

Liver Dysfunctions in Dengue Infection: An Update on its Pathogenesis

Rituraj Niranjan^{*}, Panneer D and Purushothaman Jambulingam

Unit of Microbiology and Molecular Biology, ICMR-Vector Control Research Center, Puducherry, India

^{*}Corresponding author: Rituraj Niranjan, Unit of Microbiology and Molecular Biology, ICMR-Vector Control Research Center, Puducherry, India, Tel: 91-4312272397; Email: riturajniranjan@rediffmail.com

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Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NK: Natural killer cells; DENV-2: Dengue virus-2; NS1: Nonstructural protein 1; CD: Clusture of differentiation

Mini Review

Dengue fever (dengue hemorrhagic fever or dengue shock syndrome) is a virus infection and comes under one of the major vector-borne diseases [1,2]. Dengue infection has now become the global health threat [2]. High fever, chills, rash and strong headache are the more common clinical features of this disease [3,4]. In addition to these symptoms, some special clinical manifestations appear in response to severe dengue cases where viremia is high [5]. Liver dysfunction is one of the atypical forms of clinical manifestation in the dengue infection [3]. The clinical feature of hepatic dysfunctions in dengue patients are increased liver size and elevated levels of liver enzymes mainly transaminases [4,6]. The increase in size of gallbladder was also observed as early clinical manifestations in dengue patients [7]. Around 46% of dengue infected patients from Indonesia were diagnosed to have enlarged liver size. [8]. The other atypical clinical symptoms of dengue were nausea and abdominal pain [9]. Some dengue patients also manifest jaundice and hyperbilirubinemia [4,10]. However, the number of patients is still very less having liver dysfunction with dengue infections [3]. A wide number of reports have suggested the role of immune cells and mediators of inflammation in the liver dysfunctions however, the exact mechanism is still not clear [11-13]. In this article, we discuss some facts and role of immune components involved in the dysfunctions of liver in dengue fever [14].

In a study, a number of liver parameters such as abnormal high transaminases enzyme and development of subsequent hepatic encephalopathy were observed in dengue infected patients [11,15]. Acute abnormality in the levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was observed in the patients with dengue hemorrhagic fever and dengue shock syndrome [16,17]. The presence of acute liver failure was confirmed in case of dengue hemorrhagic fever [18]. The severe cases of dengue infection resulted in mortality due to multiple organ failures including liver. A report from Myanmar on the autopsy have described that there is liver damage in these dengue cases and was associated with the huge number of complement components on hepatocytes of the alternative pathways as well as of classical pathways [19]. The cases from the Saudi Arabia have also involved the many more liver dysfunctions and show abnormal liver function with high transaminases and elevated creatine kinase [20]. The genome-wide association studies suggested the activating natural killer (NK) cells receptors involvement in the dengue diseases [21]. The dengue hemorrhagic fever has also been associated to the acute liver failure [18]. The elevated levels of liver enzymes ere also found in the dengue patients in the Vietnam [7,22]. The metabolic

functions of the patients are also altered in case of dengue infection [23]. It is further interesting to note that, dengue virus infection may be more severe in the hepatitis patients as it induces the apoptosis in the same as evident from a case report in which dengue antigen was found in the hepatocytes [24].

Studies from experimental models have suggested that dengue does a lot of liver dysfunctions via direct or via altering immune functions. In a mice model of study, it was observed that a dengue-specific CD8+ T cell possesses the pathogenic roles in case of dengue virus infections [25]. It was further observed that, secreted non-structural 1(NS1) antigen protein of dengue virus has the ability to attach to the liver cells via interactions with heparan sulfate and chondroitin sulfate E and thus modulate the functions [26]. Another important study have described that, the secreted form of dengue virus non-structural protein NS1 is engulfed by hepatocytes, that further accumulate in the endosomes showing an important mechanism for the development of dengue associated pathophysiology [14]. A study from the DENV-2 infected mouse model have revealed that focal alterations in the liver along with the infection, In addition to this, ultra structural observations disclosed the alerted hepatocytes [27]. In this model dengue virus antigen was detected in the hepatocytes and thus is associated with the altered liver functions [27]. It has recently been understood that dengue infected dendritic cells activate other cells via direct contact mediated mechanism as evident that, dendritic cells activate natural killer cells via the mechanism however its mechanism of disease is not yet properly known [28]. Therefore, it is also suggested that it can be an important mechanism of disease via which dendritic cells activate other cells by physical contact or by way of its mediators [28]. Evidence from an immunocompetent mice model of study has shown that there is a massive liver damage which is responsible for death [29,30]. Moreover hepG-2 cells also show the adaptation in dengue infected cases [31]. Co-infection with the other infectious agents shows an important area in the case of dengue infection [30,31]. It has also been important that dengue virus protein modulate the liver cells via the epigenetic mechanism of the liver cells [32]. All together it can be said that, liver dysfunctions is an important aspect in the dengue virus infection and therefore some strategies should be made for the management of liver dysfunctions.

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