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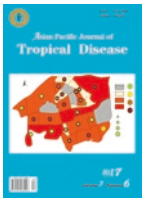

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Profile of dengue hepatitis in children from India and its correlation with WHO dengue case classification

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ABSTRACT

Objective: To study the profile of liver involvement in children with dengue fever and to compare the severity of liver involvement with World Health Organization case definition.

Methods: A prospective study was carried out from October 2013 to December 2014. Serologically confirmed dengue patients were grouped into three categories according to the World Health Organization classification. Groups 1 and 2 were dengue fever without and with warning signs, respectively; Group 3 was severe dengue. Biochemical and clinical profile of hepatic involvement was studied.

Results: A total of 162 children with dengue fever (M:F = 2.37) were included in the study. Median (inter quartile range) age was 12 years (IQR: 0.5–18 years). Hepatitis was observed in 151 (93.2%) patients. Analysis revealed that out of all liver function test parameters, total bilirubin was found to be a significant predictor of dengue category two and three and albumin and ALT levels were significant predictors for category three. Eight cases presented with ALF. Their median AST was 4 817 (range 61–26 957); median ALT was 2 386 (range 39–11 100); median INR was 2.57 (range 1.6–4.2) and their median serum bilirubin was 2.95 (range 0.6–9.0).

Conclusions: Some degree of hepatitis is very common in dengue infection with rise in AST being more than ALT irrespective of the severity of dengue. Severity of hepatitis correlates well with the severity of dengue and can help in triaging of dengue patients. Of all liver function parameters, total bilirubin levels correlate best with severity of dengue infection.

1. Introduction

Dengue fever is an arboviral infection transmitted by mosquito *Aedes ageptyi* as well as *Aedes albopictus* and causes a spectrum of illness. Approximately 50–100 million cases of dengue, a major cause of morbidity in tropical and sub-tropical regions, occur annually with around 20 000 deaths[1]. The 2009 revised World Health Organization (WHO) dengue case classification for the diagnosis and management of the illness follows previous guidelines published by WHO between 1974 and 1997[2,3]. The findings of the Dengue Control (DENCO) study formed the basis of the "revised 2009 WHO case definitions", which has classified this illness into dengue 1) with and 2) without warning signs and 3) severe dengue according to levels of severity[1,4].

Dengue virus infection is an important health problem in many Southeast Asian countries. In recent years, several epidemics of dengue have been reported from India and the number of cases each year is increasing. India is in a high risk zone of transmission of dengue infection in view of its temperature and humidity profile. According to WHO, India is amongst the top 30 countries with regards to the rate of transmission[1].

Liver involvement is known to occur in children with dengue infection. The degree of liver dysfunction in children with dengue varies from mild injury with elevation of transaminases to severe injury with jaundice to even acute liver failure. The severity of liver dysfunction varies according to the type of clinical presentation of dengue. Liver involvement in dengue fever is manifested by the elevation of transaminases representing reactive hepatitis[5,6]. Data

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regarding the pattern of liver involvement in children according to this new classification of WHO are scanty.

We therefore studied the profile of liver involvement among a group of children affected during two recent outbreaks of dengue in our institute and compared the severity of liver involvement in these patients with varying severity of this illness according to the WHO criteria.

2. Materials and methods

Data on patients (< 18 years of age) admitted to our institution from October 2013 to December 2014 were recorded prospectively on a proforma after taking informed consent. The diagnosis of dengue was based on clinical presentation with fever of short duration (≤ 15 days) and thrombocytopenia (platelet count < 100×10^9/L), and a positive dengue serology (NS 1 antigen/anti dengue – IgM antibody) irrespective of the presence or absence of hemorrhagic manifestations.

Patients were grouped into three categories according to the WHO classification: 1) dengue fever without warning signs (Group 1); 2) dengue fever with warning signs (Group 2); and 3) severe dengue (Group 3). Warning signs included abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets. Severe dengue included cases with severe plasma leakage leading to shock, fluid accumulation with respiratory distress, cases with severe bleeding and with severe organ involvement [aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 1 000, impaired consciousness, other severe organ involvement)[1].

A detailed history was taken in all patients and a detailed clinical examination was done. A complete blood count including platelet count was done and patient's sera were tested for IgM anti-dengue virus antibodies using a commercially available anti-dengue virus ELISA (IgM) assay (EUROIMMUN, AG). Dengue NS1 Ag test was done using a commercially available one step, rapid immunochromatographic test (Standard Diagnostics, Inc. Korea). Liver function tests (including bilirubin, ALT, AST, serum albumin), coagulation profile [prothrombin time (PT) and activated partial thromboplastin time (APTT)] and chest X-ray were done in patients who fulfilled the criteria for diagnosis of dengue. Abdominal ultrasonography was also done.

Hepatitis was defined as AST or ALT > 40 IU/mL in our study. It was further classified into 1) mild hepatitis – up to 3 fold elevation of either AST or ALT or both from upper limit of normal (40 IU/mL); 2) moderate hepatitis – 3 to 10 fold elevation and 3) severe – more than 10 fold elevation. Acute liver failure (ALF) was defined as acute insult to liver with no pre-existing liver disease with an INR > 2 with or without encephalopathy or INR > 1.5 with encephalopathy[7]. These various lab parameters were compared in between these three groups of dengue fever.

Data analysis included profiling of patients on different demographic, clinical diagnosis and laboratory findings. Quantitative data were presented in terms of mean, median, inter quartile range (IQR) range and standard deviation. Lab parameters *viz*. total bilirubin, AST and ALT were converted into log values to normalize the data. One-way analysis of variance test was carried out to see if there is a significant variation between the WHO classified groups. *Post hoc* pair wise comparison was carried using Sidak test. Qualitative/categorical data were presented as absolute numbers and proportions. Cross tables were generated and *Chi*-square test was used for testing of significance.

To determine cut off values of lab parameters, multinomial logistic regression analysis was carried out by taking WHO group as dependent variable (1, 2 and 3) and lab parameters as independent variables. Further, background variables such as age, gender and weight were also taken as confounding variables. Adjusted odds ratio and its 95% confidence limits were calculated. Probability value of greater than 0.5 was set off for predicted group. Based on correct classification of cases by model, 95% confidence limits were calculated, which may be validated in future prospective study. $P < 0.05$ was considered statistically significant. SPSS software IBM Version 20.0 was used for statistical analysis.

3. Results

3.1. Dengue fever

Out of 162 children with dengue fever, male children were 70.4% and median (IQR) age was 12 years (IQR: 0.5–18 years). Clinical and biochemical parameters are shown in Table 1. Age and gender distribution of patients is shown in Figure 1. A total of 61 (37.6%) dengue patients presented without warning signs, 72 (44.4%) presented with warning signs and 29 (17.9%) had severe dengue (Table 1). IgM anti-dengue virus antibodies were positive in 34 cases (20.9%) and NS1Ag was positive in 139 cases (85.8%).

Table 1
Table showing patient clinical characteristics and liver function tests in patients with dengue infection (n = 162).

Parameter	Value
Clinical and laboratory characteristics	
Hepatomegaly on clinical examination (> 2 cm)	18 (11.1%)
Ascites on clinical examination	2/162 (1.2%)
Ascites on ultrasonography	81/151 (53.6%)
Liver function tests	
Total serum bilirubin (mg/dL)	0.61 ± 0.89 (0.1–9.0)
*AST (IU/L)	635.17 ± 2 569.30 (18–26 957)
*ALT (IU/L)	289.50 ± 1 104.70 (6–11 100)
*Serum albumin (g/dL)	3.51 ± 0.76 (1.8–5.2)
Dengue without warning signs (%)	61 (37.6%)
Dengue with warning signs (%)	72 (44.4%)
Severe dengue (%)	29 (17.9%)

*Data for various biochemical parameters are shown as mean (range).

All patients had fever as the presenting complaint. The median duration of the fever was 4 days. In addition, 96 patients (59.2%) presented with vomiting, 81 (50%) had pain in the upper abdomen and 58 patients (35.8%) had petechial rash. Twenty six (16%) had bleeding manifestations, out of which 14 (53.8%) had gastrointestinal bleeding. Ten (6.17%) had myalgia and 12 (7.4 %) had neurological symptoms (seizures, altered sensorium or both) (Figure 2).

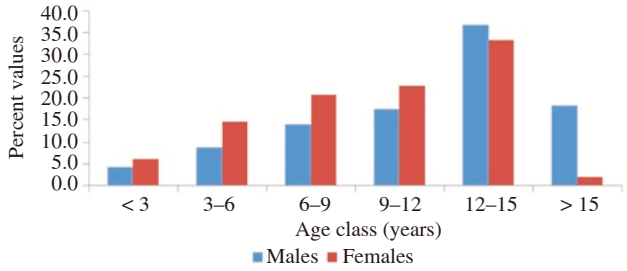

Figure 1. Age and gender distribution of study population.

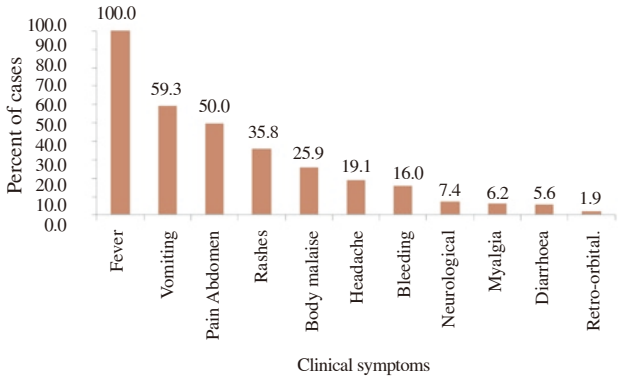

Figure 2. Distribution of presenting complaints among dengue patients.

3.2. Dengue with hepatitis

Out of 162 dengue patients, hepatitis was observed in 151 (93.2%) patients. Figure 3 shows the age and gender distribution for the dengue hepatitis patients. Out of 151 cases, 60 (39.7%) patients had mild hepatitis, 70 (46.3%) patients had moderate hepatitis and 21 (13.9%) had severe hepatitis. Liver function tests revealed raised AST in 147/151 (97.3%) patients [mean AST 635.17 (range 41–26957)] and ALT was raised in 117/151 (77.4%) patients [mean ALT 289.5 (range 41–11 100)].

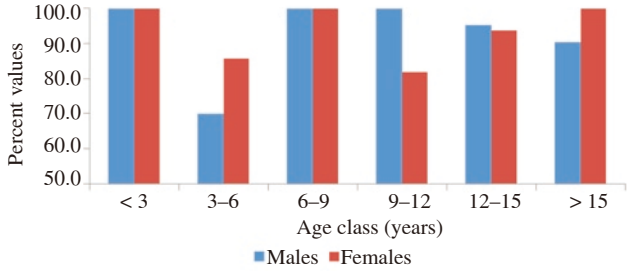

Figure 3. Age and gender distribution of dengue hepatitis patients.

Results of One-way analysis are shown in Table 2. All the parameters were found to be significantly ($P < 0.001$) varied between the groups. *Post-hoc* analysis by Sidak test showed that pair-wise comparison also revealed statistical significance ($P < 0.05$) in majority of comparisons. Since there was a significant variation in the lab parameters, multinomial logistic regression analysis was carried out by taking WHO group as dependent variable (1, 2 and 3) and lab parameters were taken as independent variables. Further, background variables such as age, gender and weight were also used as confounding variables in the analysis. The analysis revealed that the overall model (likelihood ratio test *Chi*-square = 94.33; $P < 0.001$) was statistically significant.

Table 2
Results of One-way ANOVA test on lab parameters.

Variables	Groups	*n*	Mean	SD	*F*-value	*P*-value
log_bilirubin	1	58	0.0519	0.1147	16.13	0.001
	2	71	0.1194	0.1562		
	3	29	0.2713	0.2686		
	Total	158	0.1225	0.1856		
log_ast	1	61	1.9196	0.3513	34.83	0.001
	2	72	2.1757	0.3061		
	3	29	2.7603	0.7946		
	Total	162	2.1839	0.5324		
log_alt	1	61	1.7106	0.3076	26.84	0.001
	2	72	1.8797	0.3096		
	3	29	2.4129	0.7705		
	Total	162	1.9115	0.4918		
Albumin	1	58	3.7600	0.6570	22.42	0.001
	2	71	3.5500	0.6720		
	3	29	2.7200	0.7970		
	Total	158	3.4700	0.7800		

Adjusted odds ratio and its 95% confidence limits were calculated for each lab parameter and presented in Table 3. Analysis revealed that out of all liver function test parameters, total bilirubin is found to be a significant predictor of dengue category two and three and albumin and ALT levels are significant predictors for category three. While total bilirubin value is showing on the increasing trend, the risk of getting type 2 dengue is about 2.6 times (166%) (95% *CI*: 1.05–6.25) higher compared to category one. Other lab parameters *viz.* AST, ALT and albumin are not suggestive of significant predictor for category 2. Among the patients with lower albumin and higher total bilirubin and ALT levels, the chance of getting dengue type 3 is 260% higher compared to type 1 dengue category. Based on logistic regression analysis, percent correct classification of cases for category 1, 2 and 3 are 60%, 69% and 66%, respectively. The overall percent correct classification of the cases is found to be 65%.

95% confidence limits for all the lab parameters were calculated separately for each category and are presented in Table 4. Group wise mean ± SD values for lab parameters of dengue patients are shown in Figures 4 and 5.

Table 3
Adjusted odds ratio for dengue classification.

Category	Lab. parameters	Logistic regression coefficient	Adjusted odds ratio	95% *CI*	
				Lower	Upper
Group 1 (reference)					
Group 2	T. Bulirubin	0.941	2.56	1.05	6.26
	AST	0.006	1.01	1.00	1.01
	ALT	–0.007	0.99	0.98	1.01
	Albumin	–0.484	0.62	0.33	1.15
Group 3	T. Bulirubin	1.277	3.58	1.07	12.03
	AST	0.009	1.01	1.00	1.02
	ALT	–0.009	0.99	0.98	1.00
	Albumin	–1.676	0.19	0.08	0.45

Percent correct classification for category 1 = 60% (34/57). Percent correct classification for category 2 = 69% (49/71). Percent correct classification for category 3 = 66% (19/29). Percent overall correct classification = 65% (102/157).

Table 4
Range of values that may be used for classification of dengue cases.

Category	Lab Parameter	Mean ± SD	95% *CI*	
			Lower	Upper
1 (n = 34)	T. Bulirubin	0.03 ± 0.17	0.00	0.09
	AST	88.47 ± 75.46	62.14	114.80
	ALT	60.06 ± 52.39	41.78	78.34
	Albumin	3.88 ± 0.64	3.66	4.11
2 (n = 49)	T. Bulirubin	0.49 ± 0.55	0.33	0.65
	AST	207.63 ± 133.89	169.18	246.09
	ALT	104.61 ± 67.42	85.25	123.98
	Albumin	3.57 ± 0.65	3.39	3.76
3 (n = 19)	T. Bulirubin	1.79 ± 2.18	0.74	2.84
	AST	4239.63 ± 6585.82	1065.37	7413.90
	ALT	1852.95 ± 2821.11	493.22	3212.68
	Albumin	2.47 ± 0.61	2.18	2.77

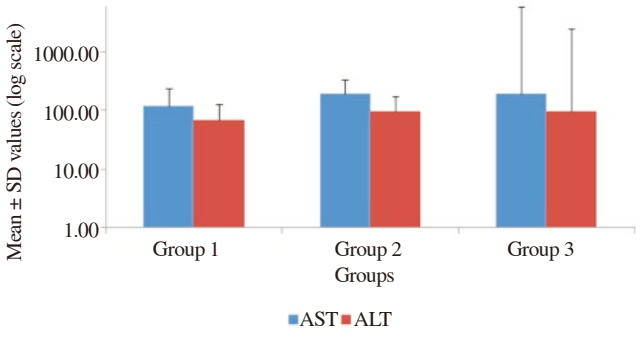

Figure 4. Group wise mean ± SD of AST and ALT of dengue patients.

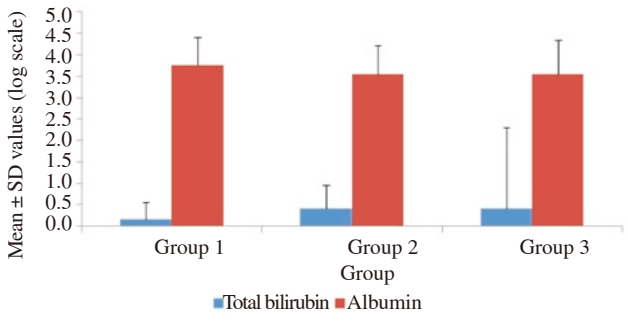

Figure 5. Group wise mean ± SD of total bilirubin and albumin of dengue patients.

Ultrasonographic evidence of ascites was observed more often among patients with more severe forms of dengue. Gallbladder wall edema was not a significant finding and did not help in differentiating severity of dengue. Hepatomegaly was seen in 29% and 30% cases in Groups 1 and 2 respectively which was statistically not significant.

3.3. Dengue with ALF

Eight cases presented with ALF during this period (5.2%). All of them were males. Mean age was 8.3 years (range 8 months–17 years). NS1 antigen was detected in 7 subjects and IgM anti-dengue virus antibodies were detected in 4 subjects. Their median AST was 4817 (range 61–26957); median ALT was 2386 (range 39–11100); median INR was 2.57 (range 1.6–4.2), median albumin was 2.55 (range 2.2–2.9) and their median serum bilirubin was 2.95 (range 0.6–9.0).

Associated co-morbidities were acute respiratory distress (ARDS), acute kidney injury (AKI), myositis, and morbid obesity. Five presented with ARDS and AKI, two with myositis and two presented with morbid obesity. One case of ALF died from the total study population.

4. Discussion

We report one of the largest cohort studies from India on hepatitis in dengue fever in children. Our data show that dengue affects children more in the 2nd decade and males were two and half times more affected. Nearly one fifth of patients had severe dengue indicating that severe dengue is not uncommon in children. Fever was a universal symptom in our study and vomiting and pain abdomen were the most common symptoms. Retro-orbital pain, myalgias and headache which are common symptoms seen in adults are not so common amongst children with dengue fever.

Some degree of liver injury was almost universally present in children with dengue. In most patients liver dysfunction was mild to moderate, presenting primarily as asymptomatic elevation of serum aminotransferases. However, some patients had clinical manifestations of liver disease, namely jaundice, hepatomegaly and ascites. Clinically detectable hepatomegaly and ascites are also not a common finding in mild to moderate cases though seen in more than half of the severe dengue cases[8-11].

It is possible to confuse dengue hepatitis to typical acute viral hepatitis, especially in countries where outbreaks of hepatitis A and E are common. However, the presence of thrombocytopenia, persistence of fever after the appearance of jaundice, low degree elevation of liver enzymes and bilirubin and AST/ALT ratio > 1 can help to make a diagnosis of dengue hepatitis. The level of hyperbilirubinemia is less as compared to the rise in transaminitis in dengue hepatitis even with cases of severe dengue.

Mechanisms of liver injury in dengue may be due to direct cytopathic effects of virus or immune response of host, and/or hypoxia caused by hypotension or localized vascular leakage inside the liver[6,12,13]. Reports have demonstrated a high affinity of the dengue virus for human liver cells and dengue virus has been isolated from the liver of fatal cases[13,14].

The fact that SGOT is raised more as compared than SGPT, as also reflected in our study, also helps in differentiating dengue hepatitis from other viral hepatitis. In our study, AST was raised in 97.3% of dengue hepatitis as compared to ALT in 77.4% of patients. Wong and Shen[15] reported that AST abnormality was predominantly higher as compared to ALT; 91% and 72% respectively, which is consistent with our study. Similar pictures have also been shown by other studies[13,16]. Mean AST in each group in our study is almost double than the mean ALT.

On comparing different LFT parameters with the severity of dengue, serum bilirubin is the parameter which has a good correlation with the severity of dengue infection. High total bulirubin value in a dengue patient increases the risk of falling in cateogry 2 and 3. Similarly hypoalbuminemia was also found to be a good predictor for category 3. An AST value of more than four times the upper limit of normal in a dengue fever child highly suggest that the child would fall in either Group 2 and should warn the need for admission [PPV 68.75% (95% *CI*: 55.94%–79.76%)]. Likewise, an ultrasound finding of ascites correlates best with the severity of dengue. We didn't find gallbladder wall edema an important finding in triaging of such patients. We find significant difference among these various subgroups implementing that this new classification is useful in triaging of patients.

We found eight cases of ALF during our study period indicating that ALF in dengue fever is not uncommon. Again, median AST was more than double of median ALT in this group. Significant hyperbilirubinemia was not a feature of dengue ALF in contrast to ALF due to hepatotropic viruses. There was one death in the whole study group indicating that dengue hepatitis has a favorable prognosis.

Our study included only serologically confirmed children of dengue infection and were not having any other concomitant infection. Our study has included only inpatients and has not included outpatients. We also did not check for the type of dengue virus.

The spectrum of hepatic involvement in dengue varies from mild elevation of liver enzymes to liver failure. Some degree of hepatitis is seen in most dengue fever cases. Severity of liver involvement correlates well with the severity of dengue infection and helps in triaging of patients.

Conflict of interest statement

We declare that we have no conflict of interest.

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