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Original Article

Internal Medicine Section

A Study on Spectrum of Hepatobiliary Dysfunctions and Pattern of Liver Involvement in Dengue Infection

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ABSTRACT

Introduction: The most common arthropod-borne viral (arboviral) disease in humans is dengue. It is transmitted by female Aedes mosquitoes. These mosquitoes are widely distributed in sub-tropical and tropical areas of the world. Study of dengue infection and its complications are scarce from countries like India.

Aim: In this prospective observational cross-sectional study, we intended to assess the frequency and degree of hepatobiliary dysfunction in adult patients with dengue infection presenting to a tertiary-care medical facility.

Materials and Methods: The details of all patients with serologically proved dengue fever admitted to a tertiary care hospital in eastern India from July 2014 to June 2015 were prospectively reviewed. We collected data including routine blood count, Liver Function Test (LFT), Prothrombin Time (PT), Activated Partial Prothrombin Time (APTT), abdominal ultrasonography from 110 patients.

Results: The maximum number of cases were seen in the age group between 46 years and 61 years and of all cases 55.5% were male and 44.5% were female. Pain abdomen and vomiting were the commonest presenting complaints next to fever which was present in all the cases. Elevated liver enzymes, abnormal values of PT and APTT, thrombocytopenia were observed more commonly in Dengue Shock Syndrome (DSS). Gall bladder wall thickening, thrombocytopenia were seen more commonly in both DSS and Dengue Haemorrhagic Fever (DHF). Plasma leakage such as ascites and pleural effusion on USG were seen more frequently in patients with DHF (76.9% and 73.1%) followed by DSS (72% and 68%) and DF (33.9% and 32.2%).

Conclusion: Hepatobiliary derangement is seen more commonly in severe case of dengue infection. Early recognition of these parameters can also be used as a predictor for assessing the disease severity.

Keywords: Dengue fever, Dengue haemorrhagic fever, Dengue shock syndrome

INTRODUCTION

Dengue virus infection is a major and important public health problem in many South East Asian countries and also in more than 100 countries of tropical and subtropical region [1,2].

Two–fifths of the world's population or 2500 million people are now at risk for dengue, and every year approximately 50 million new cases occur worldwide [3].

The global prevalence of dengue infection has increased dramatically in the recent decades [4]. Recently an increasing trend of outbreaks of DF and its complicated forms has been reported in India [3].

Occurrence of Dengue fever (DF) in the country was first reported during 1956 from the district of Vellore in Tamil Nadu. Dengue is prevalent throughout India in urban as well as rural areas. According to latest data there are 64058 cases and 135 deaths from dengue in 2015 (till 25th October 2015) [5].

Typically, people infected with dengue virus are asymptomatic (80%). They may have mild symptoms such as an uncomplicated fever [6]. Hepatic injury with dengue infection has been described since 1967 [7]. Liver dysfunction in patients with dengue varies from mild injury with elevation of transaminase activity. Hepatomegaly (tender/non tender) to severe hepatocyte injury resulting in jaundice may also occur [1]. Hepatic dysfunction is caused by a direct effect on liver cells or as a consequence of deranged host immune response against the virus. Other factors including race, diabetes, haemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs may also play a role [8]. The mechanism may be prolonged shock, metabolic acidosis and DIC in complicated dengue causing ischemia resulting in severe hepatic dysfunction [3,9]. There are isolated case reports of fulminant hepatic failure in dengue patients. But the derangements in the transaminases are usually self-limiting [10]. Dengue infection causes liver parenchyma damage [11]. Rising of aminotransferase level occurs in the acute phase of the disease. Liver enzyme levels subsequently decrease as the liver recovers [12]. Elevated liver enzymes in dengue is an early marker of dengue infection. It is also a predictor for assessing the disease severity [13].

There are some studies about hepatobiliary dysfunction in dengue. Some studies are about pediatric population only [2,3,14-16]. Studies on adult population are there but from eastern India adequate data are not available [17-21]. Since 2005 there were several outbreaks of dengue in India including Kolkata [22]. More studies will help us find out more data about this. As of now, no specific therapies or vaccines are available against dengue. For this, early detection of complications can decrease morbidity as well as mortality.

AIM

The present study was aimed to assess the frequency and degree of hepatobiliary dysfunction in adult patients with dengue infection presenting to a tertiary-care medical facility.

MATERIALS AND METHODS

A prospective, observational cross-sectional study was conducted in Indoor Patient Department of Department of General Medicine, R.G. Kar Medical College & Hospital, Kolkata (A tertiary care academic hospital in eastern India) from July 2014 to June 2015. The study was performed after approval of the Ethical Committee of the above mentioned institution.

Inclusion Criteria

1. Age ≥ 14 years.
2. Known clinically as well serologically proved (demonstration

of dengue virus antigen in serum sample by NS1-ELISA for patients with history of fever for <5 days or dengue-specific IgM by MAC ELISA for patients with history of fever ≥5 days) cases of Dengue fever (DF) or Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome.

Exclusion Criteria

1. Previously known or newly detected patients of Chronic Liver Disease of any aetiology (As evident by the clinico-radiologic and biochemical parameters).
2. Patients with known recent history of intake of any hepatotoxic or similar drugs causing derangements of liver functions.
3. Patients having other known infections causing hepatitis such as Viral hepatitis A and E, Leptospirosis, Falciparum malaria, etc.
4. Patients with altered liver functions secondary to sepsis or as a part of Multiple Organ Dysfunction Syndrome (MODS) unrelated to Dengue infection.
5. Diabetic and hypothyroid patients with Non-alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steato-Hepatitis (NASH).

About 110 patients of clinically as well serologically proved DF or DHF and DSS, admitted to the hospital. For the study to be statistically significant required sample size was calculated online by sample size calculator through "CREATIVE SYSTEM INC", which were 60 for the present study.

Following parameters were studied

1. Clinical, radiological, biochemical, pathologic and serologic parameters (mentioned below) relevant to the liver and biliary involvement in Dengue infections.
2. Comparison of these parameters with reference to the classic DF and DHF/ DSS to differentiate the ultimate outcome, morbidities and mortality between the two groups.

History was taken regarding history of high fever, headache, retro-orbital pain, myalgia and arthralgia, accompanying petechial rash with/without haemorrhagic manifestations including petechiae, ecchymoses, epistaxis, gastrointestinal bleeding and haematuria and also of hypovolemic shock.

Tests for NS1-ELISA and Dengue IgM and IgG antibodies in patient's serum (for selecting the subjects of study) were done.

Appropriate investigations for evaluation of hepatobiliary dysfunctions were performed. They were: Liver enzymes – Alanine Transaminase (ALT) /Serum Glutamic Pyruvate Transaminase (SGPT); Aspartate transaminase (AST)/Serum Glutamic Oxaloacetic Transaminase (SGOT); Alkaline Phosphatase (ALP); Total, conjugated and unconjugated serum bilirubin; Prothrombin time index/ International normalized ratio (INR); Activated Partial Thromboplastin Time (APTT); Total serum protein, serum albumin and globulin levels. Apart from these other tests were done: Abdominal and thoracic Ultrasonography. Urine for routine and microscopic examinations was also done.

Routine blood parameters: (using the standard tools and protocols used by the Departments of Pathology, Microbiology, Biochemistry of R.G. Kar Medical College & Hospital)-

- Haemoglobin level and percentage, Total and differential leukocyte counts, Haematocrit, Packed Cell Volume (PCV), Platelet count.
- Blood sugar (random), serum urea, creatinine, Sodium, Potassium.
- Tests for exclusion of other infections causing hepatobiliary insults, such as Hepatitis B surface antigen test (HbSAg), Anti HCV, Anti HAV IgM (To be done at the School of Tropical Medicine, Kolkata), Anti HEV IgM (To be done at the School of Tropical Medicine, Kolkata), Antigenic tests for Vivax and Falciparum malaria, Leptospirosis (To be done at the School of Tropical Medicine, Kolkata), Widal test – by tube method.

Clinical criteria and case definition for DF/DHF/DSS was followed according to the definitions given in national vector borne disease control programme [5].

RESULTS

A total of 110 cases formed the study subjects. After tabulating all the data they were analysed accordingly. The maximum number of cases was seen in age group between 46 years and 61 years [Table/Fig-1]. Of the all cases 55.5% were male and 44.5% were female. In our study 23.6% and 22.7% of all cases developed DHF and DSS respectively [Table/Fig-2].

Abdominal pain and vomiting were the commonest presented complaints next to fever which was present in all the cases. As depicted in the above table the incidence of pain abdomen and vomiting in DSS, DHF and DF were 42.4% 50%, and 56% and 44.1%, 23% and 48% respectively [Table/Fig-3]. Bleeding and facial puffiness were seen more frequently in DHF followed by DSS and DF. Constitutional symptoms were seen commonly with classical dengue fever as compared to complicated dengue.

Out of 110 cases 5 had (4.5%) clinical jaundice, of which 4 were in DSS group and 1 patient in DHF group. Hepatomegaly is the commonest clinical (79%) sign seen more frequently in DSS (96%) as compared to DHF (88.5%) and DF (67.8%) [Table/Fig-4].

Hepatic tenderness was observed more frequently in DSS (56%) in comparison to DF (20.3%). It was observed that convulsions and altered sensorium was more common in DSS in comparison to DF group.

As shown in the [Table/Fig-5], elevated liver enzymes were observed more commonly in dengue shock cases followed by DHF and DF.

Comparing the groups of DF, DHF and DSS, abnormal values of PT and APTT were observed more frequently in DSS. Hypoalbuminemia was observed in 66% of the total cases but there was significant difference observed in between the three groups. However, low serum globulin levels were seen more in DSS (60%) and DHF (69.2%) in comparison to classical DF (18.6%) group.

In the present study, comparing the hepatic function parameters of DF, DHF, and DSS groups as depicted, it was observed that elevated levels of AST, ALT and ALP were significantly higher in dengue shock cases as compared to non-shock cases. Mean INR ratio of PT was 1.53 in DSS cases as compared to 1.27 in DHF and 1 in DF cases respectively [Table/Fig-6].

On comparing patients in DHF group none had normal AST levels. It was also found that in DSS group only 4% had normal AST values [Table/Fig-7].

As depicted in [Table/Fig-8], 72% of cases diagnosed to have DSS had elevated ALP values in comparison to 65% patients with DHF and 46% of cases with DF. There was no significant difference in liver function test profile in patients with hepatomegaly or without hepatomegaly inferring that the patients may have deranged liver functions even in the clinical absence of hepatomegaly [Table/Fig-9]. [Table/Fig-10] compares the liver function test in DF, DSS and DHF groups with hepatomegaly. Comparison in liver function tests between three groups in patients without hepatomegaly is depicted in [Table/Fig-11].

[Table/Fig-12,13] show there are no significant differences in elevated enzyme levels in cases with tender versus cases with non-tender hepatomegaly.

Patients with increased haematocrit value and gall bladder thickening are described in [Table/Fig-14,15].

Age	No of Cases (n = 110)
14 yrs – 29 yrs	13 (11.8%)
30 yrs – 45 yrs	21 (19%)
46 yrs – 61 yrs	50 (45.5%)
≥ 62 yrs	26 (23.6%)
Total	110 (100%)

[Table/Fig-1]: Age-wise distribution of total cases.

Grouping	No of cases (n=110)
DF	59 (53.6%)
DHF	26 (23.6%)
DSS	25 (22.7%)
Total	110 (100%)

[Table/Fig-2]: Categorization of cases into DF, DHF AND DSS.

Parameter	DF (n=59)	DHF (n=26)	DSS (n=25)
Gender (male : female)	1: 0.79	1:1	1 : 0.67
Fever	59 (100%)	26 (100%)	25 (100%)
Pain abdomen	25 (42.4%)	13 (50%)	14 (56%)
Vomiting	26 (44.1%)	06 (23.1%)	12 (48%)
Body ache/Myalgia/Fatigue	39 (66.1%)	13 (50%)	11 (44%)
Headache	25 (42.4%)	04 (15.4%)	05 (20%)
Joint pain	16 (27.1%)	02 (7.7%)	01 (4%)
Retro orbital pain	11 (18.6%)	01 (3.8%)	00
Rash	20 (33.9%)	06 (23.1%)	13 (52%)
Facial puffiness/ pedal edema	14 (23.7%)	18 (69.2%)	14 (56%)
Bleeding	0	12 (46.2%)	09 (36%)

[Table/Fig-3]: Comparison of Clinical Symptomatology in DF, DHF and DSS groups.

Parameter	DF (n=59)	DHF (n=26)	DSS (n=25)
Positive Hess test	0	11 (42.3%)	11 (44%)
Petechiae/Purpura/Ecchymosis	0	16 (61.5%)	17 (68%)
Convulsions	0	3 (11.5%)	06 (24%)
Altered sensorium	0	2 (7.6%)	4 (16%)
Jaundice	0	01 (3.8%)	04 (16%)
Hepatomegaly	40 (67.8%)	23 (88.5%)	24 (96%)
Hepatic tenderness	12 (20.3%)	14 (53.8%)	14 (56%)
Clinical icterus	0	01 (3.8%)	04 (16%)

[Table/Fig-4]: Comparison between the groups with respect to clinical signs.

Parameter	DF (n=59)	DHF (n=26)	DSS (n=25)	p-value
Total Serum bilirubin >2mg/dl	0 (0%)	1 (0.03%)	4 (0.16%)	p= 0.025
Elevated ALT	41 (69.4%)	22 (84.6%)	23 (92%)	p= 0.000
Elevated AST	52 (88.1%)	26 (100%)	24 (96%)	p= 0.000
Elevated ALP	27 (45.7%)	17 (65.3%)	18 (72%)	p= 0.049
Abnormal P.Time (INR)	01 (1.6%)	08 (30.7%)	13 (52%)	p= 0.001
Abnormal APTT	00	04 (15.3%)	05 (20%)	p= 0.542
Hypoalbuminemia (<3.5)	40 (67.7%)	18 (69.2%)	15 (60%)	p= 0.831
Low serum globulin level (<2.3)	11 (18.6%)	18 (69.2%)	15 (60%)	p= 0.000
Mean serum protein (sd value)	6.5 (0.91)	6.4 (0.79)	6.4 (1.28)	p=0.688

[Table/Fig-5]: Comparison between groups with respect to liver function test.

Out of 110, 1 patient expired secondary to Disseminated Intravascular Coagulation (DIC), multiorgan involvement, renal failure, ARDS, dengue shock, coagulopathy and deranged hepatic function profile. His liver enzymes were elevated above 5 fold the normal values with no clinically evident jaundice. He had altered coagulation profile with prolonged PT and APTT values and thrombocytopenia. This was a 15-year-old child referred from primary centre presented with fever, bleeding, generalized edema, rashes, hurried respiration with altered mental status and oliguria. The child had died within 12 hours of hospitalization. Rest of all 109 cases were treated and they eventually recovered.

Parameter	DF (n=59)	DHF (n=26)	DSS (n=25)	p-value
Mean total serum bilirubin (SD value)	0.79 (0.29)	0.84 (0.60)	1.1 (0.87)	.115
Mean ALT (range) (SD value)	78.7 (16-374) (80.34)	157.3 (25-481) (140.87)	504.6 (24-3414) (692.43)	.001
Mean AST (range) (SD value)	134 (45-268) (117.17)	280 (18-450) (162.09)	883.4 (43-599) (715.55)	.002
Mean ALP (range) (SD value)	118.6 (36-277) (83.04)	157.7 (54-683) (137.52)	188.2 (58-523) (285.09)	.026
Mean serum albumin (range) (SD value)	3.37 (2.8-4.2) (0.68)	3.23 (2.5-4.2) (0.63)	3.37 (2.6-4) (0.95)	.866
Mean serum globulin (SD value)	1.9 (0.6-3.2) (0.49)	2.8 (2-3) (0.52)	2.8 (2-3.2) (0.65)	.000
Mean total protein (range) (SD value)	6.2 (5.5-7.9) (0.91)	5.9 (5-7) (0.79)	6.1 (5-7.3) (1.28)	.624
Mean P.T (INR ratio) (sd value)	1.0 (0.08)	1.27 (0.19)	1.53 (0.21)	.019
Mean APTT (sec) (SD value)	31 (3.15)	34 (2.91)	35 (4.3)	.321

[Table/Fig-6]: Comparison in mean values of liver function test between groups.

Liver enzymes (U/L)		0-45	46-200	201-400	401-600	>600	p-value
ALT (U/L)	DF (n=59)	18 (30.5%)	39 (66.1%)	2 (3.4%)	0 (0%)	0	X^2=31.77 p=.000
	DHF (n=26)	4 (15.4%)	15 (57.7%)	5 (19.2%)	2 (7.7%)	0	
	DSS (n=25)	2 (8%)	14 (56%)	5 (20%)	0 (0%)	4 (16%)	
AST (U/L)	DF (n=59)	07 (11.9%)	39 (66.1%)	11 (18.6%)	2 (3.4%)	0	X^2=33.84 p=.000
	DHF (n=26)	0 (0%)	10 (38.5%)	10 (38.5%)	5 (19.2%)	1 (3.8%)	
	DSS (n=26)	1 (4%)	7 (28%)	6 (24%)	6 (24%)	5 (20%)	

[Table/Fig-7]: Comparison of liver enzymes in DF, DHF and DSS groups (AST and ALT).

	Normal ALP	Elevated ALP
DF (n=59)	32 (54%)	27 (46%)
DHF (n=26)	09 (35%)	17 (65%)
DSS (n=25)	07 (28%)	18 (72%)

[Table/Fig-8]: Comparison of Alkaline Phosphatase enzyme in DF, DHF and DSS Groups

Parameter	With hepatomegaly (n=87)	Without hepatomegaly (n=23)	p-value
Mean Total S. Bilirubin (SD value)	0.9 (0.77)	0.8 (0.35)	.5466
Mean AST (SD value)	387 (456)	250 (230)	.1672
Mean ALT (SD value)	222 (456.3)	92 (150.1)	0.1820
Mean ALP (SD value)	144 (228.45)	140 (143.3)	0.9366
Mean Serum Albumin (SD value)	3.3 (0.8)	3.3 (0.66)	1.00
Mean Serum Globulin (SD value)	2.3 (0.55)	2.5 (0.53)	.1211
P. T mean (INR) (SD value)	1.2 (0.21)	1.1 (0.25)	.0538
APTT (sec) (SD value)	31 (3.4)	31 (3.35)	1.00

[Table/Fig-9]: Comparison of liver function test in dengue infection with and without hepatomegaly.

Parameter	DF (n=40)	DHF (n=23)	DSS (n=24)	p-value
Total serum bilirubin (sd value)	0.7 (0.29)	0.8 (0.97)	1.1 (0.89)	.046
AST (SD value)	127 (104.91)	289 (151.42)	914 (724.63)	.003
ALT (SD value)	75 (73.52)	165 (117)	523 (701.11)	.005
ALP (SD value)	111 (79.20)	156 (106.05)	187 (282.44)	.013
Serum Albumin (SD value)	3.3 (0.72)	3.2 (0.72)	3.3 (0.81)	.213
Serum Globulin (SD value)	2.8 (0.51)	1.9 (0.26)	2 (0.73)	.000
P.T (INR) (SD value)	1 (0.07)	1.3 (0.11)	1.57 (0.16)	.000
APTT (sec) (SD value)	30 (3.11)	31 (3.05)	32 (3.46)	.213

[Table/Fig-10]: Comparison in mean values of liver function test in cases with Hepatomegaly in DF, DHF AND DSS groups.

Parameter	DF (n=19)	DHF (n=03)	DSS (n=01)	p-value
Total serum bilirubin (SD value)	0.8 (0.30)	0.8 (0.36)	0.9	.058
AST (SD value)	151 (132)	215 (169.3)	147	.443
ALT (SD value)	85 (94.9)	97 (147.8)	205	.019
ALP (SD value)	133 (86.1)	168 (145.11)	205	.199
Serum Albumin (SD value)	3.3 (0.65)	3.4 (0.63)	3.7	.715
Serum Globulin (SD value)	2.6 (0.56)	1.9 (0.48)	3.2	.041
P.T (INR) (SD value)	1 (0.1)	1 (0.11)	1.2	.349
APTT (sec) (SD value)	30 (3.16)	31 (3.11)	32	.213

[Table/Fig-11]: Comparison in mean values of liver function tests in cases with No Hepatomegaly in DF, DHF and DSS groups.

Parameter	DF (n=12)	DHF (n=14)	DSS (n=14)	p-value
Total serum bilirubin (SD value)	0.69 (0.37)	0.91 (1.05)	0.81 (1.07)	.143
ALT (SD value)	68.4 (63.90)	137.4 (78.23)	608 (832.07)	.017
AST (SD value)	121 (101.53)	304 (47.18)	837 (861.79)	.091
ALP (SD value)	105.9 (52.72)	127 (80.15)	201 (304.45)	.029
Serum albumin (SD value)	3.3 (0.70)	3.2 (0.30)	3.4 (1.02)	.881
Serum globulin (SD value)	2.96 (0.34)	1.8 (0.75)	2.0 (0.66)	.002
P. T (INR) (sd value)	1 (0.02)	1.3 (0.09)	1.45 (0.22)	.060
APTT (sec) (SD value)	30 (3.05)	32 (0.57)	33 (4.37)	.881

[Table/Fig-12]: Comparison in mean values of liver function test in between Groups with tender hepatomegaly.

Parameter	DF (n=28)	DHF (n=9)	DSS (n=10)	p-value
Total serum bilirubin (SD value)	0.6 (0.3)	0.9 (0.42)	0.87 (0.3)	.143
ALT (SD value)	136 (64.30)	180 (151.54)	392 (181.74)	.017
AST (SD value)	232 (97.21)	254 (124.57)	930 (204.18)	.091
ALP (SD value)	204 (70.68)	193 (138.56)	172 (172.69)	.029
Serum albumin (SD value)	5.6 (0.72)	2.9 (0.72)	3 (0.84)	.881
Serum globulin (SD value)	4.6 (0.51)	2.1 (0.27)	1.6 (0.74)	.002
Abnormal P.T (INR) (SD value)	1.0 (0.07)	1.1 (0.12)	1.6 (0.17)	.060
APTT (sec) (SD value)	30 (3.11)	32 (3.05)	33 (3.47)	.881

[Table/Fig-13]: Comparison in mean values of liver function test in between groups with non- tender hepatomegaly.

Parameter	DF (n=59)	DHF (n=26)	DSS (n=25)	p-value
Minimum total count median (range)/µl	3100	3100	3400	
Thrombocytopenia	38 (64.4%)	26 (100%)	25 (100%)	P=.000
At admission platelet count, median/µl	33,000	31,000	42,000	
Minimum platelet count median (range)/µl	26,000	19,500	21,000	
Hct>38%	20 (33.9%)	17 (65.4%)	18 (72%)	P=.000
Maximum HCT mean (sd) %	36.5 (4.4)	38.4 (4.3)	41.2 (4.8)	

[Table/Fig-14]: Haematologic profile of DF, DHF and DSS groups

Parameter	groups	No of cases	p-value
Ascites	DF (n=59)	20 (33.9%)	X^2=18.22 P=.000
	DHF (n=26)	20 (76.9%)	
	DSS (n=25)	18 (72%)	
Pleural effusion	DF (n=59)	19 (32.2%)	X^2=16.25 P=.000
	DHF (n=26)	19 (73.1%)	
	DSS (n=25)	17 (68%)	
GB wall thickening	DF (n=59)	30 (50.8%)	X^2=10.43 P=.005
	DHF (n=26)	21 (80.8%)	
	DSS (n=25)	20 (80%)	

[Table/Fig-15]: Comparison of ultrasound findings in DF, DHF and DSS groups

DISCUSSION

Dengue viral infections are one of the most important mosquito borne diseases in the world, caused by four serotypes (DEN1, DEN2, DEN3 and DEN4) of dengue virus. Presently dengue infection is endemic in 112 countries with annually 100 million cases of DF and 50 million cases of DHF occurring globally with an average case fatality rate of around 5%. The manifestations of dengue infections are protean from being asymptomatic to undifferentiated fever, severe dengue infections and unusual complications. Recent studies suggest that there is an upsurge of complicated dengue infections especially in South East and South Asia [23,24].

Hepatomegaly is one of the commonest clinical sign of dengue infection. Hepatomegaly is frequent and is commoner in patients with DHF than in those with DF [12]. Association of hepatomegaly with cases of dengue infection has been quite variable, the incidence varying from 43% to 98% whereas in the present study, it was observed in 79% of total cases as shown in the table below. The incidence of hepatomegaly was more in shock cases as compared to non-shock cases. The maximum liver size noted was 9 cm below the right costal margin in our study. SL Senevinatne et al., observed a higher incidence of hepatomegaly with DHF than DF [13]. In the present study it was observed that tender Hepatomegaly was seen in 56% of cases in DSS group as compared to 53.8% cases in DHF and 20.3% cases of DF group. Incidence of tender hepatomegaly is significantly higher in shock cases. Maria Paulo et al., showed 30% of cases who presented in DSS to be having tender hepatomegaly [25].

Serum ALP levels also showed similar trend. It was also shown that hepatic dysfunction in the form of marked elevated enzymes were higher in severe and complicated dengue in comparison to classical dengue fever. Most of the studies showed that unlike other viral infections, in dengue the rise of AST is usually more than ALT [12,17,18,20]. By follow-up, AST levels had returned to normal levels in most of the cases. On the other hand ALT levels remained slightly increased above the normal cut-off value in approximately one-third of the patients. This pattern, with AST rising more quickly and peaking at a higher level and then returning to normal faster than ALT levels, is different from the pattern usually seen in acute hepatitis caused by hepatitis viruses.

Alanine aminotransferase is primarily released from hepatocytes. It has minimal activity in cardiac and skeletal muscle. AST is found in erythrocytes, cardiac and skeletal muscle, and kidney and brain tissue. It is often elevated as a result of damage to those sources and also to hepatic damage. The plasma half-life of ALT (32-43h) is longer than that of AST (12.5-22h). This may be possible that the slower improvement in ALT levels simply reflects slower evolution of the hepatic disease than of the musculoskeletal problems. Transaminases levels, particularly AST levels, have been suggested as a potential marker for differentiating dengue from other viral infections during the early febrile phase [12]. Moreover, the presence of thrombocytopenia and persistence of fever after the appearance of jaundice should help to differentiate DI from viral hepatitis. Serological tests for infection with hepatotropic viruses and for dengue virus would also help in confirming the aetiology of liver injury. Study by BrijMohan et al., also observed deranged AST levels frequently in DSS cases in comparison to non-shock cases and 100% of cases in DSS and DHF group had elevated ALT enzyme levels in comparison to 81% in dengue fever patients [14]. In the present study it was observed that hepatic dysfunction in the form of elevated liver enzymes was seen more in DSS as compared to non DSS cases suggesting that apart from dengue virus, hypoxemia as a result of hypovolemic shock or hosts response to infection remains to be to be determined as it may contribute to the adverse effects on the liver [19]. Kuo et al., have reported that 82.2% of cases of dengue infection had elevated ALT levels [20]. In our study AST levels were elevated in more number of patients in all the three groups compared to ALT 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 [20]. Like other studies, in the present study majority of our patients had elevated liver enzymes, with AST being more elevated than ALT values. Patients with severe and complicated dengue had higher level of hepatic enzyme dysfunction.

Elevated alkaline phosphatase (ALP) was seen in 56% of total cases in this study. Fadilah et al., had reported that mean levels of alkaline phosphatase were higher in DHF as compared to DF [21].

The appearance of jaundice in cases of DF/DHF/DSS may be multifactorial. It can be due to hepatic injury caused by the dengue virus and or hypoxia and tissue ischemia in cases of dengue shock [13]. Jaundice occur more in complicated than in uncomplicated cases. Jaundice in dengue infection have been associated with fulminant hepatic failure and it itself is a poor prognostic sign [25]. In our study 5 (4.5%) cases had clinically evident jaundice. The mean total serum bilirubin of these 5 patients was 3mg/dl. Out of these 5 cases 4 were in DSS group, 1 in DHF group. All the 5 cases had fever, 4 had pain abdomen though none had altered mental status or convulsions. Tender hepatomegaly was observed in all of them with maximum liver size of 7cm below the right costal margin in the mid clavicular line. Altered coagulopathy in the form of prolonged prothrombin time was seen in 3 patients and prolonged APTT was seen in only 2 of them. Out of the 5 cases with clinically evident jaundice, 4 of them came for follow up. Repeat liver function test, ultrasonography and coagulation profile been done for this cases and it showed a declining trend by the end of 1 week and were normalized by 2 weeks of post illness reflecting the transient nature of liver injury in dengue infection. Gall bladder wall thickening was reverted back to normal in all the 4 cases. Out of the 5 cases, hypoalbuminemia was seen in 3 cases. Hypoalbuminemia in dengue infection probably is the result of capillary leakage induced by dengue infection. Altered coagulation profile in the form of prolonged PT was seen in all the 5 cases whereas only 1 case had prolonged APTT. Cases on follow up showed normal coagulation profile in the form of normal PT and APTT. One case has been lost for follow up. Trung DT et al., reported an incidence of jaundice <2% [12].

Low serum globulin level has been reported in dengue patients. The reduction in serum globulin is an important factor in fluid loss into the third space, which is indicative of severity in dengue due to reduction in the gradient of intravascular and extra vascular pressure [13].

In the present study mean serum globulin is 2.8. There was a significant difference observed in the mean serum globulin values between the DF, DHF and DSS group with lowest seen in DF group.

Abnormal PT indicates abnormal coagulopathy. It is seen more frequently in cases of dengue presenting with acute hepatic failure, DIC, shock and hepatic encephalopathy. In cases with severe dengue because of increased hepatic cell damage would have caused decreased production of clotting factors resulting in prolonged PT [26].

In our study, 52% cases in DSS group, 30% cases in DHF group and only 1.6% cases with DF had abnormal values of PT, inferring that altered coagulation profile manifested by prolonged prothrombin time is observed significantly higher in dengue haemorrhagic and dengue shock cases in comparison to classical dengue fever.

APTT is also an important marker of coagulation profile. In our study only 5 cases of DSS and 4 cases in DHF group had abnormal APTT values which were not significant statistically. No cases in DF had abnormal APTT values. The histological changes in dengue infections in the liver reported to be micro vascular steatosis, hepatocellular necrosis, Kupffer cell hyperplasia and destruction, Councilman Bodies and cellular infiltrates at the portal tract [12]. The hepatocellular necrosis in dengue generally affects the midzonal area and sometimes the centrilobular area. Reasons for this pattern may be that hepatocytes in this zone are more sensitive to anoxia or the products of an immune response (e.g. cytokines and chaemokines) or that the dengue virus preferentially infects cells in this zone [3].

In this study, 72% of cases in DSS group, 65% in DHF group and 33.9% of cases who presented with DF had HCT>38%. It is observed that elevated HCT values are seen more frequently with increasing diseases severity. It was also observed that the median lowest platelet count was lowest in DHF and DSS as compared to DF. Ole Wichmann et al., showed that patients with dengue shock (41.6%) and DHF (40.3%) had higher HCT values in comparison to the classical dengue fever (36.3%). They also inferred that patients with DHF had significantly lower platelet values than DF [27].

Gall bladder wall thickening on USG was seen in 80% of cases of DSS and DHF compared to only 50.8% cases of DF suggesting that gall bladder wall thickening can be used as predictor to assess the severity of dengue infection. There are studies which showed thickened gall bladder wall with peri-cholecystic fluid in dengue patients. Thickened gall bladder wall could return to normal after some days. More studies are required to conclude about clinical course of gall bladder in dengue [28].

LIMITATION

1. The small study population may be statistically not that accurate in comparison to a study with a large population.
2. The patients selected in this study attended a tertiary care medical institute in a metropolitan city and so don't really reflect the truest prevalence of hepatobiliary involvement of Dengue in general population, especially the rural strata of population, who might not always have the access of this tertiary centre.
3. The past hepatic function status of all the patients couldn't be thoroughly investigated; so there may be some selection bias.
4. Liver biopsy to confirm the histopathologic changes reflecting Dengue hepatitis or Dengue virus-induced liver injury could not be done due to financial, logistic and humanitarian grounds.

CONCLUSION

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 increasing number of cases with fulminant and acute hepatic failure secondary to dengue infection. As there is a clinical overlap in dengue hepatitis with viral hepatitis, enteric hepatitis, leptospirosis, 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 the clinician to identify early the hepatic dysfunction associated with the disease in order to avoid life threatening complications. This will decrease the mortality and morbidity due to dengue infections.

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