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ORIGINAL ARTICLES

THE IMPACT OF DENGUE ON LIVER FUNCTION AS EVALUATED BY AMINOTRANSFERASE LEVELS

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Abstract:

Objective: *To evaluate the impact of dengue virus infection on liver function by measuring aminotransferases in blood samples from patients serologically diagnosed as Dengue Fever.*

Background: *Dengue, presenting as classical or haemorrhagic fever, also has some effect on liver function. This evaluation should be done for the management and deterination of prognosis of dengue with altered liver function. This study was done to find out the impact of dengue on liver function by evaluation of aminotransferase levels.*

Methods: *Serologically confirmed 100 cases of dengue were included for the study. The patients were treated in the indoor. Informations were collected in a preformed revised structured questionnaire. Degree of liver involvement was classified in four grades according to Aminotransferase levels. Grades are as follows: 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 at levels higher than three times the upper reference values; Grade D – acute hepatitis, with aminotransferase levels at least ten times or more their upper limit of normal values.*

Results: *Out of the confirmed dengue cases, 58% were female and 42% were male. Mean age was 34.5. 70% cases were classified as classic dengue and 30% as Dengue Haemorrhagic fever (DHF). Liver functions involvements were classified as Grade A in 34% cases, Grade B in 44% cases, Grade C in 20% cases and Grade D in 2% cases. High level of aminotransferases was 60% in classic dengue cases while it was 80% in DHF cases.*

Conclusion: *Many of the dengue cases have abnormal liver function which are usually overlooked. This must be taken into account for risk stratification, management and prognosis of dengue cases.*

Keywords: *Dengue, Classic Dengue, Dengue Haemorrhagic Fever, Dengue Shock Syndrome, Liver function, Aminotransferase.*

Introduction:

Dengue infection is endemic in many countries along the tropical and subtropical belt, with more than 100 million cases and 24,000 deaths annually. In humans Dengue Virus (DENV) infection leads to a spectrum of clinical manifestations that range from inapparent or mild febrile illness as dengue fever (DF) to severe and fatal haemorrhagic disease as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).[1] The etiologic agent (DENV) belongs to the Flaviviridae family and to the Flavivirus genus, with 4 serotypes.

The symptomatology of dengue varies, generally consisting of the mild forms found in cases of classic dengue, the principal manifestations of which are high fever, arthralgias, myalgias, cephalea and gastrointestinal disorders. AST and ALT are liver enzymes involved in amino acid metabolism. Hepatic dysfunction is common in dengue infection, and is attributed to a direct viral effect on liver cells or as a consequence of dysregulated host immune responses against the virus.[1]

In view of the wide range of symptomatology, the diagnosis of dengue should be based both on clinical

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and laboratory data. Complementary investigations aid in evaluating the severity of the disease and the complications resulting from this pathology. Virus isolation is the most specific laboratory test for the diagnosis of dengue. Blood sample should be collected prior to the 6th day of symptoms, the viremic period. Immunoenzymatic tests (ELISA) are an alternative for confirmation of the diagnosis and are available in the laboratories of the public healthcare network. These tests permit confirmation in samples taken from the 7th day of the disease onwards in around 80% of cases, achieving as high as 100% of cases after two weeks.[2] In the present study, the enzymatic method was used during an epidemic of dengue from March 2006 to July 2006 at Mitford hospital.

Materials and Methods:

A total of 100 patients receiving care at Mitford Hospital for Diagnosis and Treatment of dengue were included in this study between March and July 2006. Dengue was suspected when two or more of the following symptoms were present: fever, cephalea, retroorbital pain, myalgias, arthralgias, skin rash, nausea, vomiting, prostration and hemorrhagic manifestations. Patients were hospitalized in accordance with the standard protocol of the institute during the period in which symptoms were present or while laboratory tests remained abnormal.

The diagnosis of DHF was established according to the World Health Organization (WHO) criteria: thrombocytopenia <100,000/mm3, hemoconcentration and hemorrhagic manifestations such as spontaneous petechiae, or a positive tourniquet test. Hemoconcentration was defined as hematocrit >45% in men, >40% in women and >38% in children under 12 years of age. The criterion of a 20% increase in hematocrit was not applicable for this study population because in the majority of cases, previous, recently performed blood counts were not available for comparison.

Tests for the detection of anti-dengue antibodies were carried out in blood samples collected between the 7^{th} and 11^{th} day following the onset of symptoms. These samples were simultaneously submitted to two serological tests: immunoenzymatic assay IgM-Dengue- Biomanguinhos and immunoenzymatic assay IgM-Dengue- PanBio, in accordance with the manufacturer's instructions. When the results of both tests were positive, patients were considered to be currently infected by the dengue virus, while cases in which the results of both samples were negative were considered unconfirmed. Immunoenzymatic assay IgG-Dengue is also done in every cases.

The degree to which the liver was affected was evaluated in these patients and classified into four groups according to AST and ALT levels during the period of infection. The laboratory reference values of AST and ALT for males were 59 UI/L and 72 UI/L, respectively, and for women reference values were 36 IU/L and 52 IU/L, respectively. Grade A comprised patients with normal AST and ALT levels. Grade B was composed of patients in whom the level of at least one of the aminotransferases was increased but not higher than three times of the normal value. When the values of at least one of the enzymes were more than 3 but less than 10 times of the reference values, patients were classified as Grade C. Patients in whom there was an increase in one or both enzymes to levels more than or equal to 10 times of the reference values were classified as Grade D, thereby defining the presence of hepatitis caused by DENV. In this study, the patients with increased aminotransferases greater than 10 times of the reference values were tested for hepatitis viruses A, B and C (ELISA technique). In cases in which a diagnosis of dengue was eliminated, other diagnostic possibilities were investigated on an individual, case by case basis.

Results:

Only serologically proven cases of Dengue patients were included in the study. Dengue was confirmed in 100 cases by both immuno-enzymatic tests. Of these, 58 patients (58%) were female and 42 (42%) were male. Mean age of patients was 34.5 years (range 7-78 years). A total of 70 cases (70%) were classified as classic dengue and 30 (30%) as DHF (Table I). No changes in aminotransferases were detected in 34% of the population studied, (Grade A), where as aminotransferase levels were high in 66% of patients, 44% classified as Grade B, 20% as Grade C and 2% as Grade D. In the cases classified as classic dengue, aminotransferases were high in 62%, while in cases of DHF, aminotransferases were abnormal in 74% of cases. Anti Dengue- IgG was positive in 23 cases (Table I).

Table-I

Clinical presentation of dengue, type of infection and degree of liver involvement according to AST and ALT levels

Total	Grade A	Grade B	Grade C	Grade D
Dengue				
Classic	26	28	16	00
Haemorrhagic	08	16	04	02
Sex				
Male	08	22	12	00
Female	26	22	08	02
IgM				
Positive	34	44	20	02
Negative	00	00	00	00
IgG				
Positive	02	06	13	02
Negative	32	38	07	00

Discussion:

The extent to which the liver is affected by DENV ranges from mild lesions to fulminant hepatitis.[3, 4-8] Liver involvement may be characterized by manifestations such as pain in the right hypochondrium, hepatomegaly varying degrees of jaundice [9],and an increase in liver markers, principally ALT and AST, similar to those found in acute hepatitis caused by the A, B, C, D and E viruses. In this study, patients with aminotransferase levels more than 10 times of the reference values, had negative results for hepatitis A, B, C and E according to ELISA technique.

In a study carried out in Bangkok,[6] 104 patients with a clinical and serological diagnosis of dengue were classified according to severity into: classic dengue, dengue hemorrhagic fever and dengue shock syndrome. Liver function tests showed that the most severely ill patients had higher levels of aminotransferases. In children, 74% had hepatomegaly, and aminotransferase and alkaline phosphatase levels were between 80 and 87% higher compared to normal value. Therefore, AST, ALT are valuable parameters for the evaluation of the severity of the infection. In a study carried out by Nguyen et al.[10], AST values were reported to be frequently abnormal, reaching values higher than those of ALT, around 97.7% and 37.3% above normal levels, respectively. Anti Dengue IgG was present in 23% cases.

Conclusion:

Dengue is normally associated with a moderate increase in aminotransferases and, less frequently, acute hepatitis. In this present study, liver damage was more frequent among women, in patients with a primary infection and in those with DHF. In all the cases observed, dengue was found to be self limiting, and there were no cases of liver failure. DENV may, therefore, provoke varying degrees of damage to the hepatic parenchyma, ranging from mild increases in aminotransferases to increases up to 30 times of the reference values. Therefore, the use of liver tests to evaluate the degree of liver damage is of great importance, and markers such as AST and ALT may be used as parameters to evaluate severity. In complicated classic dengue, dengue hemorrhagic fever and in dengue shock syndrome, concomitant deficiency of coagulation factors and thrombocytopenia should be considered in the pathophysiology of the disease as factors that tend to aggravate hemorrhagic status.

References:

1. Schatzmayr HG, Nogueira RM, Travassos da Rosa AP. An outbreak of Dengue Virus at Rio de Janeiro - 1986. Mem Inst Oswaldo Cruz 1986; 81: 245-6.
2. Nogueira RM, Miagostovich MP, Cavalcanti SM, et al. Levels of IgM antibodies against dengue virus in Rio de Janeiro, Brazil. Res Virol 1992; 143: 423-7.
3. Souza LJ, Alves JG, Nogueira RM, et al. Aminotransferase changes and acute hepatitis with dengue fever: analysis of 1585 cases. Braz J Infect Dis 2004; 8: 156-63.
4. Lum LC, Lam SK, George R, Devi S. Fulminant hepatitis in dengue infection. Southeast Asian J Trop Med Public Health 1993; 24: 467-71.
5. de Souza LJ, Gonçalves Carneiro H, Souto Filho JT, et al. Hepatitis in dengue shock syndrome. Braz J Infect Dis 2002; 6: 322-7.
6. Kuo CH, Tai DI, Chang-Chien CS, et al. Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992; 47: 265-70.
7. Mohan B, Patwari AK, Anand VK. Hepatic dysfunction childhood dengue infection. J Trop Pediatr 2000; 46: 40-3.
8. Wang LY, Chang WY, Lu SN, Chen TP. Sequential changes of serum transaminases and abdominal sonography in patients with suspected dengue fever. Gaoxiong Yi Xue Ke Xue Za Zhi 1990; 6: 483-9.
9. Souza LJ, Lopes AC, Bastos DA. Icterícia na dengue hemorrágica: relato de três casos. Rev Bras Clin Terap 2002; 28: 198-201
10. Nguyen TL, Nguyen TH, Tieu NT. The impact of dengue hemorrhagic fever on liver function. Res Virol 1997; 148: 273-7.