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REVIEW

Pathogenesis of liver involvement during dengue viral infections

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Summary The dengue virus can infect many cell types and cause diverse clinical and pathological effects. We describe clinical and experimental observations that suggest that liver involvement occurs during dengue infections, and we outline the possible role played by host immune responses in this process.

1. Introduction

Dengue is epidemic or endemic in virtually every tropical country. It is the most important viral haemorrhagic fever in the world. Infection may be clinically asymptomatic or give rise to undifferentiated fever, dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS).

The dengue virus, an RNA virus, belongs to the Flaviviridae family, and consists of four serotypes (DEN1—4). The virus can infect many cell types and cause diverse clinical and pathological effects. Its main effects are on the vascular, muscular and haematological systems. However, both clinical and experimental observations suggest that there is liver involvement during dengue infection. This liver dysfunction could be a direct viral effect on liver cells or be an adverse consequence of dysregulated host immune responses against the virus.

In this mini-review we outline the clinical and experimental observations of liver involvement during dengue infections, and discuss the possible role played by host immune responses in this process.

2. Clinical observations

Clinical evidence of liver involvement in dengue infections includes the presence of hepatomegaly and increased serum liver enzymes. Hepatomegaly is frequent and is commoner in patients with DHF than in those with DF. Several studies document raised serum transaminase levels in dengue infection. Transaminase levels are also higher in DHF/DSS than in DF and tend to return to normal 14—21 d after infection.

Kuo et al. (1992) evaluated 270 dengue patients and found abnormal aspartate transaminase (AST) and alanine aminotransaminase (ALT) levels in 93.3 and 82.2%, respectively. Most had mild to moderate increases, while levels

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more than 10 times the normal upper limit were seen in 11.2 and 7.4% of patients. Nimmannitya (1987), investigating 145 dengue patients, found ALT levels to be normal, slightly elevated or significantly elevated in 74, 18 and 8% of patients, respectively. No mention of AST levels were found in this report. Wahid et al. (2000) studied 50 serologically confirmed cases of dengue (25 cases each of DF and DHF), and found serum AST and ALT levels to be significantly higher in patients with DHF. In addition, Mohan et al. (2000), who evaluated children with dengue (37 cases of DF, 16 with DHF and 8 with DSS), found abnormal transaminases in 96%, with higher levels in DHF/DSS. Of 1585 dengue patients (65% with primary dengue, 91% with DF) studied by Souza et al. (2004), during a dengue epidemic in Rio de Janeiro, Brazil, alterations in AST and ALT were seen in 63.4 and 45% of patients, with 3.8% having transaminase levels >10 times the upper limit of normal. Fulminant hepatic failure complicating severe DHF/DSS has also been documented, and is associated with a poor prognosis (Alvarez and Ramirez-Ronda, 1985; Lawn et al., 2003; Lum et al., 1993; Munasinghe and Rajasuriya, 1967; Nguyen et al., 1997; Subramanian et al., 2005). Nimmannitya et al. (1987) have reported 18 DHF cases with jaundice and encephalopathy, of whom 10 died.

Varying abnormalities in liver enzymes appear to be present in most patients with symptomatic dengue infections, but they tend to recover soon (Pancharoen et al., 2002). There does not appear to be chronic liver damage as with the hepatitis B and C viruses. In a subgroup of predominantly DHF/DSS patients, severe liver dysfunction occurs and is a marker of poor prognosis. During some dengue epidemics, greater degrees of liver damage are seen (Ehrenkranz et al., 1971). Although this may be a consequence of different dengue serotypes having varying tissue trophism, this has not been widely studied.

Some investigators suggest that liver damage may be potentiated by the intake of drugs (such as acetaminophen and anti-emetics) during the early phase of the illness, but others do not see this (Suvatte et al., 1990). The course appears not to be influenced by concomitant hepatitis virus infection (Chung et al., 1992). Although hepatitis B virus (HBV) is hyperendemic in parts of South America and in the Far East, no evidence exists that HBV infection acts as a co-factor for hepatic damage in dengue infections.

In dengue infections, elevations in serum AST appear to be greater than ALT levels. This differs from the pattern in viral hepatitis, in which ALT levels are usually higher than or equal to AST levels (Gholson et al., 1990), but it is similar to that seen with alcoholic hepatitis. The exact significance of this pattern seen in dengue is uncertain. It has been suggested that it may be due to excess release of AST from damaged myocytes during dengue infections (Chung et al., 1992), but this has not been formally tested. Simultaneous measurement of muscle isoforms of lactate dehydrogenase and creatinine kinase may help further clarify this observation. The elevated AST levels tend to return to normal more rapidly than ALT levels. This is possibly because AST (12.5—22 h) has a shorter half-life than ALT (32—43 h) (Hawker, 1991).

Histological changes reported in the liver in dengue include: microvesicular steatosis, hepatocellular necrosis, Kupffer cell hyperplasia and destruction, Councilman bodies and cellular infiltrates at the portal tract (Bhamarapravati, 1989; Burke, 1968). Most reports are based on small numbers of samples obtained from fatal cases. The presence of thrombocytopenia and coagulative dysfunction makes it difficult to obtain samples from others. As such, one is unsure of the degree of changes present in those with milder disease. Steatosis occurs frequently in hepatitis of viral origin and no special significance can be attributed to this process in dengue infections. Hepatocellular necrosis in dengue generally affects the midzonal area and sometimes the centrolobular area. Reasons for this pattern may be that hepatocytes in this zone are more sensitive to anoxia or the products of an immune response (e.g. cytokines and chemokines) or that the dengue virus preferentially infects cells in this zone. In fact, dengue viral RNA and protein have been detected in midzonal hepatocytes, mostly around necrotic foci. Councilman (acidophilic) bodies correspond to hepatocytes showing the characteristic morphology of apoptosis. Inflammatory mononuclear cell infiltrates (of varying intensity) are seen in most specimens studied so far.

The dengue virus has been isolated from the liver of fatal cases (Burke, 1968; Rosen et al., 1989; Sumarmo et al., 1983). Some find it the main organ from which virus could be isolated (Bhamarapravati, 1997; Huerre et al., 2001; Rosen et al., 1989). For instance, using mosquito inoculation techniques, DEN-2 or DEN-3 viruses were recovered from the livers of 5 of 17 fatal cases, but rarely from other tissues (Rosen et al., 1989).

Using dengue-specific RT-PCR on liver samples from fatal cases, dengue RNA was detected in 11 of 15 (Rosen et al., 1999). Dengue RT-PCR has been done on paraffin-embedded samples from autopsies of 10 children with a clinical diagnosis of DHF/DSS 17 years after their death. In 44, 80 and 43% of cases, DEN-2 RNA was detected in the liver, spleen and lymph nodes (Sariol et al., 1999). Dengue viral RNA has also been detected in midzonal hepatocytes of archived paraffin-embedded autopsy tissues using an in-situ PCR method (Kangwanpong et al., 1995).

Immunohistochemistry and in-situ hybridization have been used to localize dengue antigens in naturally infected human tissues (Jessie et al., 2004), with immunoperoxidase methods suggested to be reliable and specific in diagnosing dengue or yellow fever infection from human archive samples (Hall et al., 1991).

Clinical manifestations in severe dengue disease and yellow fever are similar. Viruses causing them are closely related (both are flaviviruses, transmitted by the same group of vectors). Overall liver pathology in dengue appears to be similar to that observed during the early stages of yellow fever (Bhamarapravati, 1997). However, in yellow fever, liver cell necrosis tends to be more severe and extensive. In addition, immunofluorescence patterns in infected HepG2 cells differ. While dengue viral antigens are found as large perinuclear inclusions and small cytoplasmic foci, yellow fever antigens are homogeneously distributed throughout the cytoplasm (Marianneau et al., 1998). DEN-2 infection of HepG2 cells leads to the release of only a small amount of infectious particles and a slight increase in the number of viral antigen-containing cells over time. By contrast, yellow fever viruses replicated to high titres and infected all exposed cells (Marianneau et al., 1998). Furthermore, while dengue virus-infected cells died rapidly by apoptosis, the