Liver function tests in patients with dengue viral infection

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Abstract

To assess the frequency and degree of hepatic dysfunction in patients with dengue infection, records of 214 serologically confirmed cases of dengue infection with available biochemical liver tests, admitted to our tertiary-care institute, were analysed. Patients were classified as classical dengue fever (DF) – 81.3%, dengue haemorrhagic fever (DHF) – 13.6% and dengue shock syndrome (DSS) – 5.1%. The mean age was 31.6 years (male:female = 3.3:1). Deranged total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin and prothrombin time index (PTI) [international normalized ratio (INR)] was present in 19.5% (29/143), 97.7% (209/214), 93.9% (199/214), 32.6% (47/144), 29.1% (44/151) and 15.5% (22/156) patients respectively. The mean (± SE) total bilirubin, AST, ALT, ALP, albumin and INR values were 0.93 ± 0.09 mg/dl, 353.7 ± 49.6 U/L, 218.6 ± 27.2 U/L, 135.2 ± 6.5 U/L, 3.2 ± 0.04 g/dl and 1.2 ± 0.03 respectively. The mean value of AST was significantly higher than ALT. The degree of rise of AST and ALP was significantly more in DHF and DSS, as compared to DF; but the frequency of rise was similar in all groups. Mean serum bilirubin, ALT and ALP values were significantly higher in patients with haemorrhage as compared to those without haemorrhage, in patients with secondary dengue infection as compared to primary infection, and in non-survivors. Hepatic dysfunction was very common in all forms of dengue infection, with AST rising significantly more than ALT. Serum bilirubin, ALT and ALP were significantly higher in patients with DSS, haemorrhage, sequential infection and non-survivors. While preferentially high AST may serve as an early indicator of dengue infection, high bilirubin, ALT and ALP may act as poor prognostic markers.

Keywords: Dengue infection; Hepatic dysfunction; Aspartate aminotransferase (AST); Alanine aminotransferase (ALT); Alkaline phosphatase (ALP).

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Introduction

Dengue infection, an arthropod-borne viral haemorrhagic fever, continues to be a major challenge to public health, especially in South-East Asia[1]. It has a wide geographical distribution and can present with a diverse clinical spectrum[2]. Although dengue virus is a non-hepatotropic virus, liver injury due to dengue infection is not uncommon and has been described since the 1960s[3]. The degree of liver dysfunction in dengue infection varies from mild injury with elevation of aminotransferases alone to severe injury with jaundice and even fulminant hepatic failure[2,4]. The liver dysfunction could be a direct viral effect or an adverse consequence of dysregulated host immune response against the virus[2]. Several outbreaks of dengue infection have been reported from India[5,6,7,8]. However, large clinical studies documenting hepatic involvement in dengue infection, especially in adults, are scarce.

The aim of this study was to assess the frequency and degree of hepatic dysfunction in patients with dengue infection presenting to a tertiary-care medical facility in Punjab. Punjab is a state located in north India with an area of 50 362 sq km, extending from latitudes 29° 30′ to 32° 32′ North and longitudes 73° 55′ to 76° 50′ East.

Materials and methods

An outbreak of dengue infection was noted in the state of Punjab during the last quarter of 2006. During this period, 2205 patients presented to Dayanand Medical College and Hospital, Ludhiana, Punjab, India, with acute febrile illness. The provisional clinical diagnosis of dengue infection was made on the basis of a history of fever of short duration (<15 days) and constitutional symptoms, with or without haemorrhagic manifestations. These patients were screened for dengue-specific IgM and IgG antibodies by IgM and IgG capture ELISA respectively (Panbio Diagnostics, Brisbane, Australia). IgM and IgG antibody positivity was found in 366 and 76 patients respectively. The mortality rate was 1.9% (7/366). Medical records of all adult patients with available liver function tests (LFT) (n=214) were analysed for their clinical presentation, degree of hepatic involvement, hospital course and outcome. Hepatitis markers (HBsAg, IgM antibody to HAV and HEV) were done in the clinically suspected cases (53 patients).

Patients were divided into three categories: (a) classical dengue fever (DF); (b) dengue haemorrhagic fever (DHF); and (c) dengue shock syndrome (DSS), according to the WHO criteria[9]. Non-survival was taken as poor outcome and survival as good outcome in our study.

The statistical analysis was done using the Fischer's exact test and Student's unpaired *t*-test for significance of difference in proportions and means between two groups respectively.

Results

Of the 214 patients reactive for dengue virus-specific IgM antibody, dengue virus-specific IgG antibody was also positive in 43 (20.1%) patients. One hundred and seventy four (81.3%) patients were classified as dengue fever, 29 (13.6%) as dengue haemorrhagic fever, and 11 (5.1%) as dengue shock syndrome. Further, 17.8% (31/174) patients with DF, 13.8% (4/29) patients with DHF, and 72.7% (8/11) patients with DSS had positive IgG antibody, indicating sequential infection. Markers for hepatitis A, B, C and E viruses were done in 53 patients and found to be negative in all.

The mean age of patients in our study was 31.6 years with a range of 15 to 80 years. The maximum number of patients (n=71; 33.2%) belonged to the age group of 21–30 years. There were 164 (76.6%) males and 50 (23.4%) females (male:female ratio = 3.3:1).

The main presenting symptoms were fever (100%, 214/214), myalgias (43%, 92/214), haemorrhagic manifestations (40.6%, 87/214), vomiting (37.4%, 80/214) and abdominal pain (20%, 43/214). Encephalopathy was observed in 3 (1.4%) patients; one each belonged to DF, DHF and DSS groups. The gastrointestinal tract was the most common site of haemorrhage (n=42/214, 19.6%), followed by skin rash/petechiea (n=22/214, 10.3%). The clinical examination revealed hepatomegaly in 26 (12.1%) patients, splenomegaly in 4 (1.9%) and ascites in 4 (1.9%) patients. The mean (±SE) haemoglobin, haematocrit, total leukocyte count and platelet count at admission were 13.8 ± 0.17 gm/dl, 40.6 ± 0.5%, 6123 ± 339 cells/mm^3 and 48.5 ± 2.6 x 1000/mm^3 respectively.

Hepatic dysfunction, in the form of deranged total bilirubin, AST, ALT, ALP, albumin and PTI (INR) was present in 19.5% (29/143), 97.7% (209/214), 93.9% (199/214), 32.6% (47/144), 29.1% (44/151) and 15.5% (22/156) patients respectively. The mean (±SE) total bilirubin, AST, ALT, ALP, albumin and INR values were 0.93 ± 0.09 mg/dl, 353.7 ± 49.6 U/L, 218.6 ± 27.2 U/L, 135.2 ± 6.5 U/L, 3.2 ± 0.04 g/dl and 1.2 ± 0.03 respectively. The mean value of AST was significantly higher than the mean ALT value (p=0.017). A comparison between the degree of rise of ALT and AST is shown in Fig. 1. Significantly more percentage of patients had AST values >10 times elevated as compared with ALT ($p < 0.0001$).

Figure 1: Comparison between ALT and AST elevation in patients with dengue infection (n=214)

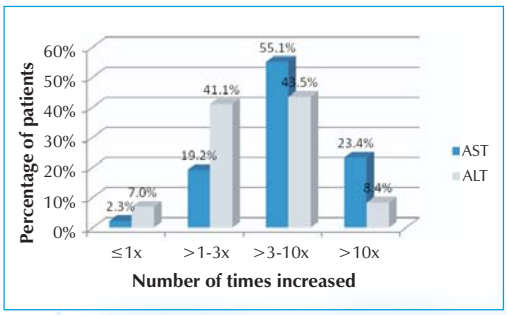


Figure 2(a): Comparison of the pattern of rise of AST in patients with DF, DHF and DSS

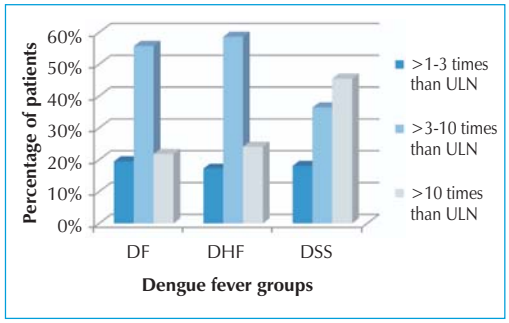


Figure 2 (b): Comparison of the pattern of rise of ALT in patients with DF, DHF and DSS

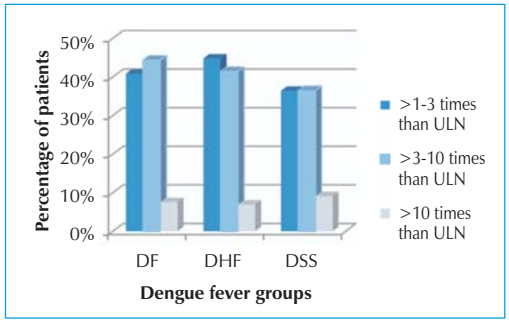
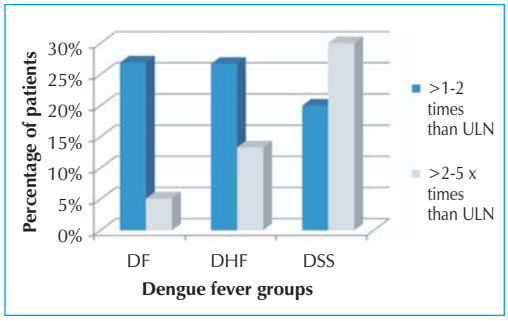


Figure 2 (c): Comparison of the pattern of rise of ALP in patients with DF, DHF and DSS



DF= Classical dengue fever, DHF = Dengue hemorrhagic fever, DSS = Dengue shock syndrome, ULN = Upper limit of normal

Table 1: Comparison of biochemical liver test derangements in patients with DF, DHF and DSS

Liver biochemical test		DF (n= 174)	DHF (n=29)	p value*	DSS (n=11)	p value**
T. bilirubin (mg/dl) (n=143)†	Mean ± SE	0.79 ± 0.08	0.89 ± 0.13	0.623	2.7 ± 0.97	0.0001
	No (%) of patients with > ULN	16/118 (13.5 %)	4/14 (28.6%)	0.226	9/11 (81.8%)	0.0001
AST (IU/L) (n=214)†	Mean ± SE	277.18 ± 20.5	478.4 ± 163.5	0.016	1234.7 ± 787.6	0.0001
	No (%) of patients with > ULN	169/174 (97.1%)	29 (100%)	1.00	11 (100%)	1.000
ALT (IU/L) (n=214)†	Mean ± SE	174.6 ± 11.05	254.5 ± 80	0.059	819 ± 431.5	0.0001
	No (%) of patients with > ULN	161/174 (92.5%)	27/29 (93.1%)	1.00	11 (100%)	1.000
ALP (IU/L) (n=144)†	Mean ± SE	122.44 ± 4.7	166.7 ± 28.9	0.007	241.5 ± 60	0.0001
	No (%) of patients with > ULN	36/119 (30.3%)	6/15 (40 %)	0.056	5/10 (50%)	0.29
Albumin (g/dl) (n=151)†	Mean ± SE	3.3 ± 0.04	3.0 ± 0.17	0.013	2.7 ± 0.18	0.0004
	No (%) of patients with < LLN	32/121 (26.4%)	8/20 (40 %)	0.283	4/10 (40 %)	0.46
PTI (n=158)†	Mean ± SE	1.1 ± 0.02	1.2 ± 0.06	0.069	1.3 ± 0.11	0.018
	No (%) of patients with > ULN	12/127 (9.4%)	4/20 (29%)	0.236	6/11 (54.5%)	0.0007

All data expressed as mean ± standard error (SE).

† = Number of patients in which the particular test was available.

*p value = p value between DF and DHF groups.

**p value = p value between DF and DSS groups.

DF = Classical dengue fever, DHF = Dengue hemorrhagic fever, DSS = Dengue shock syndrome, ALP = Alkaline phosphatase, ALT = Alanine transaminase, AST = Aspartate transaminase, PTI = Prothrombin time index, LLN = Lower limit of normal, ULN = Upper limit of normal.

A comparison between the mean values of various liver biochemical tests in different groups of dengue infection, and the number of patients with abnormal tests is shown in Table 1 and Figures 2(a), 2(b) and 2(c). All the liver biochemical tests were significantly more deranged in the DSS group as compared to the DF group. Also, the percentage of patients

Table 2: Comparison of biochemical liver test derangements between various patient groups

Characteristic	Bilirubin (mg/dl)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
1. Sex				
Male (164)	0.99 ± 0.1	380 ± 63.4	241 ± 34.9	129 ± 6.7
Female (50)	0.69 ± 0.08	266.4 ± 40.3	144.3 ± 14.9	159 ± 17.4
p value	0.109	0.333	0.131	0.053
2. Haemorrhage				
With haemorrhage (n=87)	1.13 ± 0.18	464.5 ± 116.3	290.4 ± 64.0	154.6 ± 13.6
Without haemorrhage (n=127)	0.79 ± 0.08	277.8 ± 24.4	169.3 ± 11.8	121.8 ± 5.5
p value	0.05	0.064	0.028	0.012
3. Gastrointestinal haemorrhage				
GI haemorrhage (n=42)	1.4 ± 0.32	591.4 ± 212.9	326.9 ± 107.7	158.9 ± 22.3
Without haemorrhage (n=127)	0.79 ± 0.08	277.8 ± 24.4	169.3 ± 11.8	121.8 ± 5.5
p value	0.008	0.016	0.016	0.021
4. Primary/secondary dengue infection				
IgM reactive (n=171)	0.68 ± 0.05	312 ± 33.1	190 ± 16.7	123.5 ± 5.8
IgM and IgG reactive (n=43)	1.8 ± 0.36	519 ± 56.8	332 ± 117.2	174.5 ± 20.9
p value	0.0001	0.096	0.036	0.0012
5. Survival				
Survivors (n=207)	0.84 ± 0.07	349.9 ± 50.6	207.5 ± 25.1	130.1 ± 5.9
Non-survivors (n=7)	3.15 ± 1.6	463.3 ± 250.5	544.7 ± 372.1	241.7 ± 72.4
p value	0.0001	0.684	0.026	0.001

All data expressed in mean ± standard error.

ALP = Alkaline phosphatase, ALT = Alanine transaminase, AST = Aspartate transaminase

having hyperbilirubinemia and deranged PTI was significantly more in the DSS group as compared to the DF group. On a comparison of the DF and DHF groups, it was observed that the mean values of AST, ALP and albumin were significantly different in the two groups.

A comparison of the biochemical liver tests in various patient subgroups (Table 2) showed that serum bilirubin, ALT and ALP values were significantly higher in patients with haemorrhage as compared to those without haemorrhage, and were even higher in the patients with GI haemorrhage. It was also noted that bilirubin, ALT and ALP were significantly higher in patients with secondary infection as compared to primary infection and in non-survivors as compared to those who survived. The AST value was significantly more deranged only in patients with GI haemorrhage as compared to those without haemorrhage. There was no significant difference in the LFTs between male and female patients and in the patients with or without encephalopathy.

Discussion

The clinical and biochemical impact of dengue virus on liver function was studied on 214 serologically confirmed cases of dengue infection during an outbreak in north India in 2006. In this study, DHF and DSS were present in 13.6% (29/214) and 5.1% (11/214) patients respectively. This is in accordance with the results of a recent study from Delhi[8] (DHF and DSS in 9.3% and 2.2% respectively). However a few other studies had reported a higher percentage of DHF[6,7].

Impaired consciousness was seen in only three patients in our study. LFT abnormalities in these patients were not significantly different from those without encephalopathy, indicating that liver failure was not the cause of altered sensorium in these patients. Other possible reasons for the neurological symptoms in dengue infection are metabolic acidosis, severe disseminated intravascular coagulation, gross haemorrhage or edema in the brain, or hyponatremia due to excessive fluid administration.

Hepatomegaly was observed in 12.1% patients in this study, compared to 17.6%–20.4% in other Indian studies[5,6]. The relative higher incidence of hepatomegaly reported by Sharma et al.[5] could be attributed to the fact that all their patients belonged to the DHF group. Although liver size does not correlate with disease severity, an enlarged liver is observed more frequently in shock than in non-shock cases[9]. In our study, too, hepatomegaly was more frequent in the DSS group as compared to DF group (45.5%; 5/11 v/s 10.9%; 19/174; $p < 0.05$).

Biochemical liver dysfunction, in the form of increased transaminases, was found in most of the patients in our study (93.9%–97.7%), similar to the results of other studies[5,6,7,10]. However, in a study by Souza et al.[11], AST and ALT were deranged only in 63.4% and 45% patients respectively. In our study, increased levels of ALP and serum bilirubin were noted in a smaller proportion of patients, in accordance with the results of Itha et al.[7]

The aspartate aminotransferase (AST) levels in dengue infection tend to be greater than alanine aminotransferase (ALT) levels[12,13]. This differs from the pattern in viral hepatitis but is similar to that seen in alcoholic hepatitis. The exact cause of this is uncertain, but it has been suggested that it may be due to excess release of AST from damaged monocytes during dengue infection[10]. We also noted a preferential elevation of liver enzymes, with AST being significantly higher than ALT. This abnormality may act as an early indicator of dengue infection.

Comparing the three subgroups of dengue infection (DF, DHF and DSS), we observed that the frequency of liver dysfunction (raised AST, ALT and ALP) was equally common in all the groups (Table 1, Figures 2(a), 2(b) and 2(c)). Similar results were noted in another Indian study[7]. However, Wahid et al.[14] found liver dysfunction to be more common in DHF than in DF patients.

The severity of hepatic dysfunction in dengue infection has been associated with disease severity. Indeed, liver injury has been proposed to be a good positive predictive factor for the development of DHF[13]. We noted a greater degree of hepatic injury in the DHF group (significantly higher values of AST and ALP) and DSS group (significantly higher values of all biochemical liver tests) as compared to the DF group, suggesting that the degree of liver injury may be related to the severity of dengue infection. Similar data have been suggested by Seneviratne et al.[2] and Souza et al.[11]. However, in two other studies, the degree of elevation of liver enzymes in the DF and DHF groups was not significantly different[7,14].

In our study, the mean bilirubin, ALT and ALP values were significantly higher in patients with haemorrhage as compared to those without haemorrhage, and were even higher in those with GI haemorrhage. Wahid et al.[14] also observed that the ALT and ALP levels were significantly higher in DHF patients with spontaneous bleeding than those without bleeding ($p < 0.05$), while Nguyen et al.[15] noted significantly higher elevation of AST and ALT in DHF patients with gastrointestinal haemorrhage. A possible reason for this could be an ischaemic injury to the liver due to acute blood loss.

In the present study, the mean bilirubin, ALT and ALP values were significantly higher in patients with secondary dengue infection as compared to those with primary dengue infection, while the mean AST value in the two groups was similar. Nguyen et al.[15] observed that the results of transaminases did not differ significantly between the two groups, while Souza et al.[11] noted that transaminases were significantly higher in cases with secondary infection.

Jaundice in dengue infection has been associated with fulminant liver failure and by itself is a poor prognostic factor[15]. We found hyperbilirubinemia to be significantly more common in patients with DSS, in patients with haemorrhage and in non-survivors. Thus, our observations support the fact that high bilirubin may act as a bad prognostic marker in patients with dengue infection.

The percentage of patients with deranged PTI was significantly more in the DSS group as compared to the DF group. There was no significant difference of biochemical liver tests between males and females in our study. However, in another study[11], transaminases were significantly higher among females.

Liver dysfunction was found to be significantly more severe in non-survivors as compared with survivors (Table 2). The causes of mortality ($n=7$) were adult respiratory distress syndrome in three patients, underlying cardiac dysfunction causing arrhythmias in one patient, underlying decompensated cirrhosis in one patient, sepsis in one patient and refractory shock in one patient.

We thus report the liver function test abnormalities and their clinical implications in a large group of patients with dengue infection. Non-availability of the baseline LFT values in the same patient group is a possible limiting factor. Future studies with assessment of viral titers, and their correlation with LFTs, may help to define the cause of hepatic injury in dengue infection.

In summary, liver involvement is very common in all forms of dengue infection, with AST rising significantly more than ALT. Serum bilirubin, ALT and ALP are significantly higher in patients with DSS, haemorrhage and sequential infection and in non-survivors. Therefore, while preferentially high AST may serve as an early indicator of dengue infection, high bilirubin, ALT and ALP may act as poor prognostic markers.

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