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Original Research

GESDAV

Evaluation of the hepatic function in dengue patients in Kolkata

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ABSTRACT

Aim: To evaluate the hepatic functions in dengue virus patients who were admitted in the tertiary care, Kolkata. **Materials and Methods:** A prospective study of 50 patients diagnosed and treated at our institute during an outbreak of dengue infection in Kolkata between July – September 2012. Patients were selected randomly irrespective of all age group and both sex. The diagnosis was established by clinical signs and symptoms,serological tests such as NS1 antigen (ELISA), and IgM level (MAC-ELISA). **Results:** Out of 50 patients, four had dengue haemorrhagic fever. Forty-two patients had enlarged liver In all these cases platelet count was low, NS1 and IGM were reactive. Liver enzymes such as Alanine transferase (ALT), Aspartate transferase (AST), Alkaline Phosphatase (ALP) was increased. Serum Protein levels (Total Protein), Albumin(A), Globulin(G) were less than normal level and A:G was altered, whereas as there was no significant change in serum bilirubin level. After seven days when there was complete recovery and the patient was fit to be discharged, the parameters were repeated and it was found that the values were 2 to 3 times more than the normal. **Conclusion:** In dengue fever, hepatic dysfunction is commonly found in classic dengue and severe forms. This was noted both in children and adults. Once the treatment of dengue fever was completed and the patients were near normal but the abnormal liver function persisted even after 2 weeks.

KEY WORDS: Dengue, dengue hemorrhagic fever, hepatic function

INTRODUCTION

Dengue fever is a Spanish word meaning fastidious or careful. The term came into use after 1828. Dengue fever in recent years has become a global health problem in terms of morbidity, mortality and economic cost in tropical and subtropical areas. With an estimated 100 million cases, endemic in more than 110 countries throughout the world annually [1,2]. Existence of dengue like disease was reported in 1779 when an epidemic swept Asia, Africa, and North America [3]. In India, dengue virus (DENV) was isolated in 1946 and many outbreaks were reported [4]. Dengue hemorrhagic fever (DHF) was first reported in Kolkata, West Bengal in 1963 [5]. The incidence of dengue has increased due to urbanization, population growth, increased international travel, and global warming.

Dengue fever is caused by RNA flavivirus transmitted to people through the bite of a female Aedes aegypti mosquito. Infection with DENV can be present in mild form as classic dengue fever or to more severe form of disease: The DHF and dengue shock syndrome (DSS). DENV an arbovirus circulates as four distinct serological types DENV-1,2,3,4. Contracting one form of dengue fever provides life-long immunity from that serotype but not from other serotypes. Some evidence has suggested that there is greater involvement of liver infection with DENV-2 compared to other three serotypes. Monotypic infection with DENV-1 was 9.5%; with DENV-2 was 60.8%, and with DENV-3 was 29.7% [6]. A study carried out in Brazil showed that DENV-3 was isolated in more number of cases than DENV-2 in the classic form of the disease [7].

Diagnosis of dengue is based on the findings of fever plus two of the following symptoms: Rash, generalized pain, nausea, vomiting, low white blood cell count, positive tourniquet test or any warning signs like abdominal pain, mucosal bleeding, increased hematocrit with low platelets, lethargy and liver enlargement in someone who lives in endemic area [8]. Decreased level of consciousness occurs in 0.5-6% of severe cases which is attributed either to infection of the brain by the virus or indirectly as a result of impairment of vital organs, for example, the liver [9].

Liver involvement is universally present in children and in adult patients with dengue viral infection (DVI) [10]. Hepatocytes are the site of DENV replication and hence the involvement of liver in dengue disease [11]. Liver damage is a common complication of dengue infection and aminotransferase levels are a valuable marker for monitoring dengue cases [7].

The present study aimed to evaluate the hepatic functions in DENV patients who were seen in Kali Pada Chaudhury Medical College Hospital, Kolkata, India.

MATERIALS AND METHODS

A prospective study of 50 patients diagnosed and treated at our institute during an outbreak of dengue infection in Kolkata between July and September 2012. Patients were selected randomly irrespective of all age group and both sex. All clinically suspected DVI patients as per WHO guidelines criteria were screened and the probable diagnosis was based on 2 or more of the symptoms with high fever, a detailed clinical examination, serological, and hematological tests were conducted to confirm the diagnosis of DVI. And in DHF patients who presented with high fever of sudden onset, retro-orbital pain, arthralgia, generalized malaise, bleeding particularly in skin (Petechiae), occasionally in gums and nose, melena and low blood pressure were included. Patients diagnosed with malaria, enteric fever, hepatitis by relevant investigations were excluded.

Serology

Test for the detection of antidengue Abs were carried out in serum samples collected after 5th day to 10th day following the onset of symptoms. Viremia in dengue lasts for <5 days and that IgM antibody response takes 5-10 days to develop in cases of primary DVI and 4-5 days in case of secondary DENV infection [8]. MAC-ELISA and NS1 antigen tests were conducted using Dengue Day 1 Test Kit manufactured by J. Mitra and Co. Pvt. Ltd., New Delhi, India. When results were positive, patients were considered to be currently infected with DENV. Platelet count and hematocrit also supported the diagnosis of DENV. Liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum protein levels – total proteins, albumin (A), globulin (G), A: G, serum bilirubin levels were measured on the day of admission (on the 5th day after the onset of symptoms) and also the tests were repeated before the patient was fit to be discharged from hospital.

Analysis of liver function test, that is, AST, ALT, total protein, ALP was analyzed by auto-analyzer – Mindray BS-390 Kit used Shenzuen Mindray Bio-medical Electronics Co. Ltd. China.

- Method for AST: Aspartate aminotransferase kit (International Federation of Clinical Chemistry [IFCC]) without pyridoxal phosphate activation.
- Method for ALT: Alanine aminotransferase kit (IFCC) without pyridoxal phosphate activation.
- Method for alkaline phosphatase: IFCC and laboratory medicine modified method.

Dengue fever may be diagnosed by virus isolation in cell culture, nucleic acid detection by polymerase chain reaction (PCR), viral antigen detection or specific antibodies (serology) [12]. PCR and viral antigens detection are more accurate in the first 7 days, not widely available due to their greater cost [13].

Tests for dengue-virus specific antibodies (Abs), types IgM and IgG can be useful in confirming a diagnosis in later stages of infection. In a person with symptoms, the detection of IgM is considered diagnostic [14].

RESULTS

The prospective study is an attempt to elucidate the clinical profile and laboratory findings of dengue infected patients seen in our hospital. Forty-six patients (92%) presenting with classic dengue features, and 4 (8%) were DHF; 2 of these patients went into DSS. Out of 50 patients, 22 were males and 28 females. Aged between 8 and 59 years with majority of cases ranging between 10 and 19 years. Adult were 41 and children were 9. The major presenting features are shown in Figure 1. Laboratory parameter in patients with DVI is shown in Table 1.

Serological tests showed 84% NS1 reactive and 100% IgM reactive and 6% showed IgM and IgG positive.

Liver function tests showed increased levels of aminotransferases in all our 50 cases [Table 2]. Total protein was <6 g% in (74%) and albumin <3.5 g and A: G ratio was <1. But serum bilirubin level was within normal limits.

When the presenting symptoms had subsided the tests were repeated and we found aminotransferase levels did not come to normal levels.

Statistics

Median values for all groups and both median and mean values for DHF groups.

95% Confidence interval (CI) of median for the selected parameters of dengue cases have been determined along with

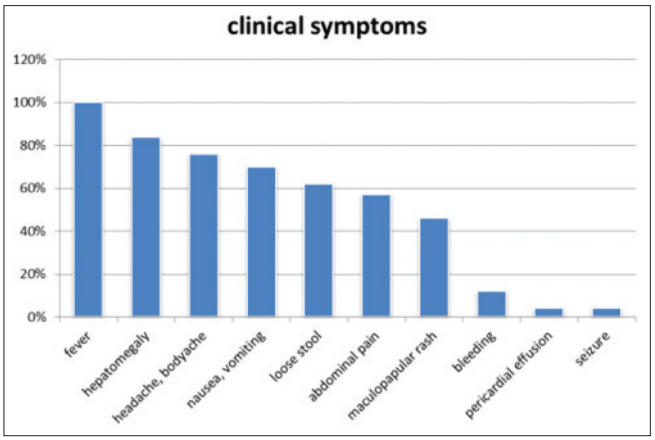

Figure 1: Clinical features in patient with dengue viral infection

Table 1: Laboratory parameter in patients with dengue viral infection (n=50)

Parameter	Values (%)
Hemoglobin (g/dl)	<10.5 (34)
Platelet count (/cu mm)	<100,000 (85)
	<50,000 (15)
WBC (/cu mm)	<3000 (24)
Prothrombin time (s)	>17 (26)

WBC: White blood cell

Table 2: Comparison of LFT between classic DF and DHF

LFT	DF (n=46)				DHF (n=4)		
	Median	95% CI of median, <200	Median	95% CI of median, <400	Median	Mean	95% CI of mean, >400
AST	121	n=19, 115-172	309	n=27, 252-331	578	619	510-728
ALT	135	n=15, 102-161	322	n=31, 284-355	612	653	547-759
ALP	152	n=21, 130-188	297	n=25, 220-346	1017	1033.5	988-1078

DHF: Dengue hemorrhagic fever; DF: Dengue fever; LFT: Liver function test; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase

95% CI of mean values of the parameter in DHF to understand the range of 95% CI.

For DF, median has been used as a representative average along with its 95% CI.

Median was used because fluctuation is less, more appropriate for large sample (>30 regarded).

For DHF was $n = 4$. Thus, for small number of values of the parameter mean being better representative average has been used along with 95% CI.

DISCUSSION

The results of the present study showed that liver injury was present in almost all cases with dengue infection as indicated by the abnormal liver function tests and clinical manifestations of liver disease namely hepatomegaly, pain in the right hypochondrium, ascitis, and pedal edema.

In our study, 84% patients had hepatomegaly which includes 9 children and 33 adults, 14% had pedal edema, 14% had ascitis on clinical examination. Wahid *et al*. has reported that in children, liver involvement is more profound in severe forms of DVI such as DHF and DSS [15].

Kuo *et al*. reported that approximately 90% had abnormal AST, ALT, ALP, bilirubin, and GGT [16]. Liver involvement occurred through an inflammatory process in parenchyma, provoked directly or indirectly by the virus, reducing the diameter of the lumen biliary canaliculi causing obstruction. In our study, AST and ALT values were more than 5 times in classic dengue infection and ALP levels were also increased. And more than 10 times in DHF patients, bilirubin level were within normal limits. The tests were repeated before discharge and it showed the enzyme values did not reach the normal limits.

In children the aminotransferase levels were >10 times indicating children are at higher risk of hepatic involvement and possibility of developing hepatic encephalopathy [17].

Hypoalbaminemia in 74% and reduction of serum globulin may be an important factor of fluid loss into third space which is indicative of severity of DVI.

None of our patients had jaundice, serum bilirubin levels were within normal limits. But 22% had itching. Mechanism of liver injury in dengue may be due to direct effects of the virus or host immune response on liver cells, circulatory compromise, metabolic acidosis and hypoxia caused by hypotension or localized vascular leakage inside the liver [10,18].

In our study, all our patients had two and more symptoms of DVI. Liver profile showed increased values to support that there was liver involvement in DF and severe in DHF or DSS but there were no deaths.

CONCLUSION

Hepatic dysfunction was observed in both classic dengue and severe forms DHF and DSS. Liver enzyme showed significant rise in children and also in adult. The abnormalities of liver function and degree of hepatic enlargement did not correlate. Even after 2 weeks aminotransferase levels were much above the reference value. In geographical areas where dengue is endemic and patient presenting with high fever, tender hepatomegaly and increased liver enzyme levels, should be strongly considered as DVI.

To define the mechanism of liver injury in DVI further studies are required. Limitation of our study was ultrasound and biopsy of liver was not done to confirm the diagnosis. Dengue hemorrhagic fever patients' number are too small, it is hard to make conclusion difference of these two groups with these results.

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