydatid disease, leprosy, amoebiasis, leptospirosis, viral hepatitis and tuberculosis. Viral hepatitis and tuberculosis are well known and well researched disease entities, and hence not discussed further.

DENGUE FEVER
Dengue fever (DF), caused by Dengue Virus, and transmitted by Aedes mosquitoes, is an important zoonotic disease with worldwide distribution. The pathogenesis of hepatic involvement in DF includes a direct cytopathic effect of the virus, killing of virus infected cells by host immune response, and non specific effects of shock & hypotension.

Liver involvement in DF is extremely common. Increase in transaminases has been observed in 93.9%–97.7% of the cases, while alkaline phosphatase and serum bilirubin increase in a smaller proportion of patients (1,2,4,5). An important finding regarding transaminases increase in DF is that AST levels tend to be greater than ALT levels (4,6) (figure1). The mechanism for this is the excess release of AST from damaged monocytes during dengue infection. This finding may help to differentiate DF from viral hepatitis (pending serology reports) and may act as an early indicator of dengue infection. Hyperbilirubinemia in DF has been found to be more common in dengue shock syndrome, in patients with haemorrhage and in non-survivors (4). Thus, increased bilirubin can act as a poor prognostic indicator. Hepatomegaly in DF has been reported 17.6%–20.4% patients (1-2). Liver size does not correlate with disease severity, but an enlarged liver is observed more frequently in shock than in non shock cases (3). In a study done at our institute (4), hepatomegaly was observed in 12.1% cases and was more frequent in DSS as compared to DF (45.5% v/s 10.9%; p <0.05). Figure 1: Pattern of AST and ALT rise in dengue fever (4).
MALARIA
Malaria is caused by a Protozoan parasites transmitted by female Anopheles mosquitoes. The disease is caused by species of the genus Plasmodium. Malaria infects 300-500 million people each year, killing more than 1 million.

India contributes 77% of the total malaria in Southeast Asia. P. vivax accounts for 50-55% and P. falciparum for 48-52% of the cases. P. malariae is found in small areas in the foothills of Orissa. 95% of the Indian population lives in malaria risk areas. WHO estimates that India has 15 million cases of malaria with 19,500-20,000 deaths annually.

Hepatic involvement in malaria can have various presentations ie hepatorenal syndrome, fulminant hepatic failure and acute hepatitis (9). The mechanism of jaundice in malaria includes a) Hemolysis-unconjugated hyperbilirubinemia without transaminitis, and b) Malarial Hepatopathy- raised bilirubin with increased GGT. Hepatic involvement is most commonly seen with P. falciparum and less with P.vivax (0-9%). Hepatic encephalopathy is rare unless co-associated with viral hepatitis. Though raised arterial ammonia is commonly seen in patients with encephalopathy, other proposed mechanisms of encephalopathy in malaria include hypoglycemia, uremia, cerebral malaria and hypoxia.

Raised serum bilirubin has been observed in 32-37% of malaria. The liver enzymes usually rise up to 3 times ULN (10). The prothrombin time is usually normal, and a deranged INR warns infection with hepatotropic virus or severe DIC with sepsis. Liver biopsy may be required to establish the diagnosis when other diagnostic methods are inconclusive. Histopathological changes due to malarial involvement of liver are specific and may aid in the diagnosis of PUO. The commonly (>80%) observed findings include Kupffer cell hyperplasia, malarial pigmentation and congestion. The pathophysiology includes release of cellular products and debris from ruptured erythrocytes and their subsequent phagocytosis by the reticuloendothelial cells. Overall, the points which favour malarial hepatopathy over fulminant hepatic failure due to viral hepatitis include hepatomegaly, preserved coagulation profile and mildly elevated liver enzymes.

In a study from Bikaner, of the 1,091 patients with malaria, 635 had P. falciparum malaria and 456 had P. vivax malaria (7). Among patients with severe manifestations, 40 had evidence of monoinfection of P. vivax malaria. Complications observed were hepatic dysfunction and jaundice in 23 (57.5%) patients, renal failure in 18 (45%) patients, severe anemia in 13 (32.5%) patients, cerebral malaria in 5 patients (12.5%), acute respiratory distress syndrome in 4 patients (10%), shock in 3
patients (7.5%), and hypoglycemia in 1 (2.5%) patient. Thrombocytopenia was observed in 5 (12.5%) patients, and multi-organ dysfunction was detected in 19 (47.5%) patients.

In another study (8), hepatic involvement in the form of raised serum bilirubin levels ≥6 mg% and prothrombin time >4 compared to controls was found in 192 cases (63.8%). Serum bilirubin ranged from 6-38 mg%. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were raised almost two-fold in 98% cases of multiorgan failure with hepatic failure, with mean values of 78 ± 30.4 IU/l and 81 ± 29.06 IU/l respectively. Nearly three-fold elevation of alkaline phosphatase was observed in 80% cases (mean 315 ±39.4 IU/l). Prothrombin time was also prolonged with mean value of 7 ±3 seconds.

HYDATID DISEASE - LIVER
Hydatid disease is caused by Echinococcus species. The disease spectrum includes- Cystic hydatid disease (caused by E. granulosus), alveolar hydatid disease (caused by E. multilocularis) and polycystic alveolar disease (caused by E. vogeli). E. oligarthrus infection is rare in humans. Hydatid infection may remains asymptomatic for years and may be diagnosed incidentally during autopsy or due to pressure effects on surrounding structures or cyst complications. Organs affected by E granulosus include liver (63%), lungs (25%), muscles (5%), bones (3%), kidneys (2%), brain (1%) and spleen (1%). In a study from India which enrolled 110 patients over duration of 21 years, 24 cases of hydatid disease at unusual sites were found. The most common site was spleen followed by skin and soft tissues (11). In another study from rural India, liver was involved in 75.2% patients, either solitarily or in association with other organs. Pain in the abdomen was the most common presenting complaint, and lump abdomen was the most common clinical finding (12).

LEPROSY
Leprosy is a chronic progressive granulomatous infection which affects various systems. Hepatobiliary system is the commonly affected in early stages, but usually diagnosed late in the disease course. The clinical presentation in cases of hepatic involvement include anorexia in 50% cases (due to hepatocellular dysfunction or due to disease process itself) and hepatomegaly in 8.8%-35% cases. The symptom profile and physical findings in various types of leprosy in a study done at our institute (unpublished data) is shown in figure 2.

Figure 2: Symptoms and signs in patients of leprosy and liver involvement.

Reports of LFTs in leprosy have been variable. The transaminases could be normal or raised. Rise in serum proteins with hypoalbuminaemia has been a common finding irrespective of extent and duration of the disease. The mechanism for this could be deranged hepatocyte function and
hyperplasia of reticuloendothelial cells. In a study conducted in our institute, significant derangement of LFTs was seen in Lepromatous Leprosy (LL), and LL with ENL varieties. The main ultrasonographic findings of patients with LL include inhomogeneous echotexture of the hepatic parenchyma (100%) and echo-dense, partly irregular areas (1.5 cm x 3 cm) throughout the liver (90%). No abnormal findings were noted in controls or patients with Tuberculoid Leprosy (13).

On histopathological examination, two types of lesions have been noted- granulomatas specific of leprosy and non-specific collection of mononuclear cells. Both types can progress to portal scarring in due course of time. M. Leprae can be seen in histiocytes and all along the sinusoids. The major HPE findings in our study is shown in figure 3.

Figure 3: Histopathological findings in patients with leprosy.

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<th>Hepatocytolysis</th>
<th>Fatty changes</th>
<th>Focal necrosis</th>
<th>Kupffer cell hyperplasia</th>
<th>Fibrosis</th>
<th>Epitheloid cells</th>
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In a study including 240 patients, histological findings were found to correlate with LFTs. Granulomas in liver were detected in 21% cases of TL and 62% cases of LL. There was direct correlation between bacterial index and presence of AFB in liver. Alteration in liver functions was more when AFB were associated with leprous granulomatous lesions. AFB persisted even after 1-5 yrs of specific anti-leprosy therapy (14).

**AMOEbic LIVER A BSCESS**

Amoebic liver abscess, caused by Entamoeba histolytica, has an incidence of 3 - 9% of all cases of amoebiasis. It predominantly involves males in the age group of 20 to 45 yrs. The most common site is the right lobe, and it is solitary in 30-70% cases. The important clinical features include abdominal pain (62-94%), fever (67-87%), jaundice (33%).(15) Tender hepatomegaly may be present in up to 80% cases, pleural effusion in 10% and ascites in 4%. With a mortality rate of 2-15%, it is the 2nd leading cause of death of all protozoal diseases. Raised liver enzymes (>3 times normal) are found in 35% cases, raised ALP in 60-80% and hyperbilirubinemia in 6% - 29% cases (16). The pathogenesis of jaundice includes pressure on hepatic ducts, parenchymal involvement, cholestasis, biliary tributaries damage or vascular injury resulting in biliovascular fistula. Hemobilia can occur due to a biliary–vascular fistula involving an artery, and bilhemia can occur due to a fistula involving venous system.

Multiple liver abscesses can occur in about 15% cases. Patients present with fever, toxaemia, deep jaundice, and encephalopathy. Encephalopathy is indistinguishable from HE due to acute hepatocellular failure. Left lobe abscess can occur in about 35% cases. It usually presents with a
longer duration of symptoms (3-4 weeks) and fever is less common. Other features include- large epigastric mass with minimal movement with respiration, weight loss with poor hepatic localisation of symptoms, peritonitis & toxaemia.

A posteriorly located ALA in right lobe may lead to IVC obstruction or hepatic outflow obstruction. Rupture of the abscess into pleural cavity may lead to empyema thoracis, and intraabdominal rupture may lead to shock and generalised peritonitis (7%).

LEPTOSPIROSIS

Leptospirosis is a zoonotic disease with varied clinical manifestations ranging from fever and myalgias to severe life threatening illness. It can be transmitted directly or indirectly from animals to humans, via infected urine, through direct contact or contaminated water and soil. Occupational exposure accounts for 30-50% of human cases. About forty per cent of the patients infected with leptospira seroconvert asymptptomatically. Of the remaining 60%, approximately 90% suffer the milder anicteric form and 10% the severe icteric form. The severe form is associated with a fatality rate of up to 40%. The presence of jaundice in hospitalised cases of leptospirosis has varied from 32% to 84% (17). In a prospective study of 214 patients of leptospirosis done by our group, 85.1% patients had icteric leptospirosis, while 14.9% had anicteric leptospirosis (18,19). The most common presenting symptoms were- fever (74.5%), myalgias (72.2%), yellowness of eyes (71.7 %), altered sensorium (41.6%), abdominal distension (35.6 %), abdominal pain (28.2%), oliguria (27.7%), haemorrhagic manifestations (22.2%) and breathlessness (16.2%). Ascites (48.1%), hepatomegaly (46.3%), splenomegaly (25%) and pleural effusion (15.8%) were common physical signs. Deranged total bilirubin, AST, ALT, ALP, albumin and INR were present in 85.1%, 85.1 %, 72.2 %, 43.1%, 40.5% and 79.1% patients respectively. The mean (± SD) total bilirubin, AST, ALT, ALP, albumin and INR values were 10.6 ±10.8 mg/dl, 230.7 ±728.1 U/L, 171.7 ± 491.3 U/L, 169.2 ± 187.4 U/L, 2.6 ± 0.6 g/dl and 2.5 ±1.4 respectively. Renal involvement was seen in 71.1 % (131/184) patients of icteric leptospirosis and 50% (16/32) of anicteric form. Factors predicting poor outcome were presence of encephalopathy, renal failure, need for artificial ventilation and dialysis, leucocytosis and high bilirubin.

Prevention, early recognition and early treatment of tropical diseases are the most important measures to reduce morbidity and mortality associated with these diseases. Some of the strategies for controlling tropical diseases include:

- Draining wetlands to reduce populations of insects and other vectors.
- The application of insecticides and/or insect repellents.
- The use of a mosquito net over a bed.
- Use of water wells, and/or water filtration, water filters, or water treatment with water tablets to produce drinking water free of parasites.
- Development and use of vaccines to promote disease immunity.
- Pharmacologic pre-exposure prophylaxis
- Pharmacologic post-exposure prophylaxis
- Pharmacologic treatment
- Assisting with economic development in endemic regions

REFERENCES