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A hospital-based study of hepatic dysfunction in children with dengue fever

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ABSTRACT

Objective: To study the hepatic dysfunction in children with dengue infection and find out its correlation with the severity of dengue fever.

Methods: Seventy-two cases of dengue fever as per the World Health Organization aged from 2 months to 18 years of age guidelines serologically confirmed by dengue NS1 antigen detection or dengue IgM capture ELISA were studied for their hepatic dysfunction after excluding malaria, enteric fever, hepatitis A and hepatitis B. The duration of the study was from April 2013 to March 2014.

Results: These 72 cases were grouped into severe dengue, dengue fever with warning sign and dengue fever without warning sign as per the World Health Organization guidelines. The spectrums of hepatic manifestations included hepatomegaly (66%), hepatic tenderness (44%), jaundice (9.72%), raised levels of aspartate transaminase (86%), alanine transaminase (90%), alkaline phosphatase (39%), prolonged prothrombin time (11%) and reduced levels of serum albumin (66%).

Conclusions: Tender hepatomegaly and elevated liver enzymes were seen more frequently in severe dengue. There was significant derangement between liver function and tender hepatomegaly. Altered liver function may be evident even in the absence of hepatomegaly.

1. Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, the incidence of the disease has increased by 30 folds with the increasing geographic expansion to new countries, and in the present decade, its incidence extends from urban to rural settings. Some 1.8 billion (more than 70%) of the population who are at risk of dengue worldwide live in the member states of the World Health Organization (WHO), South-east Asia region and Western Pacific region, which bear nearly 75% of the current global disease burden due to dengue[1]. Recently, an increasing trend of outbreaks of dengue fever (DF) and its complicated forms have been reported in India[2].

Dengue viral infections are known for presenting a diverse clinical spectrum, ranging from asymptomatic illness to fatal

dengue shock syndrome (DSS)[3]. Hepatic injury with dengue infection has been described since 1967[4]. The degree of liver dysfunction in children with dengue infection varies from mild injury with elevation of transaminase activity, hepatomegaly (tender/non-tender) to severe injury with jaundice and fulminant hepatic failure[5].

2. Materials and methods

The present study was conducted in the Department of Pediatrics of Sawai Man Singh Medical College, Jaipur, from April 2013 to March 2014. All the clinically suspected cases of dengue infections aged from 2 months to 18 years as per the WHO guidelines were screened and only serologically confirmed cases by dengue NS1 antigen detection or dengue IgM capture ELISA were included in this study. A detailed history and a thorough clinical examination were done for all those cases. Ethical approval was obtained from the Ethical Committee of the Sawai Man Singh Medical College, Jaipur, and the written informed consents were obtained from their parents. Malaria, enteric fever, hepatitis A and hepatitis B were excluded by history, examination and investigations.

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All the cases were subjected to investigate liver function tests including total serum bilirubin (TSB), direct serum bilirubin, indirect serum bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), serum albumin and prothrombin time (PT)/international normalized ratio (INR).

Estimated minimal sample size required for this study was 61 cases of dengue infection. Statistical methods employed for data analysis were descriptive statistics, and cross tables and *t*-test were used for comparison of means. A total of 75 cases formed the study group out of which 3 were excluded because they were associated with other infections.

3. Results

The study group included 72 children aged from 2 months to 18 years satisfying the WHO criteria for DF after excluding malaria, enteric fever, hepatitis A and hepatitis B.

Out of total 72 patients, 70.83% of cases were males and 29.17% of cases were females. The sex ratio was about 2.43:1. The maximum numbers of patients [29 (40.28%)] were in the age group of 6–10 years.

Out of those enrolled 72 patients, 17 (23.61%) were in severe dengue, 48 (66.67%) in DF with warning sign and 7 (9.72%) in DF without warning sign based on the classification by WHO (2009). Pain abdomen and vomiting were the commonest presenting complaints next to fever which was present in all cases. Incidence of pain abdomen and vomiting in severe dengue and DF with warning sign were 88% and 91%, respectively.

As shown in Table 1, liver markers were deranged in all three groups of DF. It was observed that all patients have raised level of serum glutamic-oxaloacetic transaminase (SGOT) above normal except one patient in DF with warning sign group. About 65 (90.28%) patients were with SGOT level raised more than normal limit. ALP level was raised in 28 (38.89%) out of 72 patients. In our study, 7 (9.72%) cases had clinically evident jaundice. Out of the 7 cases, 5 (29.41%) were in severe dengue group and 2 (4.16%) were in DF with warning sign group. PT/INR was deranged in 8 (11.11%) patients out of 72 patients. Hypoalbuminemia was observed in 48 (66.67%) out of 72 patients. In severe dengue, DF with warning sign and DF without warning sign groups, hypoalbuminemia were observed in 82.35%, 62.50% and 57.14% patients respectively.

As shown in Table 2, there was no significant difference in mean value of liver markers and increasing severity of DF.

Hepatomegaly was the commonest clinical sign [48 (66%)] seen more frequently in severe dengue group [14 (82%)] as compared to DF with warning sign [34 (70.83%)]. As shown in Table 3, there was significant association between TSB, ALP, PT/INR and presence of hepatomegaly. It was observed that convulsions and altered sensorium were seen only in 2 patients.

As shown in Table 4, hepatic tenderness was observed in 32 (44.45%) patients, more frequently in severe dengue [14 (82%)] in comparison to DF with warning sign [18 (37.5%)]. There was significant association between mean LFTs levels and increasing severity of DF in patients with tender hepatomegaly except TSB level and ALP level.

Table 1
Profile of LFT in different groups of DF. *n* (%).

Group	TSB > 2 mg/dL	Elevated SGOT/ALT (IU/L)	Elevated SGPT/AST (IU/L)	Elevated ALP (IU/L)	Hypoalbuminemia < 3.2 mg/dL	Prolonged INR > 1.5
Severe dengue (<i>n</i> = 17)	5 (29.41)	17 (100.00)	17 (100.00)	13 (76.47)	14 (82.35)	6 (35.29)
DF with warning sign (<i>n</i> = 48)	2 (4.16)	47 (97.91)	41 (85.41)	13 (27.00)	30 (62.50)	2 (4.00)
DF without warning sign (<i>n</i> = 7)	0 (0.00)	7 (100.00)	7 (100.00)	2 (28.57)	4 (57.14)	0 (0.00)

SGPT: Serum glutamic pyruvic transaminase.

Table 2
Mean values of hepatic markers in different groups of DF.

Group	Mean TSB (mg/dL)	Mean SGOT/ALT (IU/L)	Mean SGPT/ALT (IU/L)	Mean ALP (IU/L)	Mean albumin (mg/dL)	Mean INR
Severe dengue (<i>n</i> = 17)	2.03 ± 1.80	881.18 ± 383.15	652.59 ± 236.18	165.41 ± 54.00	3.05 ± 0.42	1.38 ± 0.35
DF with warning sign (<i>n</i> = 48)	1.05 ± 0.92	208.10 ± 146.13	125.08 ± 72.49	117.66 ± 52.70	3.33 ± 0.35	1.13 ± 0.16
DF without warning sign (<i>n</i> = 7)	0.87 ± 0.15	179.28 ± 116.86	92.71 ± 49.35	111.14 ± 18.54	3.30 ± 0.28	1.08 ± 0.10
<i>P</i> value	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table 3
Mean value of liver function tests according to hepatomegaly.

Hepatomegaly	TSB (mg/dL)	SGOT (IU/L)	SGPT (IU/L)	ALP (IU/L)	Albumin (mg/dL)	PT/INR
Absent (<i>n</i> = 24)	0.94 ± 0.34	265.05 ± 104.02	138.10 ± 53.34	110.45 ± 20.62	3.34 ± 0.29	1.10 ± 0.15
Present (<i>n</i> = 48)	1.40 ± 0.41	406.09 ± 154.52	290.58 ± 93.05	134.75 ± 62.07	3.21 ± 0.41	1.21 ± 0.26
<i>P</i> value	< 0.05	> 0.05	> 0.05	< 0.05	> 0.05	< 0.05

Table 4
Mean of various parameters of LFTs with tender hepatomegaly according to the severity of dengue.

Group	TSB (mg/dL)	SGOT/AST	SGPT/ALT	ALP	Albumin (mg/dL)	PT/INR
Severe dengue (<i>n</i> = 14)	2.17 ± 0.95	1023.86 ± 326.84	757.36 ± 99.58	176.28 ± 53.36	2.88 ± 0.35	1.43 ± 0.36
With warning sign (<i>n</i> = 18)	1.11 ± 0.23	177.22 ± 75.14	120.17 ± 69.76	132.72 ± 76.88	3.34 ± 0.44	1.14 ± 0.13
<i>P</i> value	> 0.05	< 0.01	< 0.05	> 0.05	< 0.01	< 0.01

4. Discussion

Hepatic involvement due to dengue infection is not uncommon and has been described since 1970[6]. Hepatic dysfunction is a well recognized feature of dengue infections and varying degree of dengue hepatitis is seen[7].

Hepatomegaly is one of the commonest clinical sign of dengue infection. The association of hepatomegaly with cases of dengue infection has been quite variable, and the incidence varies from 43% to 98%[3,6,8,9]. Hepatomegaly is considered as enlarged liver of 2 cm or more. This indicates that hepatomegaly may be used as a predictor for assessing the severity of the disease.

Senevatne *et al.* observed a higher incidence of hepatomegaly with dengue hemorrhagic fever (DHF) than DF[7]. Wahid *et al.* has observed a slightly higher incidence of hepatomegaly in DHF (60%) group compared to DF (40%) group in their study[10]. A similar study performed by Jagadish *et al.* concluded 21% of cases with hepatomegaly in DF group and 48% in DHF group[11]. Another study done by Wichmann *et al.* reported 70% of DSS cases having hepatomegaly and only 43% of DF cases presented with hepatomegaly[12]. The study by Chairulfatah *et al.* concluded that the number of children with hepatomegaly were significantly higher in DSS as compared to non DSS cases[13]. A study by Roy *et al.* reported hepatomegaly in 80.8% children out of 120 patients[14].

In the present study, hepatic tenderness was observed in 32 (44.45%) patients, and it was seen more frequently in the severe dengue group [14 (82%)] in comparison to the DF with warning sign [18 (37.5%)]. Incidence of tender hepatomegaly is significantly higher in shock cases.

Vazquez-Pichardp *et al.* showed 30% of cases presented in DSS to be having tender hepatomegaly[15]. Similar study by Wichmann *et al.* reported an incidence of 65% cases with DSS presenting with tender hepatomegaly as compared to 45% in non DSS[12]. A study by Roy *et al.* showed 46.3% patients presented with tender hepatomegaly[14]. A study by Sahana *et al.* found hepatomegaly in 51.9% and abnormal LFT in 33.3% patients[16]. Another study by Sharma *et al.* included 60 patients who tested positively for NS1 antigen for dengue[17]. Cases were divided into 3 groups: dengue without warning signs, dengue with warning signs and severe dengue in 11.7%, 83.3% and 5%, respectively. Transiently elevated transaminase levels (9%), ascites (23%) and shock were observed in 5% cases. The natural course of altered liver enzymes in dengue infection has been reported by various studies. Mohan *et al.* reported that levels of AST and ALT were raised during the 1st and 2nd week, respectively. Serum ALP levels also showed similar trend. It was also shown that hepatic dysfunction in the form of marked elevated enzymes was higher in severe and complicated dengue in comparison to classical DF[9]. In present study, it was observed that all patients have raised level of SGOT except one patient in DF with warning sign. Mean SGOT in groups of severe dengue, DF with warning sign and DF without warning sign were 881.18, 208.10 and 179.28 IU/L, respectively.

There were 7 patients who had clinically evident jaundice. The mean AST of these patients was 735.3 IU/L. The highest recorded AST was 3780 IU/L. There was no significant difference in the SGOT values in the presence of hepatomegaly.

Study by Mohan *et al.* also observed deranged AST levels frequently in DSS cases in comparison to non shock cases[9]. Souza *et al.* found that the mean value of AST in DHF was 127.1 IU/L and in DF was 89.8 IU/L[18]. They have reported an incidence of 63.4%

cases with elevated AST. Kuo *et al.* have reported that 93.3% cases of dengue infection had elevated AST levels[8]. Similarly, Nguyen *et al.* showed that 97.7% cases of dengue infection had raised AST levels[19]. In a study by Sedhain *et al.*, liver enzyme SGOT was increased with the value more than 50 IU/mL in 78.4% and 96.5% of cases of DF and DHF, respectively[20]. In a study by Gandhi *et al.* 23 (85%) of the patients had elevation of at least one of the liver enzymes ($P < 0.001$) with alterations in SGOT[21]. In a study by Roy *et al.*, there was 84.4% and 93.75% of ALT and AST elevation respectively in DF with warning sign and 94.5% and 95.9% of ALT and AST elevation respectively in severe dengue and fulminant hepatic failure was observed in severe dengue group[14].

In the present study, 65 (90.28%) patients having SGOT level raised more than its normal limit. All the patients in groups of severe dengue and DF without warning sign have raised SGOT level, while 85.41% patients in DF with warning sign have raised level. Mean SGPT in groups of severe dengue, DF with warning sign and DF without warning sign were 652.59, 125.08 and 92.71 IU/L respectively. A similar study performed by Mohan *et al.* found that 100% of cases in DSS and DHF group had elevated ALT enzyme levels in comparison to 81% in DF children[9].

Itha *et al.* didn't observe any significant difference in the enzyme values in DF (22%) and DHF (27%) group but higher incidence was observed in children who presented DSS (86%)[22]. Narayanan *et al.* found 63.7% cases in dengue shock vs. 58.7% cases in non shock cases to be having elevated ALT enzyme levels[23].

Souza *et al.* found that 45% of cases had raised ALT levels with mean value of 100.2 IU/L in DHF and 84.6 IU/L in DF[18].

There were 7 patients who had clinically evident jaundice. The mean SGPT of these 7 patients was 888.66 IU/L. The highest recorded SGPT was 3900 IU/L. There was no significant difference in the ALT values between tender and non tender hepatomegaly children.

In our study, SGOT levels were elevated in more children in all the three groups as compared to SGPT values. Similar study done by Kuo *et al.* reported similar results with elevation of AST and ALT in 93.3% and 82.2% patients respectively[8]. Petdachai *et al.* noted that levels of AST were higher than those of ALT[24].

Like other studies, the majority of our patients had elevated liver enzymes in the present study with SGOT being more elevated than SGPT values. Patients with severe and complicated dengue had higher level of hepatic enzyme dysfunction.

In present study, ALP level raised in 28 (38.89%) out of 72 patients. In groups of severe dengue, DF with warning sign and DF without warning sign groups, the raised ALP levels were 32.5%, 37.14% and 40% respectively. Vazquez-Pichardp *et al.* observed an incidence of 35.3%[15], whereas Kuo *et al.* observed a slightly lower incidence of 16% with elevated ALP values[8]. Mohan *et al.* observed that the mean values of AST, ALT and ALP were significantly higher in children with DSS as compared to DF[9]. Wahid *et al.* had reported that the mean levels of ALP were higher in DHF as compared to DF[10].

In the present study, the mean TSB in severe dengue, DF with warning sign and DF without warning sign were (2.03 ± 1.80) , (1.05 ± 0.92) and (0.87 ± 0.15) mg/dL respectively with highest of 6.21 mg/dL. All of them had elevated liver enzymes with 4 of them having more than 20 folds rise in SGOT levels. Two patients had more than 20 folds rise in SGPT value with highest SGPT of 3900. The increase in aminotransferases, mainly SGOT, has been associated

with the disease severity and may serve as an early predictor of dengue infection. Mohan *et al.* reported a higher incidence of 25% as compared to 16% by Itha *et al.*[19,22]. None of the patients had jaundice in the study by Petdachai[24].

There was statistically significant difference in serum albumin and increasing severity of DF. In patients with tender hepatomegaly, the mean serum albumin was (2.88 ± 0.35) mg/dL and it is significant. Wong and Shen reported an incidence of 16.53% with hypoalbuminemia[25]. Similarly, a case report by Mourão *et al.* had demonstrated hypoalbuminemia[26]. Petdachai reported a mean albumin value in all the cases (below 3.5 mg/dL). The mean serum albumin with hepatic dysfunction was 2.9 mg/dL and without hepatic dysfunction was 3.1 mg/dL[24].

In our study, the PT/INR was deranged in 8 (11.11%) patients out of those 72 patients. In severe dengue and DF with warning sign groups, deranged PT/INR were 54.54% and 4.34%, respectively. PT/INR level was within normal range in all patients in DF without warning sign group. A study by Roy *et al.* found abnormal PT/INR in 41.7% cases[14]. Another study by Chhina *et al.* observed deranged PT/INR in 15.5% (22/156) cases[27].

In a developing country like India, the incidence and prevalence of infectious diseases are high with upsurge in outbreaks of dengue. Hepatic involvement in dengue infection of varying and severe degrees has been reported recently in association with the increasing number of cases with secondary dengue infection. As there is a clinical overlap in dengue hepatitis with viral hepatitis, enteric hepatitis and malaria, it is likely for dengue hepatitis to be missed. As the hepatic damage in dengue infections at majority of times is transient and reversible, it is the responsibility of clinicians to identify the hepatic dysfunction associated with the disease early in order to avoid life-threatening complications. This will decrease the mortality and morbidity of dengue infections.

Conflict of interest statement

We declare that we have no conflict of interest.

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