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STUDY OF ACUTE HEPATIC DYSFUNCTION ASSOCIATED WITH DENGUE FEVER IN NORTH WEST ZONE OF RAJASTHAN

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Abstract

Background: Atypical manifestations of dengue viral fever have been described in recent past, including involvement of the central nervous system, cardiac alterations, and elevations in aminotransferase levels, with reactive hepatitis. Hepatic involvement can be characterized by manifestations of acute hepatitis, with pain in the right hypochondrium, hepatomegaly, jaundice, and raised aminotransferase levels. Although the liver is not the directly targeted organ for dengue virus, histopathological findings, including centrilobular necrosis, fatty alterations, hyperplasia of the Kupffer cells, acidophil bodies and monocyte infiltration of the portal tract have been detected in patients with dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). In most cases, hepatic involvement prolongs the clinical course of this self-limiting viral infection, but it does not constitute a sign of worse prognosis.

Methods: Hundred confirmed diagnosed inpatient cases of dengue fever were included. Clinical examination and laboratory investigations including liver function tests and serum electrolyte levels were performed regularly at appropriate interval. Viral hepatitis testing was also performed to check for any co-infection or pre-existing viral hepatitis. On the basis of increase in serum aminotransferase levels, patients were divided into two groups; Mild (up to 5 times normal) to Moderate (5- 10 times) acute hepatitis: AST or ALT 45-300 IU/L and severe acute hepatitis: AST or ALT > 300 IU/L or ≥ 10 times. On basis of serum protein levels, the patients were grouped in two groups, one with hypoalbuminemia; serum albumin <3.0 g/dL and without hypoalbuminemia

Results: In this study out of total 100 patients 67 were men (67%) and 33 were women (33%). The mean age of the patients was 39 ± 3.1 years. The patients were in the range of age 22-54 years. Maximum number of patients were in third decade of life. All the patients were tested positive for NS1 antigen test. Fever was the most common presenting complaint with mean duration of fever was 6 ± 3.27 days with mean temperature of 38.5 ± 1°C, 21% had abdominal pain, 17% had rash, 3% had jaundice. Liver function tests (LFTs) show the median ALT of 88.50 IU/L with range from 43.25-317.22 IU/L, median AST of 174 IU/L with range from 47-371.5 IU/L. 91% of the patients had elevated AST levels and almost 79% patients had elevated ALT (hepatitis). Normal levels of serum aminotransferase AST and ALT levels were seen in 9% and 21% patients respectively. Mild to moderate increase in AST and ALT levels were seen in 84% and 75% of cases respectively whereas more than 10-fold increase in AST and ALT levels were seen in 7% and 4% patients respectively as shown in Table 1. Mortality was 2% in our study.

Conclusions: Dengue viral fever contributes significantly to the disease burden in developing countries. Although the disease is self-limiting, but a significant number of cases show signs of organ dysfunction including liver dysfunction. The diagnosis of Dengue may be difficult in some cases due to false negative reports in first few days. It is thus important to investigate all suspected dengue patients with liver function test (serum transaminases levels), so that liver dysfunction can be detected early and proper management can be initiated.

Keywords: Dengue Viral Fever, Immune Hepatitis, Serum Aminotransferases, Hepatic Dysfunction.

Introduction

Dengue fever is an arboviral infection transmitted by Aedes ageptyi as well as Aedes Albopictus and causes 4 spectra of illness which are an asymptomatic phase, acute febrile illness, classic Dengue fever (DF), Dengue Haemorrhagic Fever (DHF) which includes Dengue Shock Syndrome (DSS) as per WHO 1997 guidelines [1,2]. The modified categorization of WHO in 2009 includes dengue with or without warning signs or severe dengue [3]. Dengue is defined as, 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 (≥ 20%) with rapid reduction in thrombocyte count (< 50000/mm3). Severe dengue is defined as evidence of severe plasma leakage, bleeding and organ impairment.

The dengue virus belongs to the family of Flaviviridae. It has a classic presentation of influenza-like illness with spiking fevers, fatigue, retro-orbital pain, myalgia and headaches. The incubation period is typically 3-14 days [4]. Laboratory findings include thrombocytopenia, leukopenia, hyponatremia and haemoconcentration [5]. Dengue fever normally is a self-limiting disease, but may require hospitalization and may be fatal in some cases.

Over the last few years, atypical manifestations of dengue have been described, including involvement of the central nervous system, cardiac alterations, and elevations in aminotransferase levels, with reactive hepatitis.[6] Hepatic involvement can be characterized by manifestations of acute hepatitis, with pain in the right hypochondrium, hepatomegaly, jaundice, and raised aminotransferase levels. Although the liver is not the directly targeted organ for dengue virus, histopathological findings, including centrilobular necrosis, fatty alterations, hyperplasia of the Kupffer cells, acidophil bodies and monocyte infiltration of the portal tract have been detected in patients with dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).[7,8] In most cases, hepatic involvement prolongs the clinical course of this self-limiting viral infection, but it does not constitute a sign of worse prognosis.[9]

Materials and Methods

This is a descriptive, cross-sectional study, conducted in the Department of Medicine, Sardar Patel Medical College, PBM and associate group of hospitals, Bikaner, Rajasthan. The study was conducted between 1st oct 2021 to 31st oct 2021. Hundred confirmed diagnosed cases of dengue fever admitted in Medicine ward at our hospital selected by simple random sampling. The relevant medical records of the patients admitted were studied, relevant clinical history, past history, personal history were recorded. Clinical examination and laboratory investigations including liver function tests and serum electrolyte levels were performed regularly at appropriate interval. Viral hepatitis testing was also performed to check for any co-infection or pre-existing viral hepatitis. Supportive treatment in the form of intravenous and oral fluids and vitamin K was given to the patients.

On the basis of increase in serum aminotransferase levels, patients were divided into two groups; Mild (up to 5 times normal) to Moderate (5- 10 times) acute hepatitis: AST or ALT 45-300 IU/L and severe acute hepatitis: AST or ALT > 300 IU/L or ≥ 10 times. On basis of serum protein levels, the patients were grouped in two groups, one with hypoalbuminemia; serum albumin <3.0 g/dL and without hypoalbuminemia.

Results

In this study out of total 100 patients 67 were men (67%) and 33 were women (33%).[Image 1] The mean age of the patients was 31 ± 3.1 years. The patients were in the range of age 22-54 years. Maximum number of patients were in third decade of life with 36 cases.[Table 1][Image 1] All the patients were tested positive for NS1 antigen test. Out of the total patients' studies two cases developed dengue shock syndrome. Among clinical features, fever was the most common presenting complaint with mean duration of fever was 6 ± 3.27 days with mean temperature of 38.5 ± 1°C, 21% had abdominal pain, 17% had rash, 3% had jaundice. On abdominal examination, 9% had right hypochondric tenderness and 6% had epigastric tenderness. Platelet count was reduced in most of the cases. The platelet count ranged between 15000/mm^3 and 165000/mm^3 with median value of 33000/mm^3. Blood count showed leucopenia in 73% cases. Liver function tests (LFTs) show the median ALT of 88.50 IU/L with range from 43.25-317.22 IU/L, median AST of 174 IU/L with range from 47-371.5 IU/L. Almost 91% of the patients had elevated AST levels and almost 79% patients had elevated ALT (hepatitis). Normal levels of serum aminotransferase AST and ALT levels were seen in 9% and 21% patients respectively. Mild to moderate increase in AST and ALT levels were seen in 84% and 75% of cases respectively whereas more than 10-fold increase in AST and ALT levels were seen in 7% and 4% patients respectively as shown in Table 2. Mortality was 2% in our study.

Table 1: Showing age group and gender wise distribution of cases

Age Groups	Male	Female	Total
21-30	24	12	36
31-40	18	8	26
41-50	12	8	20
51-60	13	5	18
Total	67	33	100

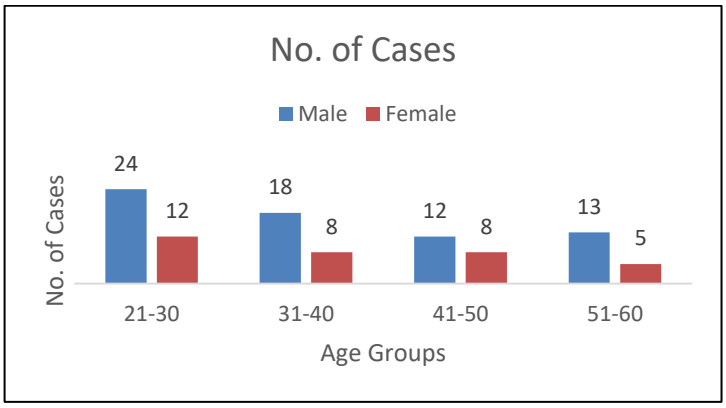

Figure 1: Age groups and gender wise distribution of cases in the present study

Table 2: Patients having elevated Serum aminotransferase levels

	No. of Patients	
	AST Levels	**ALT Levels**
Normal value	9	21
Mild to Moderate Raised	84	75
> 10 fold raised	7	4

Serum albumin levels showed that hypoalbuminemia was present in 67% of cases with serum albumin levels ranged from 2.2-3.9 g/dL with median 2.8 g/dL. All the patients with hypoalbuminemia had varying levels of raised serum aminotransferase levels. All 7% patients with more than 10 folds increase in AST/ALT had hypoalbuminemia whereas 71% patients with mild to moderate raised ALT/AST had hypoalbuminemia. The clinical characteristics are shown in Table 3.

Table 3: Details of clinical parameters in the present study

Parameter	**Median Values**
Avg. platelet count	33000/mm^3
Aspartate aminotransferase	174 IU/L
Alanine aminotransferase	88.50 IU/L
Serum Albumin	2.8 g/dL

Discussion

Currently dengue is perhaps the most common rapidly emerging viral infection throughout the world especially in developing countries. Rajasthan has recently witnessed an epidemic like state with sudden increase in cases of dengue viral fever estimated to more than 10000 reported cases and 39 deaths as of Oct 2021.[10] Deranged liver functions are frequently seen in patients with dengue infection due to dysfunction of liver cells or unregulated host immune response against the virus.[11] Hence measurement of AST and ALT are mandatory to see the liver involvement [12]. We have found in our study that deranged liver functions are an important feature in patients with dengue infection. Almost 91% of the patients had elevated AST levels and almost 79% patients had elevated ALT (hepatitis). Parkash et al [9] reported that AST abnormality was predominantly higher as compared to ALT with 95% and 86% respectively, which is consistent with our study. Wong et al [11] also reported similar findings, however percentage of patients with raised AST and ALT is more in our study population than reported by Wong et al and other studies. [11,13,14] Souza et al [12] also reported the similar trend of AST/ALT in dengue fever but with much lower level as compared to our population. This difference can be explained on the basis that in our study all patients were inpatients while in their study all the patients were outpatients with less severe disease. We can assume that reasons for higher ALT or AST levels in our population are probably due to difference in virulence and hepatotoxic nature of dengue virus and difference in geographic and ethnic variables. Therefore, further studies are required to highlight the possible hepatotropic nature of this virus as well as virulence and type of virus. The comparative results are tabulated in Table 4.

Table 4: Comparison of various studies with present study

Study	Patients	Raised AST	Raised ALT	AST>ALT	> 10 folds raise (AST,ALT)
Parkash et al [9]	699	95%	86%	Yes	-
Wong et al [11]	127	90.60%	71.70%	Yes (75.6%)	13.4%
Souza et al [12]	1585	63.40%	45%	Yes	3.4%, 1.8%
Present Study	100	91%	79%	Yes	7%, 4%

The level of increase in hepatic transaminases can easily mimic acute viral hepatitis. AST has various sources including the heart, striated muscle, erythrocytes, etc., apart from the liver, whilst ALT primarily is hepatic in origin [15]. Acute insult to these non-hepatic tissues by the dengue virus can result in higher elevations of AST when compared to ALT rise. Thus AST/ALT levels may give a clue to differentiate between viral hepatitis where AST/ALT is usually less than 1, from dengue associate hepatitis where AST/ALT is greater than 1. In our study 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 which is consistent with other studies. [9, 11,12,13]. This hints at a possible association between increased transaminase levels with increasing disease severity.

Hypoproteinaemia or hypoalbuminemia is seen in 67% of cases in our study. This is consistent with the study done by Jagadish kumar et al [16] who reported similar results. In another large study from Kolkata, India by Saha et al [17], hypoproteinaemia have been seen in 12.9% cases only, the heterogeneity in the population and severity of the disease may be responsible for such a wide range observed in the different studies. Hypoproteinaemia is a marker of acute hepatic dysfunction and can be associated with severity of illness. However hypoproteinemia and proteinuria is also seen due to increased capillary permeability in dengue illness. [18,19]

Immune responses including the innate and acquired, play important role in determining the response to any virus. Causation of the severity dengue infection has been explained by the hypothesis of immune enhancement and virulence nature of virus [20]. Based on this we can hypothesize the similar mechanism responsible for hepatoxicity in our study population. Dengue antigens have been identified within the liver parenchyma on postmortem of these patients hence virus seems to be able to replicate within the hepatocytes. Unregulated host immune response may play some part in severity of dengue infection therefore by modifying the immune response; severe infection can be prevented [20].

Conclusion

Dengue viral fever contributes significantly to the disease burden in developing countries. Although the disease is self-limiting, but a significant number of cases show signs of organ dysfunction including liver dysfunction. The diagnosis of Dengue may be difficult in some cases due to false negative reports in first few days. It is thus important to investigate all suspected dengue patients with liver function test (serum transaminases levels), so that liver dysfunction can be detected early and proper management can be initiated.

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