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Research Article

STUDY OF HEPATIC DYSFUNCTION IN DENGUE FEVER AND IT'S PREDICTOR OF OUTCOME

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ABSTRACT

Introduction: Dengue fever can present with a diverse clinical spectrum. Although liver is not a major target organ, hepatic dysfunction is a well recognized feature. In this study we attempted to study the pattern of hepatic involvement in children with dengue and its association with outcome of the disease.

Methods: The present study was Prospective observational study consisting 220 confirmed cases of dengue fever. World Health Organisation (WHO) guidelines were applied for categorization of patients into dengue without warning signs (DWWS), dengue with warning signs (DWS) and severe dengue (SD)[1,2].

Details clinical evaluation, hematological and radiological investigations to confirm diagnosis of Dengue, exclude other diagnosis, presence hepatic dysfunction, multiorgan dysfunction syndrome (MODS), shock, fulminant hepatic failure (FHF) were done in all subjects.

Statistical analysis was done to know the strength of association between different clinical, biochemical and radiological variables and outcome of the disease.

Results and Conclusions: Our data suggests that hepatic dysfunction more common in subjects with SD. Presence of Hepatomegaly and gall bladder wall thickening were maximum in children with SD and may indicate presence of severe disease ($P<0.001$). Serum bilirubin, serum albumin, liver enzymes like ALT, AST, ALP were significantly raised in subjects with SD as compared to other two groups ($P<0.001$). MODS and FHF were found to be significant ($p<0.001$) in predicting outcome in patients with severe dengue.

Awareness and early identification of hepatic dysfunction in dengue may be helpful in arriving at early diagnosis and help avoid morbidity and mortality.

INTRODUCTION

Dengue is the most common mosquito borne, arboviral infection in many tropical and sub-tropical regions of the world. The incidence has increased 30-fold with increasing geographic expansion to new countries, and in the present decade from urban to rural settings.[1]

Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome. It causes a wide spectrum of illness from mild asymptomatic illness to severe fatal dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Unusual clinical manifestations of dengue fever (DF) have become more common in the last few years. Although the liver is not a major target organ, hepatic dysfunction is a well recognized feature. Liver dysfunction as a result of dengue infection can be a direct viral effect on liver cells or an adverse consequence of dysregulated host immune response against the virus. Hepatic involvement in dengue is known with a protean of manifestations ranging from hepatomegaly, elevated liver enzymes to fulminant hepatic failure.

Awareness of these manifestations of hepatic involvement in dengue may be helpful in arriving at early diagnosis and help avoid morbidity and mortality. However, very few studies regarding the hepatic dysfunction in children with dengue infections have been reported in India. In this study we attempted to study the pattern of hepatic involvement in children with dengue and its association with outcome of the disease.

MATERIALS AND METHODS

The present study was Prospective observational study conducted at a tertiary care centre for period of 2 years. Institutional Ethics Committee permission was obtained prior to starting of the study. The study group consisted of 220 confirmed cases of dengue fever.

All serologically confirmed cases (with either Dengue NS1 antigen or Dengue IgM antibody positivity) in the age group 2

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months to 12 years of either sex admitted in the paediatric wards and ICU were included in the study after obtaining written informed consent from the parents of the patients.

Patients with underlying comorbidities like previous hepatic disease, bleeding disorders, coagulation disorders, malaria, enteric fever, Hepatitis A and Hepatitis B or those testing negative for Dengue NS1 antigen or Dengue IgM antibody were excluded from the study.

World Health Organisation (WHO) guidelines were applied for categorization of patients into dengue without warning signs (DWWS), dengue with warning signs (DWS) and severe dengue (SD)[1,2].

A detailed history and a thorough clinical examination were done in all the cases. Data was collected in a prewritten proforma. All the cases were subjected to following investigations. Dengue NS1Ag, IgM ELISA, Complete blood count (Hb, TLC, DLC, Platelet count) Hematocrit and PS, Liver function test {serum bilirubin, serum alanine transaminase (ALT), serum aspartate transaminase (AST), serum alkaline phosphatase (ALP), serum albumin} Prothrombin time (P.T), INR, Widal test, Chest X-ray, Ultrasound abdomen and thorax.

Statistical analysis was done using software STATA version 13.1. Continuous variables like age, laboratory parameters like serum bilirubin, serum albumin, ALT, AST, ALP were presented as mean ± standard deviation. Categorical variables like sex, residence, symptoms, clinical signs were expressed in actual numbers and percentages. Categorical variables were compared across three groups by performing one- way ANOVA test. Pearson's chi- square test was used to compare outcomes with mortality.

For small numbers, Fischer exact test was applied. P value < 0.05 was considered as statistical significance.

RESULTS

Out of total 220 patients that were enrolled, 118 (53.6%) were in the group of DWWS, 52 (23.6%) subjects were allotted to DWS and 50 (22.7%) subjects were allotted in the SD group. Age distribution showed that 26 (11.8%) subjects belonged to the age group of 2 months- 1 year, 42(19%) subjects were in the age group of 1 year- 5 years while majority of the patients, 152 (69.2%) were in the age group of 5 years- 12 years.

Distribution of symptoms and signs in different groups is as shown in Table 1.

Fever (100%) was the chief complaint in all cases followed by body aches (58%), rashes (41.3%), edema (40.9%), headache (30.9%), petechiae (25.9%) abdominal pain (25%), vomiting (23.6%), mucosal bleed (15.4%) and jaundice (7.2%). Out of 220 children, 40.09% had hepatomegaly which was noticed more in SD and DWS (96% and 85%) than in DWWS (13.5%) group (*P*=0.006). Hepatic tenderness was observed in 26.8% of children, which was more in SD (56%) and DWS (53.8%), compared to DWWS (20.3%) group (*P*=0.001).

Hepatic involvement was seen in 90.45% out of which SD group had maximum no. of patients with hepatic dysfunction (96%). Profile of liver function tests (LFT) and ultrasound findings in different groups in dengue infection is shown in Table 2. Findings suggested that abnormal liver functions were significantly more in SD and DWS group.

Jaundice was present in 24% subjects with SD, 5.7% subjects with DWS and 0.8% subjects with DWWS. Hepatomegaly was present in 96% of the subjects with SD, which was statistically significant when compared with 13.5% and 85% in the other two groups.

Hypoalbuminemia was present in 65.3% subjects with DWS, 60% subjects with SD and 8.4% of the subjects with DWWS. ALT levels were raised in 92%, 85%, 72% of the subjects with SD, DWS, DWWS respectively which statistically significant with p value 0.008. Although AST levels were raised in 96% subjects with SD, 90% subjects with DWS and 88.1% of subjects with DWWS, the difference was not statistically significant. Alkaline phosphatase levels were raised in 46.61% cases with DWWS, 81% cases with DWS and 84% cases of SD and the difference was statistically significant with p value <0.001.

Coagulation abnormalities occurred in more numbers in subjects with SD as compared to the other groups. PT was prolonged in 40% and INR was deranged in 46% of the subjects with SD which was clinically significant.

Gall bladder wall thickening occurred in 58% subjects with SD, 21.1% subjects with DWS and 5.93% subjects with DWWS and the difference was statistically significant.

Outcome of subjects with severe dengue with hepatic involvement is shown in Table 3. Out of 50 subjects with severe dengue, 48 had hepatic dysfunction. Out of 20 subjects who developed Multiorgan Dysfunction Syndrome (MODS) 10 (50%) died. 38 subjects developed shock, of which 10 (26.31%) died.

Table 1 Distribution of symptoms and signs of dengue in the study population

Symptom	Dengue without warning signs n=118)	Dengue with warning signs (n=52)	Severe dengue (n=50)	Total (n=220)
Fever	118 (100%)	52 (100%)	50 (100%)	220 (100%)
Edema	28 (23.7%)	36 (69.2%)	26 (52%)	90 (40.9%)
Headache	49 (41.52%)	09 (17.30%)	10 (20%)	68 (30.9%)
Vomiting	07 (5.9%)	10 (19.2%)	35 (70%)	52 (23.6%)
Abdominal Pain	07 (5.9%)	13 (25%)	35 (70%)	55 (25%)
Bodyache	71 (60.16%)	34 (65.38%)	23 (46%)	128(58.1%)
Mucosal bleed	02 (1.6%)	15 (28.84%)	17 (34%)	34 (15.4%)
Petechiae	21 (17.79%)	19 (36%)	17 (34%)	57(25.9%)
Rash	56 (47.45%)	14 (27.1%)	21 (42%)	91(41.3%)
Jaundice	01 (0.8%)	03 (5.7%)	12 (24%)	16(7.2%)
Hepatomegaly	16 (13.5%)	44 (85%)	48 (96%)	108(49.09%)
Hepatic tenderness	07 (5.9%)	28 (53.8%)	28 (56%)	63(28.6%)

Table 2 Hepatic involvement in study population

Parameters		Dengue without warning signs (n= 118)	Dengue with warning signs (n= 52)	Severe dengue (n=50)	p-value
Clinical	Jaundice	1(0.8%)	3 (5.7%)	12(24%)	0.004,HS
	Hepatomegaly	16(13.5%)	44(85%)	48(96%)	<0.001,HS
Biochemical	Hyperbilirubinemia	1(0.8%)	3(5.7%)	12(24%)	0.004,HS
	Hypoalbuminemia	10(8.4%)	34(65.3%)	30(60%)	<0.001,HS
	Elevated ALT	85(72%) 104(88.1%)	44(85%)	46(92%)	0.008,HS
	Elevated AST		47(90%)	48(96%)	0.340,NS
	Elevated ALP	55(46.61%)	42(81%)	42(84%)	<0.001,HS
Coagulation	Prolonged PT	2 (1.6%)	16 (30%)	20(40%)	<0.001,HS
	INR		14(26.92%)	23(46%)	
Radiological	Hepatomegaly	18(15.2%)	45(86.5%)	48(96%)	<0.001,HS
	Gall bladder wall thickening	7(5.93%)	11(21.1%)	29(58%)	<0.001,HS

All the 7 subjects who developed fulminant hepatic failure (FHF) died (P <0.001).

Table 3 Outcome of subjects with severe dengue with hepatic involvement

Cases of severe dengue with hepatic involvement (n=48)	Number of cases	Death	Survival	
MODS	20	10 (50%)	10 (50%)	P < 0.001
Shock	38	10 (26.31%)	28 (73.68%)	p 0.094
Fulminant hepatic failure	7	7 (100%)	0	P <0.001

DISCUSSION

In this study, an attempt has been made to study the profile of hepatic involvement and its prognostic significance in children with dengue infection.

Although dengue virus is a non- hepatotropic virus, liver injury due to dengue infection is not uncommon.[3,4] One-third of dengue infections experience liver derangements. Histopathological changes such as fatty changes, centrilobular necrosis, and monocyte infiltration of portal tract have been described. Strong correlation between T-cell activation and hepatic cell infiltration have been noted.[32] Fulminant hepatic failure due to hepatitis or focal necrosis of the liver and hepatic encephalopathy have been reported increasing the risk of mortality in dengue.[5]

The mechanism of hepatocyte damage in dengue infections is poorly understood. Some of the mechanisms proposed are direct viral effect of the dengue virus and induction of apoptosis, dysregulated host immune responses against the virus, nonspecific effect of shock and hypotension, localized vascular leakage inside the liver capsule, hepatotoxic effects of drugs such as acetaminophen or traditional herbal remedies. [6-9]

Hepatic manifestations can be characterised by manifestation of acute hepatitis with pain in the right hypochondrium, hepatomegaly, jaundice, raised aminotransferase levels and rarely as acute liver failure. Liver enlargement is the most obvious sign of the liver involvement in dengue infections. The frequency of liver enlargement was similar in both primary and secondary dengue infections. While some studies suggest that a moderate liver enlargement may be a part of the 'normal' pathological response to dengue infections, other studies support a higher rate of hepatomegaly in DHF/DSS cases. Shivbalan *et al* found ALT, tender hepatomegaly and abdominal pain to be significant predictors for bleeding in dengue children.[10]

An Indian study reported correlation between mortality and severe liver dysfunction in children with dengue infection.[11]

Our data suggests that hepatic dysfunction more common in subjects with SD. The degree of liver function tests derangement was significantly more in SD as compared to other two groups.

Hepatomegaly is one of the common clinical signs (96% of subjects with severe dengue) and gall bladder wall thickening is common radiological sign (58% of subjects with severe dengue) of dengue infection and may indicate presence of severe disease (P<0.001).

Similar association of hepatomegaly in dengue has been reported in study done by Kalenahalli *et al*. [12]

In our study serum bilirubin, serum albumin, liver enzymes like ALT, AST, ALP were significantly raised in subjects with SD as compared to other two groups. P value is significant for all parameters except for AST. AST is raised in all the three groups and the p value is insignificant and cannot predict the severity and outcome of dengue. While majority of the patients have only mild or moderate elevation of these transaminases, some of them have levels elevated by 10-fold or greater. In dengue infections, the levels of serum AST are greater than serum ALT, which is in contrast to the normal finding with viral hepatitis. It has been suggested that this may be due to excess release of AST from damaged myocytes during dengue infection. The elevation of the AST level is usually higher than that of ALT in patients with dengue fever during the first week of infection, with a decrease to normal levels within three weeks. Similar findings were presented in study done by Gandhi K. *et al* and they predicted that the prominence of musculoskeletal symptoms in dengue, skeletal muscle injury could explain the higher AST levels.[13]

FHF is unusual in dengue infection and comparatively more common in paediatric age group than adults. Predisposing factors include race, diabetes and sickle cell anaemia. FHF is a severe complicating factor in dengue infection predisposing to life threatening haemorrhage, disseminated intravascular coagulation and encephalopathy.[14] In our study, 10 subjects died, 22 subjects had MODS and 40 subjects had shock and all belonged to the severe dengue group. Fulminant hepatic failure was present in 7 subjects none of them survived.

CONCLUSION

Hepatic involvement is common in severe forms of dengue and increases the risk of mortality in these cases. Clinical signs and symptoms make it difficult to differentiate hepatic dysfunction

in dengue from other commoner causes such as viral hepatitis. High index of suspision is important for diagnosis of these patients for improving outcome of the disease. Presence of fever, jaundice and hepatomegaly in endemic areas should arouse the suspicion of dengue hepatitis. Elevated serum ALT, hepatomegaly were consistently associated features of dengue hepatitis however, association with the severity of the disease could not be ascertained due to the small sample size. In this study, MODS and fulminant hepatic failure were found to be significant ($p<0.001$) in predicting outcome in patients with severe dengue.

As the hepatic damage in dengue infection at majority of times is transient and reversible, it is important to identify hepatic dysfunction in dengue to avoid life threatening complications. This will decrease the mortality and morbidity due to dengue infections.

Small sample size and follow up only till discharge are the limitations of this study and more studies are required to know long term residual hepatic dysfunction in dengue.

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