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REVIEW

Dengue and its effects on liver

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Abstract

Dengue has emerged as an important arboviral disease with significant impact on the disease burden in population residing in tropical countries. Dengue is spread by the bite of Aedes mosquito. The virus seems to have some hepatotoxic effects. Affliction of liver in form of derangements in the liver function tests is common and may include mild elevations in serum bilirubin, elevated transaminases and derangements in serum albumin. Although asymptomatic in most cases, clinical manifestations like jaundice, and acute liver failure (ALF) may occasionally complicate the clinical picture. Indeed, dengue has been implicated as an important cause of ALF in endemic countries. The present review focuses on the hepatic manifestations and the pathogenesis of the liver injury in dengue.

Key words: Dengue; Liver; Viral hepatitis; Acute liver failure; Transaminases; Bilirubin

Core tip: Dengue is an important cause of febrile illness in the tropical countries. It may affect the liver but the hepatic involvement is usually asymptomatic. However it is recognized as an important cause of acute hepatic failure in endemic counties. Dengue must be considered as a differential in the evaluation of acute hepatic failure and as an acute precipitant in patients presenting with acute on chronic liver failure.

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INTRODUCTION

Dengue or "break bone fever" has gradually evolved as one of the important causes of febrile illness in the tropical and subtropical region. Second only to malaria, dengue is a common mosquito-transmitted disease, and currently, it is the most common cause of arboviral disease globally. Around 2.5 billion people in 100 endemic countries are believed to be susceptible, so are the equally significant number of travelers to these tropical and subtropical regions[1,2]. Presenting with a wide range of severity, "severe" dengue (Group C) as categorized by World Health Organization (WHO) in 2009 includes the dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[3]. Despite the inadequate surveillance of cases from the underdeveloped tropical countries, the average number being reported per year has

increased drastically[1,4]. A host of factors including the relentless urbanization with poor hygiene, dilapidated health systems to increasing international travel fuel the spread of this disease geographically and increase the disease burden of tropics significantly[1,2].

This disease has been found to have profound effect on multiple organ systems, the commonest being the liver. Starting from asymptomatic elevated transaminase levels to acute liver failure (ALF), dengue has all the properties of a hepatic illness. In this paper we review, the pathogenesis, pathology, clinicobiochemical parameters and management of the effects of dengue on liver.

DENGUE VIRUS

Dengue virus (DENV) has 4 serotypes (DEN 1-4) and is a member of the Flaviviridae family and the genus Flavivirus[5]. Though initially DEN1 and DEN2 were found around Central America and Africa, and all 4 serotypes found in Southeast Asia, currently all the serotypes have diffused in all tropical and subtropical regions of the world[1,6]. The serotypes sharing a mere 65% of the genotype among each other produce a uniformly wide array of manifestations, with most of them being asymptomatic[2].

DENVs are transmitted *via* the species Aedes aegypti, and less commonly by Aedes albopictus. The Aedes aegypti mosquito with its anthropophilic nature is well adapted for urban thriving and frequently bites several times before completing oogenesis[3,7].

If during the 5 d period of human viremia, the mosquito feeds, it gets infected and the DENV migrates from insect mid-gut to the salivary glands. After 8-12 d of life cycle of DENV inside the mosquito, with optimum high temperatures, the mosquito becomes infective, and can bite and transmit the virus to another host[1,3]. High concentrations of virus are exhibited in mosquito cell cultures with persistent infection[8].

DENV is an RNA virus with a single-stranded positive-sense RNA acting as the genome. The virus has an envelope and is icosahedral in shape. The structural proteins encoded by the DENV are capsid, precursor membrane, and envelope [E]. The virus also encodes for seven non-structural (NS) proteins one of which (NS1) has found use as a diagnostic antigen in initial phases of the disease. The E glycoprotein plays a crucial role in the biology of the DENV, starting from receptor binding to immune response[1,9].

Endocytosis of virus occurs after binding mediated by various molecules including glycoproteins like heparin sulfates as also dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, and a carbohydrate recognizing mannose receptor[10,11]. Upon internalization, the acidic pH induces change in the classically described "herring-bone" pattern of E glycoprotein. The uncoating and release of the genome occurs once the nucleocapsid is exocytosed into the cytoplasm[12].

CASE DEFINITION

Before going into the various hepatic manifestations of dengue, the evolution of dengue case definition will be briefly discussed. Dengue has been traditionally classified into dengue fever (DF), DHF and DSS (WHO 1997 Classification)[13,14].

DF: Fever and at least two features: ocular pain, headache, muscle or joint pains, cutaneous rash, bleeding manifestations and reduced leukocyte count.

DHF: Fever, thrombocytopenia ($\leqslant 100 \times 10^9$/L), bleeding manifestations and evidence of plasma leakage.

DSS: DHF with tachycardia or low pulse pressure (< 20 mmHg) or hypotension (systolic blood pressure < 90 mmHg).

The modified categorization of WHO in 2009 includes dengue with or without warning signs or severe dengue[3].

Dengue: Fever and two of these: nausea, vomiting, skin rash, bodyache, leukopenia, or any warning sign.

Warning signs include pain in the abdominal or presence of tenderness, persistent vomiting, clinical evidence of fluid accumulation like effusions and ascites, bleeding, lassitude or restiveness, liver enlargement, or rise in hematocrit ($\geqslant$ 20%) with rapid reduction in thrombocyte count (< 50000/mm^3).

Severe dengue: Evidence of severe plasma leakage, bleeding and organ impairment. Organ impairment includes hepatic involvement in form of transaminases elevated beyond 1000 IU/L and central nervous system manifestations like alteration in sensorium or cardiac or other organ involvement.

In spite of the recent categorization, the majority of the studies widely use the more popular DF, DHF and DSS classification for case definition.

DENV INFECTION AND LIVER

With DENV infection, high level of viremia is associated with involvement of different organs (liver, brain) in the severe form of the disease[15]. The liver is the commonest organ to be involved in dengue. Hepatic manifestations are either a result of direct viral toxicity or dysregulated immunologic injury in response to the virus. The spectrum of involvement includes asymptomatic elevation of hepatic transaminases to occurrence of severe manifestation in form of ALF.

PATHOGENESIS OF LIVER INJURY

Hepatic dysfunction is a crucial feature seen in DENV

infection. Hepatocytes and Kupffer cells are prime targets for DENV infection[16-18], as confirmed in biopsies and autopsies of fatal cases[19]. For infecting cells, the major rate limiting step is the viral attachment to the receptors present on surface of host cell. The E protein has a role in the attachment of the virus[20], although the nature of the receptor used is yet to be determined[18]. Heparan Sulphate plays a pivotal role for the intrusion of the DENVs into liver (HepG2) cells[21]. A cell to be infected by a virus requires essentially viral entry and a conducive environment for the invader to grow inside the host cell and this property is influenced by viral serotype, strain and cell type. For example, the G_2 phase cells are more prone to infectivity and enhance virus replication[22]. It has been postulated that the binding of DENVs onto hepatocytes is facilitatory, one binding promotes the binding of successive particles, similar to binding of oxygen on hemoglobin. After binding of the virus, internalization is by either direct fusion or endocytosis. The entry pathway may either be mediated through the presence of receptors or even in their absence[18].

An eventual outcome of hepatocyte infection by DENV is cellular apoptosis, a phenomenon demonstrated both *in vivo* and *in vitro*[23]. After apoptosis, what stays of the cells are the Councilman Bodies[19]. The various pathways involved in this apoptotic process include viral cytopathy, hypoxic mitochondrial dysfunction, the immune response[17] and accelerated endoplasmic reticular stress. Expression of DENV-induced TRAIL[24] and TNF-α and Fas signaling[25] have also been implicated in this process. Activation of the mitochondrial cell death pathway stems from the functional and morphological defects of these mitochondria[26].

Enhancement of immune reaction due to recurrent infections is believed to be responsible for causation of severe dengue disease. DHF and DSS occur as a consequence of several factors interacting, involving the microbial and host features, with antibody-dependent enhancement which explains the phenomena of more severe disease on second infection[27]. Dengue infection induces a cytokine storm and concentrations of cytokines like interleukin (IL)-2, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ reach peak levels in the initial 3 d. IL-4, IL-5 and IL-10 contribute to later in the course of disease[28]. Currently, the exact mechanism by which the host immunity damages liver is unknown, albeit a role of T cells entering the liver causing cytopathology cannot be ruled out. Thus, pathogenesis of hepatic injury in dengue is believed to be primarily a T cell mediated process involving interaction between antibodies and the endothelium and a concomitant cytokine storm often labeled as cytokine "Tsunami," and host factors like genetic polymorphisms.

PATHOLOGY

A wide spectrum of hepatic histological changes have been noted in dengue. This comprises fatty change (micro vesicular), hepatocyte necrosis, hyperplasia and destruction of Kupffer cells, Councilman Bodies and mononuclear cell infiltrates at the portal tract[29,30]. Hepatocyte injury including necrotic changes commonly involves the midzonal area followed by the centrilobular area. Probable explanation for such a finding could be that the liver cells in this area are more sensitive to the effects of anoxia or immune response or may be a preferential target zone of the DENVs. A recent autopsy series of dengue patients from Myanmar[31] showed varying degrees of damage in the liver, with majority of subjects having sinusoidal congestion of moderate to severe degree with predominant midzonal and centrilobular area cell death. Diffuse fatty change was noted within the hepatic lobules. The investigators noted no evidence of any significant fibrosis[31].

CLINICOBIOCHEMICAL PROFILE OF HEPATIC INVOLVEMENT

Clinical features suggesting dengue related hepatic involvement are the presence of liver enlargement and elevated transaminases[32].

Among the clinical features of hepatic involvement, patients have abdominal pain (18%-63%), nausea/vomiting (49%-58%) and anorexia[33,34]. Symptoms such as abdominal pain and anorexia have been found to be significantly more common in DF than DHF[35]. Hepatomegaly is present in both DF and DHF but more common in DF[35]. The frequency of hepatomegaly in the adult dengue patients ranges from 4%-52%[34-36]. Clinical jaundice has been detected in 1.7%-17% in various series[33,35,36] and hyperbilirubinemia has been found to be as high as 48%[34].

The commonest abnormality detected has been raised transaminase levels (Table 1). Raised AST levels have been seen in 63%-97% of patients, while raised ALT levels in 45%-96% of patients. In a majority of the studies, elevation in AST is more than ALT, more during the first week of infection, with a tendency to decrease to normal levels within three weeks[37]. The AST released from damaged myocytes could explain the higher levels of AST than those of ALT in patients with dengue fever at an earlier stage[38]. The increased AST/ALT ratio is useful for differential diagnosis from acute hepatitis caused by the hepatitis A, B or C viruses where it is rarely observed.

The average levels of AST ranged from 93.3 U/L[39] to 174 U/L[33], while ALT from 86 U/L[39] to 88.5 U/L[33] in various studies. More than a 10-fold rise

Table 1 Liver function abnormalities in dengue patients

Ref.	Patients	Raised AST	Raised ALT	AST > ALT	Hyper-bilirubinemia	> 10 fold rise (AST, ALT)
Kuo *et al*[37]	270	93.30%	82.20%	+	7.20%	11.1%, 7.4%
Souza *et al*[39]	1585	63.40%	45%	+	-	3.4%, 1.8%
Itha *et al*[41]	45	96%	96%	Equal	30%	-
Wong *et al*[40]	127	90.60%	71.70%	+ in 75.6%	13.4%	10.2%, 9.5%
Parkash *et al*[33]	699	95%	86%	+	-	15%
Trung *et al*[36]	644	97%	97%	+	1.7%	-
Lee *et al*[14]	690	86%	46%	-	-	1%
Karoli *et al*[34]	138	92%		+	48%	-
Saha *et al*[35]	1226				16.9%	

AST: Aspartate transaminase; ALT: Alanine transaminase.

has been seen in 3.8% cases in a large study from Brazil[39], whereas in other studies were between 1.8% and 11.1% of cases[34,40]. Severe hepatitis was present in 15% in one study[33], while in another study it was 1%[41]. The level of increase in hepatic transaminases can easily mimic acute viral hepatitis.

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[14,35,39,42]. This hints at a possible association between increased transaminase levels with increasing disease severity. Interestingly the values of liver enzymes were noted to be higher in the febrile and the severer phases of dengue vis-à-vis the convalescent phase[14].

AST has various sources including the heart, striated muscle, erythrocytes, *etc*., apart from the liver, whilst ALT primarily is hepatic in origin[14,43]. Acute insult to these non-hepatic tissues by the DENV can result in higher elevations of AST when compared to ALT rise. Therefore, rise in AST might not be a true reflection of hepatic involvement. Moreover, patients with high levels of enzymes may be labeled as severe disease without any effect on the final outcome.

Liver damage has been found to be more common among females in the large study from Brazil[39] (74.6% of females compared to 52.2% of males) with 4.2% of them having acute hepatitis. However, no significant difference could be elicited between males and females as far as the level of transaminase elevation was concerned.

Hypoproteinemia or hypoalbuminemia have been seen in 12.9% in one of the large studies from Kolkata, India[35], while it ranges from 16.5%-76% in various other studies[34,40,41]. The heterogeneity in the population and severity of the disease may be responsible for such a wide range observed in the various studies.

Coagulation abnormalities have been found in multiple studies. International normalized ratio (INR) > 1.5 have been found in 11% of patients in one study[35], while abnormal prothrombin time (PT), partial thromboplastin time noted in 34%-42.5% of the cases in other studies[34,40]. Increasing bleeding episodes have been found with increasing AST/ALT levels[33,37], but only a weak correlation could be demonstrated between PT and transaminase levels during the convalescent period, suggesting that liver synthetic function in terms of coagulation factor production was generally well compensated.

Dengue has a slightly different profile of hepatic involvement among children (Table 2). They have been found to have a higher percentage of liver enlargement as compared to adults.

Various factors which predict liver damage are DHF, secondary infection, thrombocytopenia, high blood concentration, female sex and children[39,40,44].

DENGUE AND LIVER FAILURE

The liver injury in dengue, as already mentioned, ranges from asymptomatic hepatic transaminase elevation to fatal ALF. Dengue related ALF has been well described in the literature, although the majority of reports are amongst children with few case reports in adults[32,49-55]. Although viral hepatitis and drugs are the predominant cause of ALF, infectious diseases such as dengue are being more and more recognized as an etiological agent.

In a study from Thailand, Poovorawan *et al*[56] found dengue to be a major cause of ALF among children, with 12 out of 35 children (34%) aged 1-15 years of age, enrolled between February 2000 to December 2001, having positive dengue serology. In a further extension, the same group enrolled 14 children of ALF from June 2002 to December 2006, in a recent study and found 2 of them to be due to dengue[57]. Jagadishkumar *et al*[46] have reported 5 (18.5%) confirmed dengue cases in a study cohort of 27 children with ALF from Northern India. The presentation can be varied, either classical presentation of dengue with hepatitis and shock syndrome or there may be less classical dengue characteristics[46]

Deepak *et al*[58] in a study from Mumbai, India, have found 5 cases of dengue associated ALF out of a total of 56 cases (8.9%) of ALF, while Tan *et al*[59] from Malaysia showed 8 out of 155 adult ALF cases (5.2%)

Table 2 Liver function abnormalities among children with dengue

Ref.	Patients (*n*)	Raised AST/ALT	Hepatomegaly	Jaundice	Hypoalbuminemia
Pires Neto Rda *et al*[45]	32	96%	37.50%	-	77%
Mohan *et al*[44]	61	87%	74%	25%	-
Jagadishkumar *et al*[46]	110	-	79%	4.50%	66%
Kulkarni *et al*[47]	948	90%	36.70%	0.95%	-
Roy *et al*[48]	120	94%	80.80%	60%	-

AST: Aspartate transaminase; ALT: Alanine transaminase.

to have dengue. Adult dengue patients developed ALF at a median of 7.5 d (5 to 13 d) after the inception of fever. Occasionally, ALF may in patients who seem to be recovering from dengue[59]. Dengue can mimic ALF and needs to be considered in differential diagnosis of acute liver failure and cerebral malaria in endemic areas[60]. Occasionally, dengue has been reported to cause ALF in patients with underlying liver disease including a HBV carrier[61].

After a period of 3-7 d incubation, the natural course runs in form of fever lasting for 2-7 d, and subsequently a critical phase may occur during defervescence starting from 3-7 d of the illness when plasma leakage dominates the clinical picture[59]. Those surviving this phase of plasma leakage would eventually recover[3,62]. More severe disease is associated with higher viral load[63].

ALF due to paracetamol (PCM) overdose may be due to either a single large overdose or cumulative, multiple overdoses. The latter has been increasingly being recognized as an important cause of ALF due to PCM overdose. Mild to moderate hepatitis is well known in dengue. However there have been ample evidences, obtained both *in vitro* and *in vivo*, that the metabolism of PCM is reduced in patients with hepatitis [64,65]. Moreover, WHO guidelines discourages the use of other nonsteroidal antiinflammatory drugs, such as ibuprofen or antipyretics, in DF[3].

Interestingly, dengue has also been implicated as the cause of worsening of chronic liver disease, *i.e.*, being the acute component of acute on chronic liver failure (ACLF)[61,66,67]. Therefore in endemic areas one should be aware of dengue as a possible cause of ACLF.

Dengue pathogenesis as outlined earlier is not fully understood and is multi factorial ranging from direct viral injury, dysregulated immune response to hypoxic/ischemic injury and even secondary to drugs such as PCM used commonly for such symptoms. Mortality data are comparable with other causes of ALF, although adults have been reported to have a slightly better prognosis as compared to children, in whom it is 50%-66%[68].

In the management of patients with dengue with ALF, besides supportive measures specific measures have also been tried with success. There have been reports of use of N-acetyl cysteine (NAC) in various case series; use of NAC by Senanayake *et al*[69] from Sri Lanka on seven children and Lim *et al*[70] from Singapore on a single child showed clinical improvement. Kumarasena *et al*[71] used NAC on 8 adult patients, 5 of which having grade I-II hepatic encephalopathy and recovered completely while the remaining 3 with higher grades of encephalopathy (grades Ⅲ and Ⅳ) died. Use of molecular adsorbent recirculating system (MARS) has also been[51] reported in dengue associated ALF. Liver transplantation becomes a difficult proposition in lieu of hemodynamic compromise, bleeding, and organ impairment seen during dengue infection.

CONCLUSION

Dengue has a wide spectrum of manifestations. The effects on liver are usually asymptomatic but can be atypical and have varied severity. From asymptomatic elevated transaminase levels to fulminant hepatic failure, the variable manifestations are a big challenge to the clinicians treating the condition. Hepatic involvement is more common and more severe in children as compared to adults. Management is primarily supportive and the outcome is usually good. Care must be taken regarding the diagnosis and use of drugs which may worsen the liver damage.

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