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Dengue Induced Hepatic Injury

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I. Introduction

Dengue is a febrile illness caused by Flavivirus transmitted by Aedes mosquito. Dengue is the most rapidly spreading mosquito borne viral disease in the world. It is endemic in Asia, the Pacific, Africa and the Americas. Approximately 50 million infections occur annually [1] with 500,000 cases of dengue haemorrhagic fever and 22,000 deaths (CDC 2014). WHO categorised severe dengue as group C which includes dengue haemorrhagic fever and dengue shock syndrome due to its wide spectrum of manifestations.(Figure 1)[2]

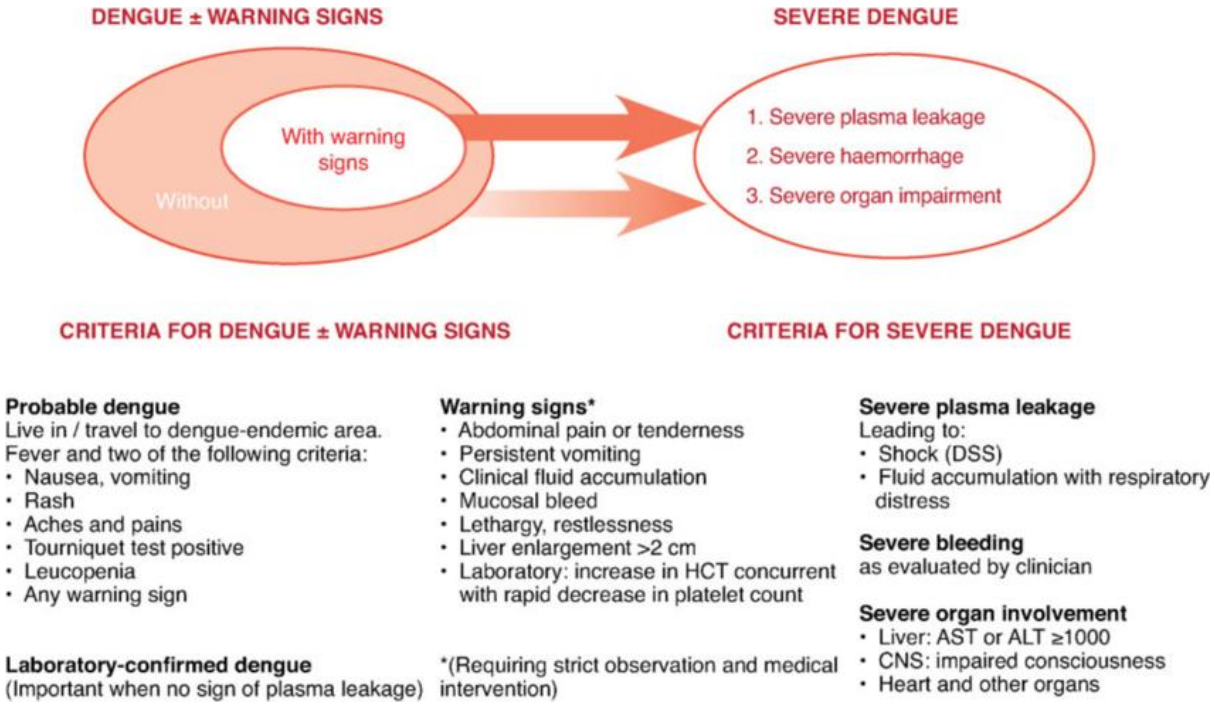


Figure 1

Numerous factors contribute to the increase in disease burden like inadequate safe water supply, urbanization, poor hygiene and viraemic travellers spreading the disease geographyically[3].

Dengue is an important cause of acute viral hepatitis in endemic areas. Elevated AST,ALT levels have been associated with bleeding [4] and dengue haemorrhagic fever [5].Liver failure has been recognised as a complication and unusual manifestation of dengue [1] .This article focuses on the pathogenesis ,clinical manifestation, investigation and treatment modalities for dengue induced liver dysfunction.

DENGUE VIRUS

Dengue virus (DEN) is a small single stranded RNA virus comprising four distinct serotypes(DEN1-4).These closely related serotypes of dengue virus belong to the genus Flavivirus ,family Flaviviridae. It is transmitted via Aedes Aegypti and less commonly Aedes Albopictus. The virus encodes for 7 non-structural proteins of which NS1 is used as diagnostic antigen in the initial phase of the disease.

PATHOGENESIS AND PATHOLOGY

Hepatic dysfunction is an important feature in dengue infection. The virus replicate in hepatocytes and kuffer cells. This could be due to the fact that viral particles enter the cells by phagocytosis leading to viral

degradation. The exact mechanism of interaction between dengue virus and hepatocyte is poorly defined. The interaction varies with different serotypes. Glucose regulated protein 78(GRP78) was reported to be used by DEN-2 to gain entry into Hep- G2 cells(a human hepatoblastoma cell line)[6].High affinity Laminin receptor was reported to be used by DEN-1 to enter liver cells [7]. Heparin sulphate plays an important role in the entry of all dengue serotypes into HepG2 cells [7]. The other cellular proteins reported to be used by viruses to enter the cells are: DC Specific ICAM- 3 Grabbing Non integrin (DC-SIGN),used by the virus to gain entry into monocyte derived dendritic cells [8], and the Fc receptor used in cases of secondary infection to gain entry into monocytes [9]. The susceptibility of a cell to infection depends on two factors .They are 1) the ability of the virus to enter the cell and 2)the factors within the cell that enable the virus to replicate successfully .For example,HepG2 cells in G2 phase of the cell cycle are more susceptible for infection and has higher replication rates[8]. Children have most of their cells in G2 phase hence shows why they are more susceptible to severe forms of dengue [10].

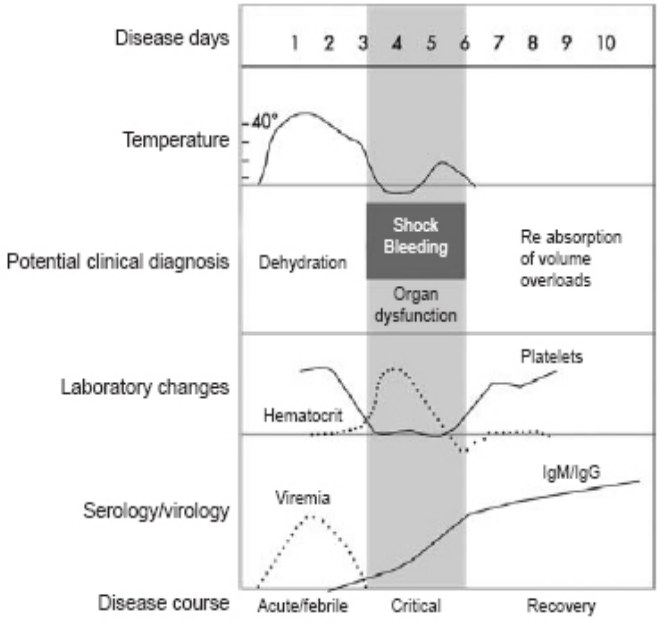
The end result of dengue induced infection of hepatocytes is apoptosis. Several mechanisms are involved. These include direct cytopathic effects on the virus, mitochondrial dysfunction due to low flow hypoxia and their influence on cellular and humoral immune factors in the liver. The process of apoptosis in hepatocytes is independent of p53.

Different immune responses are seen in dengue infections resulting in liver dysfunction. Antibody dependant enhancement could explain the cause of more severe disease in second infection. Effective CD4 and CD8 cells play important role in clearance of acute dengue fever. Serotype specific and serotype cross reactive memory cells are formed after primary infection. On secondary exposure, cross reactive CD4+ and CD8+ cells increase the severity of infection by producing various cytokines. The first 3 days of illness has highest concentration of TNF -alpha,IL-2,IL-6 and TNF-gamma while IL-5,IL-10 appear later. Levels of RANTES(regulated upon activation, Normal T cell expressed and secreted),a CC chemokine has chemotactic activity for T cells, monocytes, natural killer cells and eosinophils have been reported to be higher in dengue infection [9].

Pathological changes include microvascular steatosis ,hepatocellular necrosis, kuffer cell hyperplasia and destruction, councilman bodies and cellular infiltrates at portal tract [10].

CLINICAL AND LABOROTORY FINDINGS

In patients presenting with clinical features of dengue virus infection, three distinct phases can be identified during the course of the disease: febrile, critical and recovery (figure 2)[1].



Adapted from: World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control [Internet]. New edition. Geneva: WHO; 2009.[cited 2011 Mar 1]. Available from: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf

Figure 2

- Febrile phase: The symptoms include fever, myalgia, headache, arthralgia and exanthema, and it is frequently indistinguishable from other acute febrile diseases. Mild bleeding manifestations can occur as bleeding of the gums and epistaxis. The recognition of progression to severe forms may be difficult during this phase. To determine whether progression to more severe forms of the disease has occurred, the warning signs should be observed . Duration of this phase is generally 2-7 days.
- Critical or defervescence: This phase is characterized by clinical and laboratorial evidence of endothelial cell dysfunction caused by the viral infection, resulting in increased capillary permeability and plasma leakage to the extravascular space. This phase is marked by sudden defervescence, circulatory and perfusion changes (hypotension and hypovolemic shock), serosal effusions (pleural and ascites) and organ dysfunctions, such as liver failure, encephalitis, myocarditis and clotting disorders. Progressive leukopenia and sudden platelet count drop precedes plasma leakage, and the progressive haematocrit increase mirrors the magnitude of the volume lost to the extravascular compartment. However, it should be noted that severe organ dysfunctions might be present, including hepatitis, encephalitis, myocarditis and clinically significant bleedings, in the absence of clinical signs of plasma leakage. The critical phase, which is evident in 10-15% of dengue cases, discloses the progression to severe disease. The duration of this phase is 1-3 days.
- Recovery phase: This phase is characterized by progressive improvement of endothelial function with gradual fluid resorption from the extravascular space, haematocrit stabilization and progressive platelet recovery. A rash may present as white islands in a red sea, along with pruritus and bradycardia. During this phase, due to the progressive recovery of the endothelial function, fluid administration (and eventually diuretics) should be prescribed with caution to prevent volume overload, congestive heart failure and perpetuation of respiratory failure and serous effusions. The duration of this phase is 1-3 days.

CORELATION WITH CASE STUDIES

We did a study involving 94 patients with dengue fever in K S Hegde Medical College. Inclusion criteria was patients positive for NS1antigen. It was seen that 50% of the patients had elevated AST levels and 29% of patient had elevated ALT. Thus showing that AST was more elevated than ALT. Hypoalbuminemia was seen in 57% of the cases. Total bilirubin was raised in 36% of the cases.(Table 1)

TABLE 1.LIVER FUNCTION ABNORMALITY

PATIENTS	RAISED AST	RAISED ALT	HYPOALBUMINEMIA	RAISED BILIRUBIN
94	50%	29%	57%	36%

Table 2 illustrates various studies interpreting liver function abnormalities in dengue. Wong et al reported that AST abnormality was higher as compared to ALT [12]. Souza et al also reported a similar trend of AST/ALT elevation in dengue. [5] A similar study from Taiwan by Kuo et al also showed 90% abnormality in AST levels [4].

AST is released by damaged monocytes which could explain higher levels of AST than ALT in dengue at earlier stage. AST is also released from heart, striated muscle, erythrocytes, etc apart from the liver, whilst ALT primarily is hepatic in origin . Numerous studies have shown that AST and ALT values were higher in severe forms of dengue than in uncomplicated Dengue. The reversal of alanine transaminase and aspartate transaminase (AST/ALT) ratio is helpful to differentiate it from other acute viral hepatitis like HAV, HBV, HCV, etc., where this is rarely seen except in alcoholic hepatitis [13].

In our study, 48.27% (28) patients had normal liver enzymes, 31.03% (18) patients had AST elevated 2-4 times the upper normal limit and 13.7% (8) patients had AST elevated more than 4 times the upper normal limit on the first day of admission [14].

	ALT NUMBER	ALT %	AST NUMBER	AST %
NORMAL	30	51.72	36	62.06
2-3 FOLD RISE	12	20.68	12	20.6
>4 FOLD RISE	10	17.24	10	17.24

The median Aspartate transaminase (AST) and Alanine transaminase (ALT) values have been found to be higher for severer forms of dengue than for uncomplicated dengue fever. This hints at a possible association between increased transaminase levels with increasing disease severity [15].

Suoza et al reported liver damage more in females in a large study from Brazil [5]. Hypoalbuminemia has also been seen in dengue and its value has wide range depending on the severity of the disease .Saha et al reported low albumin in 12.9% of the cases which was similar to the study reported by Wong and Shen which showed 16.5% cases to have hypoalbuminemia[16,17]. However, Itha et al reported hypoalbuminemia in 76% of the cases [18]. There is an increased bleeding tendency with raised liver enzymes. Saha et al reported INR of more

than 1.5 in 11% of the patients[16]. Liver Damage depends on various factors like Dengue haemorrhagic fever, secondary infection, thrombocytopenia, female gender, and children[5,17].

TABLE 1 LIVER FUNCTION ABNORMALITIES

Studies	Patients	Raised AST	Raised ALT	Hypoalbuminemia	Raised bilirubin
Itha et al[26]	45	96%	96%	76%	30%
Wong et al[24]	127	90.6%	71.7%	16.5%	13.4%
Saha et al[21]	1226	52% (5 times normal was criteria)	50%	12.9%	16.9%
Kuo et al[3]	270	93.3%	82.2%	-	7.2%
Souza et al[4]	1585	63.4%	45%	-	-

Dengue related acute liver failure have been reported more in children than in adults. Jagdeshkumar et al reported 5 dengue cases in a study of 27 children with acute liver failure [19]. Acetaminophen overdose can play an important role in causing acute liver failure in dengue infected patients [20].

MANAGEMENT

Fluid administration is the main modality in treatment of dengue especially during the critical phase of illness. N-Acetyl cysteine has been reported to be used according to many studies. Kumarsena ,et al used NAC on 8 patients and 5 of them recovered from hepatic encephalopathy and 3 died [21]. The reason for NAC use is its ability to restore hepatocellular glutathione stores and its action as free radical scavenger. It also improves antioxidant defence. Molecular Adsorbant Reticulating system(MARS) and SPAD(Single pass albumin dialysis) which are modalities of artificial liver support, also have been suggested for treatment of liver failure. Liver transplant is the final option but it becomes a difficult option in view of hemodynamic compromise, multiorgan dysfunctions and bleeding seen in dengue patients.

Celastrol has been reported as a potential anti-dengue agent that induces IFN-α expression and stimulates a downstream antiviral response, making the drug a promising therapeutic modality [22].

A vaccine to prevent dengue (Dengvaxia®) is licensed and available in some countries for people ages 9-45 years old. The World Health Organization recommends that the vaccine only be given to persons with confirmed prior dengue virus infection. The vaccine manufacturer, Sanofi Pasteur, announced in 2017 that people who receive the vaccine and have not been previously infected with a dengue virus may be at risk of developing severe dengue if they get dengue after being vaccinated.

II. Conclusion

Dengue showcases a wide range of hepatic manifestation. Patients may even have asymptomatic transaminasemia to liver failure. The severity is more in children than in adults. Acetaminophen overdose, co infection and underlying chronic liver disease play an important role in causing liver failure in dengue patients. Dengue is mainly managed via supportive therapy and has good prognosis.

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