ORIGINAL ARTICLE

Liver Involvement in Patients with Dengue

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ABSTRACT

Background: Dengue is a global health problem, endemic to most tropical and subtropical countries. Liver involvement in dengue fever is not uncommon. It is one of the predicting factors of severe dengue.
Objective: To evaluate the impact of dengue virus infection on liver function tests (LFTs) of patients with dengue fever.
Design: Prospective, follow up study
Place and duration of study: Department of Medicine, Shaikh Zayed Medical Institute, Lahore from 5th October, 2010 to 20th November, 2010.
Patients and methods: Forty-seven serologically confirmed cases were categorized into, dengue fever(DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) according to WHO guidelines and evaluated daily for 7 days to see the serial changing pattern of LFTs including serum total bilirubin (ST bilirubin), albumin, aspartate and alanine aminotransferases (AST and ALT) and alkaline phosphatase (ALP). Based on the levels of aminotransaminases degree and severity of liver damage were classified into grades A to D and severe dengue.
Results: Forty-seven diagnosed cases of DF with male to female ratio 1.09:1, mean age of 31.3±15.4 years were included in the study. DF, DHF and DSS were found in 70.83%, 18.67%, 10.6% cases respectively. Maximum number of male patients belonged to second decade of life. Hepatic dysfunction in form of raised levels of ST bilirubin, AST, ALT and ALP and the decreased value of serum albumin were seen in 31.9%, 100%, 95.7%, 68.1%, 63.8% respectively. Serial reports of LFT showed ST bilirubin more than 1mg/dl in 7 patients on day 2 while highest value 8.6 on 5th day, serum albumin less than 3.5 g/dl in 13 patients on days 3 and 4, continuous increasing levels of ALP from day 1 to day 7 and decreasing levels of AST and ALT throughout the hospital stay. 13, 26 and 8 patients were classified as Grade B, C and D of liver damage. Five female patients (10.6%) had severe dengue with AST or ALT ≥1000 U/L. All patients recovered except one female who died of DSS on second day of admission.
Conclusion: Liver involvement is universal in patients with DF to a variable extent. Majority of patients had mild to moderate liver dysfunction though 10% had acute hepatitis without significant complications. Serial monitoring of LFTs in these patients throughout hospital stay should be done for early diagnosis of liver dysfunction, proper management and better outcome of cases.

Keywords: Dengue fever, Liver function tests.

INTRODUCTION

Dengue fever also known as break bone fever is an acute infection caused by dengue virus- an arbovirus in the flavivirus genus, transmitted to humans by mosquito Aedes aegypti. It is caused by one of the four serotypes of dengue virus (DENV1-4).According to WHO approximately 50-100 million people are infected annually.[1] Each year there are 500,000 cases of DHF and 20,000−25,000 deaths, mainly in children.[2] Data from India and Bangladesh suggests increasing incidence of disease with all four serotypes.[3] Pakistan has reported sporadic cases of DF and DHF. The Dengue infection was first documented from Punjab in 12 out of 174 samples collected in 1968 and 1978.[4] First epidemic of DHF was recorded from Civil Hospital, and Aga Khan University Hospital, Karachi in 1994−5, published in 1997−8.[3]

Clinically dengue virus infection may manifest as classical DF, DHF, DSS. DF is an acute illness of sudden onset of symptoms such as high grade fever, headache, skin rash (dengue triad), exhaustion, severe muscle and joint pain and swollen glands. Infection with one serotype does not protect against the others and sequential

infections put people at greater risk for DHF and DSS.[5] According to WHO 1997 criteria DF classification requires fever and at least two of the following: headache, eye pain, myalgia, arthralgia, rash, bleeding and leucopenia. DHF requires all of the following: fever, platelet count ≤100x10^9/liter, bleeding and plasma leakage (manifested by an increase in haematocrit of ≥20% during the course of hospitalization or a rise in haematocrit ≥20% of baseline). DSS is a case of DHF with either tachycardia and pulse pressure<20mmHg or systolic blood pressure <90 mm Hg. [6]

Most patients recover from dengue infection. Mortality can occur in DHF [7] and DSS unless prompt and adequate management is provided. [8]

Over the past few years, atypical manifestations of dengue have been reported with multiple organ involvement. [9] Although dengue virus is a non hepatotropic virus, liver injury due to dengue infection is not uncommon and has been described since the 1960s.[10] Liver involvement is characterized by right hypochondrial pain, hepatomegaly, jaundice and elevated aminotransferase levels peaking at ninth day and gradually returning to normal within 4 weeks. Elevation of the liver enzymes AST and ALT is common in acute dengue illness, occurring in 65-97% of dengue patients peaking during the convalescent period of illness (days 7-10). Elevated AST and ALT levels have been associated with bleeding and DHF. Liver failure has been recognized as a complication and unusual manifestation of dengue. [9,11]

Histopathology findings include centrilobular necrosis, fatty alteration, hyperplasia of Kupffer cells, acidophil bodies and monocyte infiltration of portal tract.[12]

The current study was conducted to document the extent of liver damage in dengue infection in our patients.

MATERIALS AND METHODS

Fifty nine suspected cases of DF of all ages and both genders were included in the study. Those with underlying chronic liver disease or known positive serology for viral hepatitis (HBsAg or anti HCV) or malaria were excluded. Sera of all cases were tested for anti dengue immunoglobulins (IgM and IgG) by Enzyme linked immunoassay (ELISA). Forty seven cases were confirmed to have DF on the basis of Ig M alone or both IgM and IgG positivity. After written consent, detailed clinical evaluation and daily blood samples were taken for 7 days to see the serial changing pattern of liver function tests including ST bilirubin, albumin, aminotransaminases and ALP. They were followed up for demographical, serial clinical, laboratory and outcome data.

Cases were categorized as DF, DHF or DSS using WHO 1997 criteria.[6] The degree to which liver was involved was classified into four grades based on serum AST and ALT levels. These enzymes were analyzed using the RXL autoanalyser. The baseline value of AST and ALT was 40U/L. Patients with normal ALT and AST levels were assigned Grade A. Those with at least one of them elevated but less than three times the reference range were assigned Grade B. ALT/AST level more than three times but less than ten times normal was graded C, while level of either enzyme more than ten times normal was graded as D/acute hepatitis. Cases with AST/ALT ≥1000U/L were categorized as severe dengue according to the WHO 2009 guidelines.[13]

All information was entered in SPSS 22.0. Demographic variables were reported as frequency and percentages. Numerical data was reported as Mean±SD.

RESULTS

During the study period 59 patients with suspected dengue were admitted. Out of these 37 cases (16 males and 21 females) were found to have positive Ig M and 10 cases (8 males and 2 females) had positive Ig M and Ig G to dengue virus.

Table 1: Age distribution according to gender (n=47)

Gender	Range (years)	Mean±SD (years)
Males (n=24)	5-65	33.3±17.6
Females (n=23)	9-68	29.2±12.8
Total (n=47)	5-68	31.3±15.4

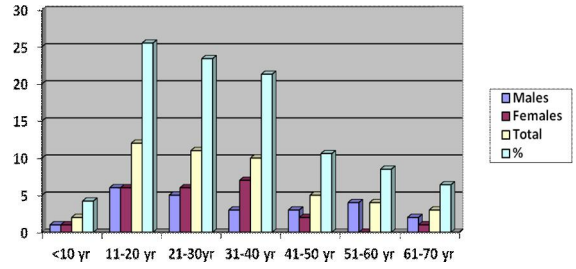

Figure 1: Age and gender distribution of patients with dengue fever (n=47)

Among these 47 cases 24 were males and 23 females (male to female ratio 1.09:1) their ages ranged from 5 to 68 years with a mean age of 31.32±15.39 years (Table 1).

Maximum number of male and female patients belonged to second and fourth decades of life, respectively (Figure 1).

Hepatic dysfunction in form of raised levels of ST bilirubin, AST, ALT and ALP and the decreased value of serum albumin were seen in 31.9%,100%,95.7%,68.1%,63.8% respectively (Table 2).

Table 2: Liver function tests of patients with dengue fever (n=47)

Parameter		N	Range	Mean± SD
Serum total bilirubin (>1mg/dl)	Male	10	1.1-5.4	2.2±1.5
	Female	5	1.1-8.6	4.1±2.4
	Total	15	1.1-8.6	2.9±2.1
Serum Albumin (<3.5 g/dl)	Male	11	1.8-3.4	2.9±0.4
	Female	19	1.2-3.4	2.9±0.5
	Total	30	1.2-3.4	2.9±0.5
Serum AST (>40U/L)	Male	24	42-249	120.5±54.9
	Female	23	55-4534	442.5±838.7
	Total	47	42-4534	290.5± 629
Serum ALT (>40 U/L)	Male	23	42-371	142.7±75.5
	Female	22	42-4379	437±854
	Total	45	42-4379	291± 624
Serum ALP (>96 U/L)	Male	17	98-485	157±74.6
	Female	15	97-1036	216.6±191
	Total	32	97-1036	261.7±236.6

Analysis of available serial data from day 1 to 7(Figure 2) , (Table 3) of dengue patients revealed that level of ST bilirubin more than 1mg/dl was seen in 7 patients on day 2 while highest value 8.6 was observed on 5th day. Serum albumin less than 3.5 g/dl was seen in 13 patients on days 3 and 4 (mean values 3.4±0.5 and 3.5±0.5 g/dl respectively). After initial decrease in serum albumin from day 1 to 5, its levels started improving after 5th day. Levels of ALP more than 96 U/L increased from day 2 to 7. Maximum level of serum AST was seen on day 2 which decreased from day 2 to 7 with initial sharp decrease from 2nd to 4th day. ALT levels were maximum at admission and decreased markedly over the next six days in a ladder shape pattern.

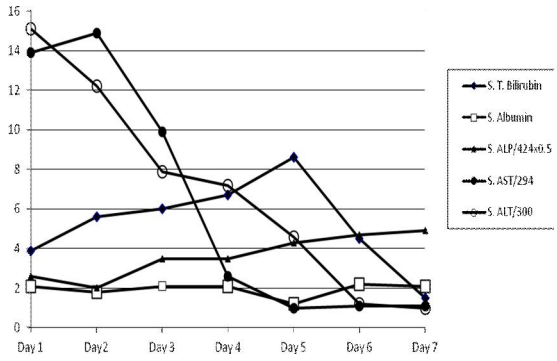

Figure 2: Levels of Serum total bilirubin, albumin, ALP, AST and ALT (n=47)

Table 3: LFTs of dengue patients from Day 1 to 7 (n=47)

	Day 1	D ay 2	D ay 3	D ay 4	D ay 5	D ay 6	D ay 7
Serum Total Bilirubin (mg/dl)							
No of pts	29	27	26	26	19	16	5
N (0.3-1.0)	26	20	21	21	14	11	4
N (>1)	3	7	5	5	5	5	1
Range	0.1- 3.9	0.2-5.6	0.2- 6.0	0.3- 6.7	0.3- 8.6	0.3- 4.5	0.5- 1.5

Mean ± SD	0.7±0.8	1.1±1.3	1.0±1.3	1.1±1.5	1.5±2.0	1.0±0.9	0.8±0.4
Serum Albumin (g/dl)							
No of pts	19	25	25	24	24	17	13
N (3.5-5.5)	8	14	12	11	13	12	12
N (<3.5)	11	11	13	13	11	5	1
Range	2.1-5.1	1.8-4.4	2.1-4.4	2.1-4.2	1.2-4.4	2.2-4.8	2.1-4.6
Mean ± SD	3.4±0.8	3.4±0.6	3.4±0.5	3.5±0.5	3.4±0.8	3.6±0.7	3.6±0.7
Serum ALP (U/L)							
No of pts	34	32	33	34	27	21	13
N (33-96)	15	18	16	18	18	11	7
N (>96)	19	14	17	16	9	10	6
Range	40-560	40-424	43-733	30-737	37-913	55-988	62-1036
Mean ± SD	121±95	121±84	138±130	148±143	147±175	138±197	183±263
Serum AST (U/L)							
No of pts	34	32	34	34	27	21	13
N (<40)	3	1	1	4	1	2	1
N (≥40)	31	31	33	30	26	19	12
Range	24-4088	37-4379	39-2925	25-752	27-294	37-315	27-314
Mean ± SD	309±715	351±831	256±503	178±169	129±76	129±76	164±83
Serum ALT (U/L)							
No of pts	34	31	33	34	27	19	13
N (<40)	10	5	3	3	1	1	0
N (≥40)	24	26	30	31	26	18	13
Range	16-4534	20-3662	31-2360	30-2157	33-1365	36-363	47-300
Mean ± SD	247±766	264±671	202±412	184±358	182±249	143±82	173±72

No patient had normal levels of ALT/AST from day 1 to 7(Grade A), 13 (28 %) had altered level of at least one of the two (Grade B), 26 (55%) had at least one enzyme level increased to 3 times its reference value (Grade C) and 8 (17%) had acute hepatitis (Grade D) (Figure 3).

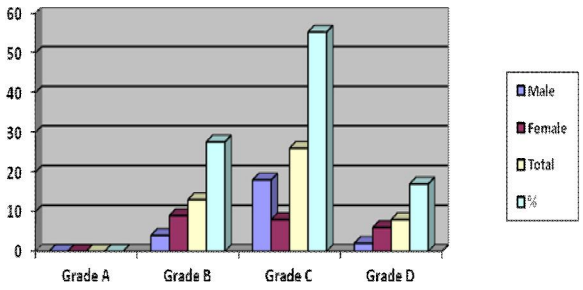

Figure 3: Degree of liver damage in dengue patients (n=47)

5 female patients (10.63%) had severe dengue according to WHO 2009 criteria concurrent with AST or ALT≥1000 U/L. (Table 4).

Table 4: Severity of liver damage according to serum transaminases (n=47)

Liver Enzyme	Level	Male	Female	Total	%
AST (U/L)	<1000	24	20	44	93.6
	>1000	0	3	3	6.4
ALT (U/L)	<1000	24	21	45	95.7
	>1000	0	2	2	4.3

DISCUSSION

Dengue infection affects about 2.5 billion people worldwide; being endemic to over 100 countries of tropical and subtropical countries in South-east Asia, the Pacific and America. [1] In Pakistan DENV has become a serious issue and it has caused many epidemics from 1994 to 2011.Liver

involvement ranging from mild elevation of transaminases to fulminant hepatitis in DF is not uncommon as reported since 1970. It predicts poor outcome in DF. [10]

In the present study, the biochemical impact of dengue virus on LFTs was studied in 47 serologically confirmed cases of DF. Our study includes more males than females as is reported in other studies from Pakistan [14,15] and India.[12,16] In our study mean age of patients was 31.32±15.4 years whereas in other studies it was 35.7±12.9 years [17] and 31.9±13.6 years. [14]

In present study DF, DHF and DSS were found in 70.83 %, 18.67% and 10.6% of patients respectively. In a study from Pakistan[18] the frequency of these conditions between 2000-2004 were 73%, 24% and 2.4% while after 2005 it was 58%, 39% and 3% respectively.[19] In another study from Pakistan [3] these values were 78%, 19.4% and 2.4%. In a study from India these were 23.1, 66.9% and 32% respectively. [17]

In most of published reports about liver dysfunction mainly the levels of AST and ALT were studied and evaluated while in current study values of ST Bilirubin, albumin, AST, ALT and ALP of patients were evaluated from day 1 to 7 of the hospital stay. In our study ST bilirubin, AST, ALT and ALP were raised in 31.9%, 100%, 95.7 and 68.1% patients respectively while in a study from India [17] these were raised in 31.2%,99.3%, 96.6% and 68.2% patients in that order which is in concordance with our study. The mean values of LFTs in our patients were: ST Bilirubin 2.9±2.1mg/dl, Albumin 2.9±0.5 g/dl, AST 290.5±629 U/L, ALT-291±624 U/L and ALP 261.7±236.6 U/L. In a study from India [12] these values were 1.2±1.4 mg/dl, 3.85±0.38 g/dl, 390.69±730.68 U/L, 296.9±562.0 U/L and 98.78±51.01 U/L respectively. Our patients' values of ST bilirubin and ALP were higher while those of albumin, AST and ALT were lower than the corresponding values of the Indian study.

In current study maximum levels of AST and ALT were recorded on the first two days of admission while in a study by Lee LK [20] the maximum values of these LFTs were recorded on the fourth day of illness.

In present study 100% patients had elevated AST levels. In 95.7% patients this elevation was associated with higher values of ALT. Similar trend has also been reported in other studies [21,22, 23]. The exact cause of this is uncertain but it has been suggested that it may be due to excess release of AST from damaged myocytes during DF. [24]

No patient had normal levels of ALT/AST (Grade A) while 28 %, 55%and 17% patients were categorized as Grade B, C and D in that order. In a study, [12] 11% patients were graded as A, 37% as B, 30% as C and 22% as Grade D. De Souza et al classified 42% as Grade B,17.5% as Grade C and only 1.8% as grade D.[25]

Five female patients (10.63%) had severe dengue according to WHO 2009 criteria concurrent with AST or ALT≥1000 U/L. in other studies [14,20] 7 (1%)and 103 (15%) patients had severe dengue. None of our patients developed liver failure and death occurred in just one patient (2%) whereas in other studies [14,26] the mortality rate was 2.7% and 3% respectively. The majority of patients recovered uneventfully. This lack of acute liver failure is not unusual as is reported in other studies as well. [20,22,24]

Strengths and limitations: The present study is based on a small sample size. It is one of its kind in the respect that serial change in LFTs was observed. This study has limited external validity since patients admitted in a tertiary care hospital were included in whom the impact of co-infection, underlying immune status and serotyping of DENV was not assessed.

CONCLUSION

Liver involvement is universal in patients with DF to a variable extent. Majority of patients had mild to moderate liver dysfunction though 10% had acute hepatitis without significant complications. Serial monitoring of liver function tests in these patients throughout hospital stay should be done for early diagnosis of liver dysfunction, proper management and better outcome of cases.

Suggestion

Large scale, multicentre studies are needed to confirm and better interpretation of findings in Pakistani patients.

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