

Original Article

LIVER AND GASTROINTESTINAL ASPECTS OF DENGUE INFECTED PATIENTS, IN LAHORE, PAKISTAN

Muhammad Irfan, Naveed Aslam, Atif Masood, Muhammad Arif Nadeem and Aftab Mohsin

Objective: To evaluate the liver and gastrointestinal (GI) aspects of Dengue infected patients during 2011 outbreak in Lahore, Pakistan.

Methods: In a prospective analysis of 301 Dengue infected patients, gender, sleep pattern, family history of Dengue disease, history of co-morbid disease, history of NSAIDs intake, gallbladder edema, ascites, pleural effusion, hepatomegaly, splenomegaly, hypoalbuminemia, type of Dengue disease, Leucopenia during hospitalization, Leukocytosis, grade of thrombocytopenia, hyperbilirubinemia, elevated Alanine Aminotransferase (ALT), prolonged International Normalized Ratio (INR), episode of upper GI bleed were the qualitative variables. Age, weight, minimum white blood cells count (WBC), maximum WBC, minimum platelets count, Maximum Bilirubin, maximum ALT and maximum INR during hospitalization were quantitative variables. The statistical relation of multiple predictive factors with upper GI bleed as well as liver parameters with outcome were checked in Dengue infected patients using SPSS version 15.

Results: Out of the total of 301 patients, 71.4% were male and 28.6% female. 43.2% were defined as Dengue fever (DF), 49.2% as Dengue hemorrhagic fever (DHF), 4.3% as Dengue shock syndrome (DSS) and remaining 3.3% as unusual Dengue syndrome (UDS). During hospitalization, thrombocytopenia, leucopenia, leukocytosis, hypoalbuminemia, hyperbilirubinemia, elevated ALT and prolonged INR were observed in 100%, 50.1%, 15.6%, 49.8%, 13.9%, 92.3% and 4.3% patients respectively. Ultrasonographic findings were gallbladder (GB) edema, ascites, pleural effusion, hepatomegaly and splenomegaly. 18.9% patients suffered upper GI bleed and main endoscopic finding was erosive gastritis with punctate hemorrhages. H/O NSAIDs intake ($p=0.000$), hypoalbuminemia ($p=0.001$), absence of leucopenia (0.000), leukocytosis (0.000), hyperbilirubinemia (0.002) and prolonged INR (0.004) were the predictors for upper GI bleed, while hyperbilirubinemia ($p=0.000$) and prolonged INR ($p=0.000$) were predictive for death in Dengue infected patients.

Conclusions: Dengue is a male predominant disease, where prohibition of NSAIDs intake is necessary to avoid upper GI bleed. Abnormal liver parameters predict upper GI bleed as well as mortality in Dengue infected patients.

Keywords: dengue, outbreak, liver and GI aspects, bivariate analysis, odds ratio.

Introduction

Dengue is an important etiology of acute febrile illness all over the world.¹ The virus belongs to genus, Flavivirus and is transmitted via bite of daytime active female mosquito, Aedes. It has 4 serotypes (DEN-1, DEN-2, DEN-3, and DEN-4).² The disease is suspected if patient has acute febrile illness of duration less than 10 days plus two parameters out of headache, retrobulbar pain, myalgias, arthralgia, rash or bleeding manifestation. Suspected patient with bicytopenia are labelled as probable cases, which are then offered confirmatory laboratory tests like NS1, PCR and IgM & IgG antibodies. The disease spectrum is clinically classified³ as asymptomatic infection, undifferentiated viral fever, Dengue fever, Dengue

hemorrhagic fever and unusual Dengue syndrome. The last one includes all other rare manifestations like Dengue encephalitis⁴, Disseminated intravascular coagulation (DIC)⁵ and liver failure etc.⁶

In Pakistan, the first outbreak of Dengue was observed in Karachi in 1994.⁷ In subsequent years, cases were reported from multiple regions of the country especially during rainy seasons. In 2011, a tsunami-like Dengue outbreak affected Lahore. According to WHO, Dengue is now endemic in Pakistan, where only in 2011, 252935 were suspected cases, 17057 were laboratory confirmed cases and 219 deaths occurred.⁸

The objective of this study was to evaluate the liver and GI aspects of Dengue infected patients during 2011 outbreak in Lahore, Pakistan. In addition, our

will also suggest predictors of upper GI bleed and will correlate liver parameters with outcome in Dengue infected patients.

Method

A prospective analysis of the patients who presented with Dengue at medical unit 3, Services hospital Lahore during an epidemic in Lahore from mid-September 2011 to mid-November 2011, was done. All the patients with febrile illness of duration less than 10 days plus two parameters out of headache, retrobulbar pain, myalgias, arthralgia, rash or bleeding manifestation were suspected for dengue disease and were advised urgent complete blood count. The probable cases were offered confirmatory laboratory tests like NS1, PCR and IgM & IgG antibodies. All the probable and confirmed cases of Dengue of age more than 12 years were enrolled. Suspected cases with warning signs like persistent vomiting, abdominal pain etc were also hospitalized, however enrollment was only made once they fulfilled criteria.

The dengue patients were categorized into Dengue fever and Dengue hemorrhagic fever depending on absence or presence of plasma leak.⁹ To document plasma leak, all these patients were offered abdominal and chest ultrasonography. Gall-bladder edema, tender hepatomegaly and hypoalbuminemia were predictive findings for plasma leak while ascites and pleural effusion were confirmatory for plasma leak. Patient with signs of circulatory failure clinically in term of cold extremities with compromised pulse and blood pressure in addition to plasma leak were labelled as Dengue shock syndrome. Other presentations like Dengue encephalitis, Acute Liver failure etc was labelled as Unusual Dengue syndrome. During whole hospitalization, hematological parameters, liver function tests, renal functions tests and other relevant investigations were obtained on daily basis. The patients were managed according to standard protocol.^{10,11} Urgent upper GI endoscopy was offered to all those patients who complained of hematemesis or melena.¹² The endoscopic findings were noted and relevant management was provided.

During data interpretation, Leucopenia and Leukocytosis were defined by WBC count less than $4 \times 10^9/L$ and more than $11 \times 10^9/L$ respectively.¹³ Thrombocytopenia was labelled to a platelet count below $150 \times 10^9/L$. Its severity grading was done as mild thrombocytopenia (100 to $150 \times 10^9/L$),

moderate thrombocytopenia (50 to $100 \times 10^9/L$) and severe thrombocytopenia ($<50 \times 10^9/L$).¹⁴ Hypoalbuminemia was labelled to a value less than $3.5g/dl$ while hyperbilirubinemia was defined by a value above its upper normal limit ($1.2 mg/dL$). Similarly, INR was labelled prolonged if its value was above its upper normal limit (1.4).¹⁵

The gender, sleep pattern, family history of Dengue disease, history of comorbid disease, history of NSAIDs intake, gallbladder edema, ascites, pleural effusion, hepatomegaly, splenomegaly, hypoalbuminemia, Type of Dengue disease, episode of upper GI bleed, Leucopenia during hospitalization, Leukocytosis, grade of thrombocytopenia, hyperbilirubinemia, elevated Alanine Aminotransferase (ALT), prolonged INR during hospitalization were the qualitative variables. Age, weight, minimum WBC during Hospitalization, maximum WBC during Hospitalization, minimum PLT count during Hospitalization, Maximum Bilirubin during hospitalization (mg/dl), maximum ALT during hospitalization and Maximum INR during hospitalization were quantitative variables.

The valuable data was evaluated on SPSS version 15. During descriptive interpretation of data, means and standard deviations were calculated for quantitative variables, and frequencies and percentages were computed for presentation of qualitative variables. The bivariate analysis was performed in order to determine the significant relation of different predictive factors with upper GI bleed in Dengue infected patients. A similar analysis was also performed to see significant association between liver parameters and outcome of Dengue infected patients. While applying chi-square test of independence, a p value of equal to or less than 0.05 was considered as significant. Moreover, odds ratio along with their 95% confidence interval (CI) were also calculated for each association.¹⁶

Results

A total of 301 Dengue disease patients were managed, out of which 215 (71.4%) were male and 86 (28.6%) were female. Age ranged from 12-70 years, with a mean value of 34.90 ± 14.94 (Table 1). The sleep pattern in last 2 weeks was in close room consistently of 207 (68.7%) patients. Only 99 (32.9%) patients had history of Dengue in their family members. 57 (18.9%) patients had a history of NSAIDs intake in last 2 weeks for IHD, joint disease or fever etc.

Among total of 301 patients, 130 (43.2%) were

will also suggest predictors of upper GI bleed and will correlate liver parameters with outcome in Dengue infected patients. encephalitis, 2 of Liver failure, 1 of GB syndrome, 1 of DIC, 1 of subdural hematoma and 1 of mixed picture with a positive slide for malaria. During hospitalization, thrombocytopenia was universal i.e. observed in 100% patients. The grade of thrombocytopenia was severe in majority patients (84.7%). Leucopenia, leukocytosis and hypoalbuminemia was seen in 151 (50.1%), 47 (15.6%) and 150 (49.8%) patients respectively. Among Liver function tests, hyperbilirubinemia, elevated ALT and prolonged INR was found in 42 (13.9%), 278 (92.3%) and 13(4.3%) patients respectively.

Among abdominal and chest ultrasonographic findings, 195 (64.8%) patients had GB edema, 143 (47.5%) had ascites, 96 (31.9%) had pleural effusion, 27 (9%) had hepatomegaly and 5(1.7%) had splenomegaly. Ascites was mainly mild (in 67.8% patients), while pleural effusion was predominantly minimal right sided (in 78.1% patients) (Table 2)

Among total 301patients, only 57 (18.9%) suffered an episode of upper GI bleed in term of hematemesis or melena. 54 patients underwent upper GI endoscopy, where main finding was erosive gastritis with multiple punctate hemorrhages. Among patients who underwent upper GI endoscopy, 53 required conservative management and one having duodenal ulcer with overlying clot required electrocoagulation (Table 3)

Multiple predictors of upper GI bleed in Dengue infected patients were evaluated. H/O NSAIDs intake (p=0.000), hypoalbuminemia (p=0.001), absence of leucopenia (0.000), leukocytosis (0.000), hyperbilirubinemia (0.002) and prolonged INR during hospitalization (0.004) had a statistically significant association with occurrence of upper GI bleed. Among patients with H/O NSAIDs intake, 34 (59.6%) patients suffered upper GI bleed while 29 (11.9%) did not suffer upper GI bleed. Among patients with hypoalbuminemia, 40 (70.2%) suffered upper GI bleed while 110 (45.1%) did not. Similarly, among patients with leucopenia, 15 (26.3%) patients suffered upper GI bleed while 136 (55.7%) did not. Among patients with leukocytosis, 20 (35.1%) patients suffered upper GI bleed while 27 (11.1%) did not. Among patients with hyperbilirubinemia, 16 (28.1%) patients suffered upper GI bleed while 26 (10.7%) did not. Lastly, among patients with prolonged INR, 7

(12.3%) patients suffered upper GI bleed while 6 (2.5%) did not. (Table 4)

The outcome of the dengue infected patients was as follow: Among 301 patients, 290 (96.3%) recovered and 11 (3.7%) died. Liver parameters were statistically correlated with outcome. Hyperbilirubinemia (p=0.000) and prolonged INR (p=0.000) had significant association. Among patients with hyperbilirubinemia, 7 (63.6%) patients died while 35 (12.1%) recovered. Among patients with prolonged INR, 6 (63.6%) died while 6 (2.1%) recovered (Table 5)

Quantitative Variables/ categories	Min.	Max.	SD
Age (years)	12	70	34.90±14.94
Weight (kg)	25	11.	62.61±14.0
Minimum WBCs during hospitalization (109/L)	1.2	21.4	4.78±2.73
Maximum WBCs during hospitalization (109/L)	1.9	29.2	7.92±4.03
Minimum Platelets during hospitalization (109/L)	02	149	28.88±26.40
Maximum Bilirubin during hospitalization (mg/dl)	.3	23	1.08±1.72
Maximum ALT during hospitalization (IU/L)	14	4866	208.97±406.75
Maximum INR during hospitalization	0.9	4.4	1.11±0.28

Table-2: Ultrasonographic findings of Dengue infected patients (n = 301).

Ultrasonographic findings /Categories	Freq. (Present)
Gallbladder edema	Yes 195 (64.8%)
	No 106 (35.2%)
Ascities	Mild 97 (32.2%)
	Moderate 45 (15%)
	Severe 1 (0.3%)
Pleural effusion	No 158 (52.5%)
	Right sided, minimal 75 (24.9%)
	Bilateral 16 (5.3%)
	Left sided 5 (1.7%)
Hepatomaegaly	No 205 (68.1%)
	Yes 27 (9%)
Splenomegaly	No 274 (94%)
	Yes 5 (1.7%)
	No 296 (98.3%)

Table-3: Endoscopic findings of Dengue infected patients who presented with Upper GI bleed (n = 54/301).

Endoscopic findings	Frequency (percent)
Erosive gastritis with multiple punctate hemorrhages	23 (42.5%)
Erosive gastritis & duodenitis with multiple punctate hemorrhages	18 (33%)
Esophagitis, gastritis & duodenitis with punctate hemorrhages	7 (13%)
Isolated duodenitis with punctate hemorrhages	3 (5.5%)
Clean base gastric ulcer	1(2%)
Clean base duodenal ulcer	1(2%)
Duodenal ulcer with overlying clot	1(2%)

Discussion

Dengue is important public health issue in Pakistan that threatens us especially in every rainy season. It is transmitted via bite of Aedes, a daytime active predator. In our study, main gender infected was male (71.4%). Similar results were shown by M. Aamir & colleagues from GTTH, Lahore, where 81.1% Dengue patients were male.¹⁷ This may be because of fact that in our society, males are more commonly present outdoor in parks or public places, more than females. So, they are more prone to get attacked by this daytime predator.

Like thrombocytopenia, ALT elevation was more universal in Dengue infected patients than leucopenia

Table-4: Predictors of Upper GI bleed in Dengue-infected patients (n = 301).

Predictors/Categories		Episode of Upper GI bleed		p-value	Odd ratio with 95% Confidence interval
		Yes	No		
Gender	Male	42 (73.7%)	173 (%)	0.746	1.149 (0.599-2.204)
	Female	15 (26.3%)	71 (29.1%)		
Sleep pattern in last 2 weeks:	Close Room	40 (70.2%)	167 (68.4%)	0.875	0.922 (0.492-1.728)
	Open Air	17 (29.8%)	77 (31.61%)		
H/O Dengue in family members	Yes	15 (26.3%)	84 (34.4%)	0.275	0.0680 (0.357-1.298)
	No	42 (73.7%)	160 (65.6%)		
H/O Comorbid disease:	Yes	13 (22.8%)	65 (26.6%)	0.617	0.814 (0.412-1.607)
	No	44 (77.2%)	179 (73.4%)		
H/O NSAIDs intake in last 2 weeks for IHD, Joint disease or fever etc:	Yes	34 (59.6%)	29 (11.9%)	0.000	10.960 (5.687-21.120)
	No	23 (40.4%)	215 (88.1%)		
Hypoalbuminemia:	Yes	40 (70.2%)	110 (45.1%)	0.001	2.866 (1.540-5.333)
	No	17 (29.8%)	134 (54.9%)		
Type of Dengue disease:	DF	27 (47.4%)	102 (41.8%)	0.461	0.798 (0.447-1.424)
	Other variant (DHF,DSS, Unusual Dengue syndrome)	30 (52.6%)	142 (58.2%)		
Leucopenia during hospitalization:	Yes	15 (26.3%)	136 (55.7%)	0.000	0.284 (0.149-0.539)
	No	42 (73.7%)	108 (44.3%)		
Leukocytosis:	Yes	20 (35.1%)	27 (11.1%)	0.000	4.344 (2.212-8.534)
	No	37 (64.9%)	217 (88.9%)		
Grade of Thrombocytopenia	Mild to moderate	9 (15.8%)	37 (15.2%)	0.841	0.953 (0.431-2.107)
	Severe	48 (84.2%)	207 (84.8%)		
Hyperbilirubinemia:	Yes	16 (28.1%)	26 (10.7%)	0.002	3.272 (1.614-6.632)
	No	41 (71.9%)	218 (89.3%)		
Prolonged INR during hospitalization:	Yes	7 (12.3%)	6 (2.5%)	0.004	5.553 (1.790-17.230)
	No	50 (87.7%)	238 ((97.5%)		

H/O = History of; DHS = Dengue Hemorrhagic Syndrome; DSS = Dengue Shock Syndrome;

Table-5: Correlation of Liver parameters with outcome in Dengue infected Patients (n = 301).

Liver parameters/Categories		Outcome		p-value	Odd ratio with 95% Confidence interval
		Death	Discharge		
Hepatomegaly:	Yes	1 (9.1%)	26 (9%)	1.000	0.985 (0.121-8.000)
	No	10 (90.9%)	264 (91%)		
Gallbladder edema:	Yes	7 (63.6%)	188 (64.8%)	1.000	1.053 (0.301-3.683)
	No	4(36.4%)	102 (35.2%)		
Hyperbilirubinemia:	Yes	7 (63.6%)	35 (12.1%)	0.000	0.078 (0.022-0.282)
	No	4(36.4%)	255 (87.9%)		
Elevate ALT:	Yes	11 (100%)	267 (92.1%)	1.000	1.041 (1.017-1.066)
	No	0 (0%)	23 (7.9%)		
Prolonged INR during hospitalization:	Yes	7 (63.6%)	6 (2.1%)	0.000	0.012 (0.003-0.053)
	No	4(36.4%)	284 (97.9%)		

H/O = History of; DHS = Dengue Hemorrhagic Syndrome; DSS = Dengue Shock Syndrome;

Discussion

Dengue is important public health issue in Pakistan that threatens us especially in every rainy season. It is transmitted via bite of Aedes, a daytime active predator. In our study, main gender infected was male (71.4%). Similar results were shown by M. Aamir & colleagues from GTTH, Lahore, where 81.1% Dengue patients were male.¹⁷ This may be because of fact that in our society, males are more commonly present outdoor in parks or public places, more than females. So, they are more prone to get attacked by this daytime predator.

Like thrombocytopenia, ALT elevation was more universal in Dengue infected patients than leucopenia in our study (50.1% vs 92.3%). Absence of Leucopenia and leukocytosis were also predictive of upper GI bleed. Perhaps, overt & covert GI bleed, secondary bacterial infection or a third mechanism were responsible for the absence of leucopenia in approx. half of the patients. I think, for defining probable Dengue, where bicytopenia is a criterion, high transaminases esp. elevated ALT may be a more useful marker than leucopenia. Further studies will validate this point. In our study, main ultrasonographic finding was GB edema (64.8%). Others were ascites (47.5%), pleural effusion (31.9%), hepatomegaly (9%) and least common finding was splenomegaly (1.7%). Similar findings were observed by Indians in 2012¹⁸, where observations were GB edema (66.7%), ascites (64.5%), pleural effusion (50%),

hepatomegaly (16.7%) and splenomegaly (17.7%). Hence, Ultrasound is a good quick non-invasive too with consistent findings to support diagnosis of Dengue in majority patients as well as to confirm the plasma leak in term of ascites and pleural effusion.

In our study, 18.9% Dengue infected patients suffered upper GI bleed. In a large 1156 patients study from Taiwan¹⁹, only 8.4% patients faced upper GI bleed. Our 18.9% patients had H/O NSAIDs intake that was significantly associated with occurrence of this upper GI bleed (P.000). Hence, this percentage of bleeding patients could be reduced by proper public awareness regarding NSAIDs prohibition in acute febrile illness especially during rainy season.

In our study, endoscopic findings were mainly mucosal erosions & punctate hemorrhages in upper GI tract. Only 3 patients have ulcer, 2 with clean base and one with overlying clot. In Taiwan study¹⁹, more than 50% patients had ulcer disease. This diversity may escape our patients from therapeutic endoscopic management and strengthen the need of immediate medical management. Depending upon these findings, prophylactic role of proton pump inhibitors (PPI) to avoid upper GI bleed in our population infected with Dengue can be assessed in future studies.

In our study, two abnormal liver parameters (hyperbilirubinemia, prolonged INR) were predictive of upper GI bleed. International data is scarce on this issue that whether liver involvement has a role in

Were also predictive of death in Dengue infected patients in our data. Hence, liver involvement may be the main etiology of morbidity and mortality in Dengue infected patients in our population. Further studies are required to validate this hypothesis.

Conclusion

This study concluded that Dengue is a manageable disease with male predominance. Prohibition of

NSAIDs intake during acute febrile illness is necessary to avoid upper GI bleed. Liver abnormality has a vital role in morbidity and mortality of Dengue infected patients as well as in occurrence of upper GI bleed.

*Department of Medicine,
Teaching hospital, Gujranwala*

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