

Dengue and the Liver

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Abstract

An estimated 50 million dengue infections occur annually across approximately 100 tropical and subtropical countries. There is extensive clinical, biochemical, histological, radiographic, and experimental evidence of liver involvement in dengue virus infections. Transaminase elevations are commonly seen. Most cases of dengue-associated liver disease are mild. Severe acute hepatitis due to the dengue virus is uncommon. Proposed causes of liver dysfunction in dengue virus infections include a direct viral effect on hepatocytes and a dysregulated host immune response against the virus. Several avenues of future research are suggested.

Introduction

It is estimated that 50 million dengue infections occur annually across approximately 100 tropical and subtropical countries. The dengue virus is a single-stranded, enveloped RNA, *Aedes aegypti* mosquito-borne virus and is a member of the genus *Flavivirus*. The dengue virus has four serotypes, numbered 1 through 4. The spectrum of dengue virus infections ranges from asymptomatic infections or mild febrile illnesses in the majority of cases to severe and fatal disease in a minority. The most recent World Health Organization (WHO) classification scheme divides patients into either dengue or severe dengue [1]. Patients, who recover completely without major complications, are determined to have dengue. Severe dengue is characterized by the presence of any of the following conditions: severe bleeding, severe organ impairment (AST or ALT greater than 1000 U/L, CNS involvement manifested by impaired consciousness, other target organ involvement), and severe plasma leakage resulting in respiratory distress or shock. Dengue infections are described as having an incubation period of 3 to 7 days, followed by the following three phases- an initial febrile phase, a critical phase during which a systemic vascular leak syndrome may occur, and a spontaneous recovery phase. The liver is frequently involved in dengue infections.

Clinical Manifestations of Liver Involvement in Dengue Virus Infections

Liver involvement clinically manifests as right hypochondrium pain, hepatomegaly, and jaundice. A study from India reported a 15% occurrence of jaundice with dengue infections [2]. Hepatomegaly is frequently seen with dengue infections and is noted to be more common in DHF than in Dengue Fever (DF). Hepatomegaly has been reported in up to 90% of Thai children and 60% of adults [3]. Abdul Wahid et al. reported hepatomegaly in 60% of DHF and 40% of DF patients [4]. Hepatomegaly is the most frequent physical sign found in dengue shock syndrome, with values ranging from 30% to 79% [4,5]. A study from Thailand evaluated clinical differences among the different serotype infections and found no serotype-specific difference in the frequency of hepatomegaly [6]. Although hepatomegaly is common in DHF, it is not always associated with abnormal liver chemistries. Nimmannitya et al. reported a series of 145 Thai children with DHF, of whom 98% had hepatomegaly and 74% had normal ALT levels [7]. A study from India reported a 20% frequency of clinically detectable ascites with dengue virus infections [2]. A review of published Thai dengue cases reported an 8% occurrence of hepatic encephalopathy with liver dysfunction [8].

Natural History of Dengue Virus-Associated Liver Disease

In a Taiwan study, Kuo et al. reported that AST begins to increase from the third day of illness, peaks on the seventh or eighth day, and then declines, normalizing by three weeks [9]. ALT changes were noted to have a later onset and lower peak. The minority of patients, who develop severe liver dysfunction including liver failure, do so during the critical phase of the infection when a systemic vascular leak syndrome may develop. A study evaluating children with acute hepatic failure in Thai children found that dengue was a major cause [36]. Chronic liver disease, chronic hepatitis, and cirrhosis have not been reported with dengue.

Pathogenesis of Liver Involvement in Dengue Infections

A true understanding of the pathogenesis of severe dengue infection is limited by the lack of an animal model, particularly one that recreates the transient capillary permeability seen in these patients. The dengue virus is thought to enter both the blood stream and the epidermal Langerhans

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cells and keratinocytes on mosquito inoculation [10]. Infected cells migrate to lymph nodes through the lymphatic system and reach the liver macrophages as well. Two phases of kupffer cell activation have been described. The first phase occurs shortly after infection and involves nitric oxide and IFN- α production. The second phase of kupffer cell activation occurs a few hours later with IL-6 and TNF α synthesis [11]. Dengue virus replication occurs in hepatocytes and Kupffer cells. Virus-mediated hepatocyte necrosis and/or apoptosis occur resulting in the release of cytokines and toxins into the blood. These, in turn, activate the fibrinolytic system and coagulation factors. Although dengue virus-induced hepatocyte apoptosis has been suggested as the pathogenesis of severe forms of dengue infection, the mechanism of apoptotic induction is not clear. The innate and host immune responses play an important role in determining the severity and natural history of dengue infections. DHF is thought to be immunologically driven. The Halstead hypothesis states that secondary infection by a different dengue strain results in an antibody-dependent immune infection enhancement of mononuclear phagocytes [12]. During secondary dengue infections, preexisting non-neutralizing antibodies formed from previous infections, may form complexes with the virus and enhance its uptake and replication in macrophages [13]. The role of the host immune response in liver damage is, however, less clear. Chen and colleagues reported a strong correlation between T cell activation and hepatic cellular infiltration in immunocompetent mice infected with dengue virus [14]. Furthermore, the kinetics of liver enzyme elevation also correlated with that of T cell activation. Cytokine activation, particularly that of tumor necrosis factor- α , is thought to play a fundamental role in the pathogenesis of dengue infections, including liver involvement. Tsal et al. reported that the JAK/STAT3 pathway plays a critical role in the chemokine production from dengue virus-infected hepatocytes [15]. Thepparit and Smith have shown that the 37-kilodalton/67-kilodalton high-affinity laminin receptor is the receptor for entry of the serotype 1 dengue virus into liver cells [16]. Dengue serotypes 2, 3, and 4 do not enter liver cells by means of this receptor. Their mechanism of entry into liver cells is yet to be elucidated.

Biochemical Patterns of Liver Involvement in Dengue Virus Infections

Multiple investigators have documented elevated serum liver enzymes with dengue infections, particularly the transaminases Aspartate Transaminase (AST) and Alanine Transaminase (ALT). Kuo et al. published a series of 270 dengue patients and found elevated ALT and AST levels in 82% and 93%, respectively [9]. Most AST and ALT elevations were mild to moderate but elevations greater than ten times the upper limit of normal were seen in 11.1% and 7.4%, respectively. In a study of 169 serologically confirmed dengue cases in Rio de Janeiro, Brazil, 65.1% (110/169) had abnormal aminotransferases [17]. This cohort of patients was divided into the following four categories, based on the pattern and level of aminotransferase elevations: grade A- normal enzyme levels, grade B- increased levels of at least one of the enzymes, grade C- increased, with at least one of the enzymes being greater than three times the upper limit of normal, and grade D- acute hepatitis, with aminotransferase levels at least ten times the upper limit of normal. Of these cases, 3 (1.8%) met their criteria of grade D acute hepatitis, with 25 (14.8%)

having grade C liver involvement, and 82 (48.5%) having grade B liver involvement. Lee et al. reported 690 dengue patients from Singapore [18]. In this series, AST and ALT elevations occurred in 86% and 46%, respectively. 7/690 patients had transaminase levels greater than or equal to 1000 U/L. A review of published Thai cases of dengue infection reported an overall rate of biochemical liver dysfunction of 35% [8]. In contrast to other viral hepatitis infections, dengue infections are characterized by elevations in serum AST that are greater than that of ALT. The significance of this pattern is not clear. This relatively greater elevation of AST compared to ALT in dengue, can be used to help distinguish dengue virus infections from other acute viral hepatitis infections.

Hypoalbuminemia has been described with dengue infections. A study from Lucknow, India reported hypoalbuminemia in 76% of their patients [2]. In contrast, a study from Hong Kong reported a 28% frequency of hypoalbuminemia with dengue infection [19]. In the latter study, there was no difference in the frequency of hypoalbuminemia among the four different dengue serotypes.

Histologic Patterns of Liver Involvement in Dengue Virus Infections

During acute infections, it is often not possible to do a liver biopsy due to thrombocytopenia, coagulation disturbances and/or the presence of ascites. Therefore, most of the published histological data on dengue-associated liver dysfunction comes from autopsy specimens. As a result, these data are skewed towards the more severe end of the disease spectrum. Histologic patterns of liver disease in milder cases are not clear. The available histologic data describe hepatocellular necrosis, apoptosis-induced Councilman Bodies, steatosis, and inflammatory cell infiltrates. Hepatocellular necrosis seen in dengue affects the midzonal and centrilobular areas of the hepatic acinus, which are the area's most susceptible to anoxia. Fatal Dengue Hemorrhagic Fever (DHF) autopsy findings are characterized by the presence of variable degrees of hepatocyte necrosis, primarily midzonal. The dengue virus may also preferentially infect this zone and viral RNA has been found in midzonal hepatocytes [20]. In fatal cases, dengue viral RNA is often isolated only from liver tissue and not other organs. Councilman bodies and Torres bodies seen in the livers of dengue patients are also seen in yellow fever virus infections, another member of the genus Flavivirus. Overall, the liver pathology of dengue appears similar to that seen in the early stages of yellow fever, but with less severe and extensive hepatocyte necrosis [37]. Dengue viral antigens are found as small cytoplasmic foci and large perinuclear inclusions, unlike the flavivirus Yellow Fever virus, whose antigens are seen distributed throughout the cytoplasm.

Radiographic Evidence of Liver Involvement in Dengue Virus Infections

Some investigators have evaluated the abdominal sonographic findings in dengue and whether these findings can be used to help in the early diagnosis and prognostication of dengue infections. Sonographic findings in acute dengue infection include gallbladder wall thickening, a finding commonly associated with acute hepatitis, splenomegaly, and ascites, all of which resolve spontaneously [21]. Investigators from India and Indonesia found abnormal liver

parenchyma on ultrasonography of dengue infected patients, attributing this to intraparenchymal and subcapsular hemorrhages [22,23]. Shukla et al. published a series of dengue cases admitted from August to November 2010 at Lucknow Medical College in Lucknow, India [24]. Of this series of 70 patients, 36 had hepatomegaly on ultrasonography and 27 had clinically evident hepatomegaly as well. 42 patients had ascites on ultrasonography and 42 had clinically detectable ascites. Ascites in all patients was minimal or mild. Mia et al. from Bangladesh found that ultrasonographic findings of dengue fever included a thickened gallbladder wall, hepatomegaly, hepatic intraparenchymal fluid, and ascites [25]. The frequency of these findings increased with the degree of clinical severity. Hepatomegaly was seen in 38% of those patients with grade I severity and 80% of those with grade IV severity. Hepatic intraparenchymal fluid occurred in 0% of grade I severity patients and 20% of those with grade IV severity. Finally, ascites was seen in 14% of patients with grade I severity and 100% of patients with grade IV severity.

Liver Involvement as an Indicator of Dengue Virus Infection Severity

Data on the ability of elevated aminotransferase levels to predict dengue infection severity are conflicting. In a study of 690 dengue patients from Singapore, AST or ALT levels did not discriminate between DF and DHF or between non-severe and severe dengue [18]. However, median AST and ALT levels were significantly higher with increasing dengue severity by both 1997 and 2009 WHO criteria. Prakash et al. published a series of 699 dengue patients from Karachi, Pakistan [26]. In this study, the overall mortality was 33% in the mild to moderate hepatitis group and 67% in the severe hepatitis group ($p < 0.002$). Severe hepatitis, defined as an ALT level greater than 300 IU/L, was associated with prolonged length of hospital stay, mortality, bleeding, and renal failure. Nawaz and colleagues from Lahore, Pakistan evaluated the ability of liver chemistries to predict the severity of dengue infection [27]. They found that AST levels were two fold greater than ALT levels. However, AST levels did not correlate with the development of complications or the duration of hospital stay. In contrast, ALT levels had a significant correlation with the development of dengue shock syndrome ($p = 0.000$), septicemia ($p = 0.000$), hepatic failure ($p = 0.000$), encephalopathy ($p = 0.000$), and renal failure ($p = 0.0000$). ALT was also significantly associated with the mean duration of hospital stay ($p = 0.00$). However, there was no significant relationship between ALT levels and dengue hemorrhagic fever ($p = 0.546$) or the development of respiratory failure ($p = 0.062$). Investigators from Malaysia have found that ALT and alkaline phosphatase levels were significantly higher in DHF patients with spontaneous bleeding than in those without bleeding ($p < 0.05$) [4]. Wiwanitkit's review of published Thai dengue cases found that the rate of liver biochemical dysfunction was not significantly different in those with and without shock [8].

Experimental Evidence of Liver Involvement in Dengue Infection

Given the lack of an animal model for dengue infections, in vitro studies have been conducted to evaluate the effects of the dengue virus on the liver. Dengue virus-induced cellular apoptosis in the liver has been described [28]. RANTES (regulated upon activation, normal T cell expressed and secreted) is a chemokine with chemotactic activity for T cells, monocytes, natural killer cells and eosinophils. In vitro

association between dengue infection and upregulated RANTES gene expression in liver cells has been described [29]. Experimental evidence for immunopathogenic mechanisms of dengue-induced liver injury has also been published. Bhamarpravati et al. examined liver specimens in fatal dengue cases and described lymphocytoid cells, megakaryocytes, and occasional neutrophil infiltration in the sinusoids [30]. Chen et al. infected immunocompetent C57BL/6 mice with high titers of dengue virus and studied lymphocyte activation and hepatic cellular infiltration [14]. Liver enzyme elevations and hepatic T cell infiltration coincided with the kinetics of T cell activation. Although Gagnon and colleagues have suggested that CD4+ cytotoxic T cells may cause liver damage in dengue through a process involving bystander lysis, this hypothesis has not yet been experimentally proven [31].

Clinical Relevance of Liver Involvement

Apart from a possible role in determining the severity of dengue infection, there is other clinical impact of liver involvement in these infections. Liver involvement has clinical significance because the symptomatic pharmacologic treatment of dengue needs to be modified accordingly. Hepatotoxic drugs and those with hepatic metabolism and clearance need to be avoided. Dengue virus-induced hepatitis could be particularly consequential in patients with underlying chronic liver disease. It is well documented that acute-on-chronic hepatitis can have potentially fatal consequences. There are limited data, primarily case reports, of severe dengue infections in patients with underlying chronic liver disease or those who have undergone liver transplantation [32,33]. Kittittrakul C, et al. recently published a retrospective study of 127 adult patients with dengue and found abnormal AST and ALT in 88.2% and 69.3%, respectively [34]. Patients with nausea/vomiting, fever duration of greater than seven days, and petechiae were more likely to have abnormal transaminases. Abnormal AST during the febrile stage was associated with bleeding and shock was associated with elevated ALT during the febrile stage.

Unresolved Questions- Avenues for Future Research

- There is a glaring need for an animal model of dengue infection
- Why is the ratio of AST and ALT elevations different from other viral infections? Are the AST elevations seen in dengue due, in part, to myocyte damage?
- Given the suspected immunopathogenesis of liver involvement in dengue infections, what therapeutic opportunities exist in modulating the immune response to these infections?
- Are patients with underlying chronic liver disease who become infected with the dengue virus, more likely to develop severe dengue infection or more severe liver-related complications.
- Does the degree of liver involvement vary by dengue serotype? It has been noted that during some dengue epidemics, greater degrees of liver damage are seen [35]. This suggests that different dengue virus serotypes may have different degrees of hepatic tissue tropism. This requires further study.

Conclusion

There is extensive clinical, biochemical, histological, radiographic, and experimental evidence of liver involvement in dengue virus infections. Transaminase elevations are commonly seen, with a

tendency towards higher AST compared to ALT levels. Most cases of dengue-associated liver disease are mild. Severe acute hepatitis due to the dengue virus is uncommon. There are conflicting data regarding the ability of liver dysfunction to predict the clinical severity and outcome of dengue infection. The liver dysfunction seen in dengue virus infections could be a direct viral effect on hepatocytes or a result of a dysregulated host immune response against the virus. Several avenues of future research are suggested.

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