

Hepatic Involvement in Dengue Fever in Children

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Abstract

Objective: Hepatic dysfunction is common in dengue infection and the degree of liver dysfunction in children varies from mild injury with elevation of transaminases to severe injury with jaundice. This study was undertaken to assess the spectrum of hepatic involvement in dengue infection.

Methods: 110 children with serologically positive dengue fever aged between 2 months - 14 years were studied for their hepatic functions both clinically and biochemically after excluding malaria, enteric fever, Hepatitis A and Hepatitis B with relevant investigations.

Findings: All cases were grouped into DF (Dengue fever), DHF (Dengue hemorrhagic fever) and DSS (Dengue shock syndrome) according to WHO criteria. The spectrum of hepatic manifestations included hepatomegaly (79%), hepatic tenderness (56%), jaundice (4.5%), raised levels of aspartate transaminase (AST)(93 %), alanine transaminase (ALT)(78%), alkaline phosphatase (AP) (57%), prolonged prothrombin time (PT) (20%), reduced levels of serum albumin (66%) and abnormal abdomen ultrasound (65%).

Conclusion: Hepatic dysfunction was observed more in DHF and DSS group compared to DF group. About 17.27% of children had >10 fold increase in the liver enzymes. There was no correlation between the degree of hepatic enlargement or hepatic tenderness with the abnormalities of liver functions. Any child with fever, jaundice and tender hepatomegaly in geographical areas where dengue is endemic, the diagnosis of dengue infection should be strongly considered.

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Key Words: Dengue; Hepatomegaly; Liver enzymes; Children; Jaundice

Introduction

Dengue infection is the most rapidly spreading mosquito-borne viral disease in the world and an estimated 50 million dengue infections occur annually [1]. Case fatality rates for the South-East Asian region are 1%, but in India, Indonesia and Myanmar, focal outbreaks have reported rates of 3%-5% [1]. Unusual manifestations involving liver and central nervous system in dengue infection

have been reported [2,3]. The degree of liver dysfunction in children with dengue infection varies from mild injury with elevation of transaminases to severe injury with jaundice and liver cell failure [4-7]. The incidence of hepatic dysfunction is more in Dengue shock syndrome (DSS) and Dengue hemorrhagic fever (DHF) [2,4-10]. Aminotransferase levels are useful in predicting the occurrence of hepatic dysfunction and spontaneous bleeding [4]. In recent studies from

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India and Thailand, dengue infection was the most important cause of acute hepatic failure in children contributing to 18.5% and 34.3% of the cases respectively [11,12]. Hence early recognition and prompt initiation of appropriate supportive treatment can decrease the morbidity and mortality. Most of the data reported on abnormal liver functions in dengue are retrospective [2,6,8,9]. Therefore this cross sectional study with new data was undertaken to assess the spectrum of hepatic involvement in children with Dengue infection.

Subjects and Methods

This prospective study was conducted in the department of pediatrics, JSS Medical College Hospital, Mysore, India, from November 2008 to July 2010. All clinically suspected dengue infection children as per the WHO guidelines between 2 months to 14 years of age were screened and only serologically confirmed cases by dengue IgM capture ELISA were included. Ethical approval was obtained from Ethical Committee of the JSS Medical college Hospital, Mysore and written informed consent was obtained from the parents. A detailed history and a thorough clinical examination were done in all the cases. Data was collected in a prewritten proforma. Malaria, enteric fever, Hepatitis A and Hepatitis B were excluded by history, examination and investigations. All the cases were subjected to following investigations: Dengue IgM capture ELISA, Hemoglobin (Hb), total count (TC), differential leukocyte count (DLC), Platelet count, Hematocrit (HCT), Peripheral Blood Smear, Serum Bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AP), serum albumin, serum globulin, total proteins, Prothrombin time (PT) Activated partial thromboplastin time (APTT), Quantitative Buffy Coat for malarial parasite, blood culture, chest x-ray, Widal test, IgM Anti Hepatitis A virus, HbSag, Ultrasound abdomen and thorax.

Estimated minimal sample size required for this study was 100 cases of Dengue infection. Statistical methods were carried out through the

SPSS for Windows (version 16.0). Statistical methods employed for data analysis are Descriptive statistics, Cross tabs, Chi-Square test for categorical outcomes and t-test for comparison of means. Comparison of multiple means/non parametric data was done using One Way-ANOVA. A total of 115 cases formed the study group out of which 5 were excluded because of associated other infections (Hepatitis A=5).

Findings

The study group included 110 children aged between 2-mo-14 years satisfying the WHO criteria for dengue fever after excluding malaria, enteric fever, Hepatitis A and Hepatitis B [13]. All 110 children were grouped into Dengue Fever (DF) (53.6%), DHF (23.6%) and DSS (22.5%) according to WHO criteria [13]. The majority (76 %) were above 5 years. Fever (100%) was the chief complaint in all cases followed by body aches (57%), pain in abdomen (47%), vomiting (40%) facial puffiness (40%) and rashes (36%). Petichiae and purpura were seen in 30% of cases, while 19 % had mucosal bleeding. Five (4.5%) children presented with jaundice. Out of 110 children, 79 % had hepatomegaly which was noticed more in DHF and DSS (88.5% and 96%) than in DF (67.8%) group ($P=0.006$). Hepatic tenderness was observed in 36.3% of children, which was more in DHF (53.8%), DSS (56%) compared to DF(20.3%) group ($P=0.001$). Profile of liver function tests (LFT) and ultrasound findings in different groups in dengue infection is shown in Table 1. As shown in Table 1 abnormal liver functions were significantly more in DSS and DHF group.

Table 2 shows the comparison of ALT and AST levels between the groups. The rise in the levels of the enzymes were significantly more in DSS and DHF group. More than 10 fold increase in the levels of both ALT and AST were observed mainly in the DSS and DHF group.

Table 3 shows comparison of liver function tests with or without hepatomegaly and tender/non tender hepatomegaly. Interestingly there was no significant difference in the LFT's in

Table 1: Profile of liver function test and ultrasound findings in different groups of Dengue infection

Parameter	DF (n=59)	DHF (n=26)	DSS (n=25)	P value
Total serum bilirubin >2mg/dl	0 (0%)	1 (0.03%)	2 (0.08%)	0.025
Mean total S. bilirubin (mg/dl)	0.79	0.84	1.1	0.1
Elevated ALT (U/l)	41 (69.4%)	22 (84.6%)	23 (92%)	<0.001
Mean ALT	78.7	157.3	504.6	0.001
Range	(16-374)	(25-481)	(24-3414)	
Elevated AST (U/l)	52 (88.1%)	26 (100%)	24 (96%)	<0.001
Mean AST	134	280	883.4	0.002
Range	(45-268)	(18-450)	(43-899)	
Elevated Alk Ph (U/l)	27 (45.7%)	17 (65.3%)	18 (72%)	0.049
Mean AP	118.6	157.7	188.2	0.03
Range	(36-277)	(54-683)	(58-523)	
Mean serum albumin (gm/l)	33.7	32.3	33.7	0.9
Range	(28-42)	(25-42)	(26-40)	
Mean serum globulin(gm/l)	19	28	28	<0.001
Range	(06-32)	(20-30)	(20-32)	
Mean total protein (gm/l)	62	59	61	0.6
Range	(55-79)	(50-70)	(50-73)	
Prolonged INR (>1.5)	1 (1.6%)	08 (30.7%)	13 (52%)	0.001
Abnormal APTT (>3 sec above control)	0	04 (15.3%)	05 (20%)	0.5
Mean APTT in seconds	31	34	33	0.3
Ascites	20 (33.9%)	20 (76.9%)	18 (72%)	<0.001
Pleural effusion	19 (32.2%)	19 (73.1%)	17 (68%)	<0.001
Gall bladder thickening (>5mm)	30 (50.8%)	21 (80.8%)	20 (80%)	0.005

ALT: alanine transaminase; AST: aspartate transaminase; Alk. Ph: alkaline phosphatase; APTT: Activated partial thrombo-plastin time, INR: International Normalized Ratio

children with or without hepatomegaly. Among those with hepatomegaly also there was no significant difference in the LFT's with/without hepatic tenderness. Ultra sound revealed gall bladder thickening, ascites, and pleural effusion more in the DHF (80%, 77%, 73%) and DSS (80%, 72%, 68%) compared to DF (50.8%, 33.9%, 32.2%) group.

Jaundice was present in 5 (4.5%) cases out of 110 children. All of them had tender hepatomegaly, decreased platelet count, elevated hematocrit, and deranged liver enzymes. Four children recovered completely by 3 weeks both

clinically and biochemically and one was lost for follow up after discharge. Out of 110 dengue cases one child (6 months old) with deranged LFT, adult respiratory distress syndrome (ARDS), coagulopathy and multi organ dysfunction expired.

Discussion

Hepatic involvement in dengue infections is often demonstrated by hepatomegaly and mild-to-

Table 2: Comparison of AST and ALT values in DF, DHF and DSS groups.

		0-45 [u/l]	46-200 [u/l]	201-400 [u/l]	401-600 [u/l]	>600 [u/l]	P-value
ALT	DF	18(30.5%)	39(66.1%)	2(3.4%)	0(0%)	0	X ² =0.47
	DHF	4(15.4%)	15(57.7%)	5(19.2%)	2(7.7%)	0	P=<0.001
	DSS	2(8%)	14(56%)	5(20%)	0(0%)	4(16%)	
AST	DF	07(11.9%)	39(66.1%)	11(18.6%)	2(3.4%)	0	X ² =0.47
	DHF	0(0%)	10(38.5%)	10(38.5%)	5(19.2%)	1(3.8%)	P<0.001
	DSS	1(4%)	7(28%)	6(24%)	6(24%)	5(20%)	

Table 3: Comparison of liver function tests with or without hepatomegaly and tender and non tender hepatomegaly

Parameter	Hepatomegaly		P Value	Tender Hepatomegaly		P Value
	Yes (n=87)	No (n=23)		Yes (n=40)	No (n=47)	
Mean Serum Bilirubin	0.9	0.8	0.5	0.8	0.8	0.8
Range (mg/dl)	(0.4-4.92)	(0.5-1.60)		(0.6-2.3)	(0.2-4.48)	
Mean AST	390	145	0.2	232	304	0.6
Range (U/l)	(19-7390)	(30-275)		(44-1230)	(18-7390)	
Mean ALT	228	78	0.2	127	178	0.5
Range (U/l)	(16-3414)	(30-143)		(22-654)	(16-2907)	
Mean Alkaline Ph	145	134	0.6	138	147	0.7
Range (U/l)	(36-683)	(54-234)		(47-523)	(36-683)	
Mean Serum Protein	61	63	0.06	61	61	0.6
Range (gm/l)	(50-79)	(56-73)		(50-70)	(50-79)	
Mean Serum Albumin	33	33	0.8	33	3.3	0.9
Range (gm/l)	(25-42)	(29-42)		(2.6-4.0)	(1.8-4.2)	
Mean Serum Globulin	24	25	0.5	2.4	2.5	0.5
Range (gm/l)	(10-34)	(15-32)		(1.1-3.2)	(1-3.3)	
Mean INR	1.2	1.1	0.1	1.2	1.1	0.02
Range	(1-4.48)	(1-1.6)		(1-2.4)	(1-2.1)	
Mean APTT	32	32	0.1	32	32	0.7
Range (sec)	(31-33)	(31-33)		(32-33)	(32-33)	

moderate increases in transaminase levels. Presentation with jaundice is important as it can simulate acute hepatitis. In recent years high mortality have been reported in children with dengue infection with acute liver cell failure [2,11,12,14]. Hepatomegaly is one of the common clinical signs of dengue infection. Out of 110 cases in our study, 79% had hepatomegaly which was more common in DHF (88.5%) and DSS (96%) group than in DF group. Similar association of hepatomegaly in dengue has been reported in 43%-100% of cases in children [4-6,9,15-18]. In fact Petdachai and Faridi et al reported hepatomegaly in all children with DSS [4,16]. Hepatic tenderness was observed in 36.3% of children and was more in DHF (53.8%), DSS (56%) which is similar to observations made in a study from Thailand [15]. Abnormal hepatic enzymes in dengue infection have been reported by various workers and the range varies from 36.4%-96% both in children and adults [4-9,16,19,20]. We observed elevated ALT in 69.4% of DF, 84.6% of DHF and 92% of DSS, and raised AST in 88% of DF, 100% of DHF and 96% of DSS group. The hepatic enzymes were elevated significantly in DSS and DHF when compared to DF group which is similar to other studies [4-10]. Petdachai noticed 34.2% of DSS children with 5

fold elevation of ALT [4]. We found more than 10 fold rise of AST in 44% of DSS, 22.8 % of DHF and only in 3.4% of DF group. More than 10 fold rise in ALT in 16% of DSS, 7.7% of DHF and 0% of DF group was observed in our study. More than 10 fold increase in transaminases levels was observed mainly in DSS and DHF group than in DF group which was statistically significant. In a large study from Brazil, out of 1585 dengue cases, elevation in AST and ALT were seen in 63.4% and 45% of patients respectively, with 3.8% of cases having 10 fold increase in transaminase levels [20]. Similar increase of more than 10 fold rise in the liver enzymes was recorded by other authors also in adults and it varies between 1.8%-11.2% [8,19,20]. Higher incidence of more than 10 fold rise was observed in our study when compared to adult series. This may indicate that, children are at higher risk of hepatic involvement compared to adults. Detection of abnormally high transaminase enzymes among patients with dengue is important since the possibility of consequent hepatic encephalopathy can be expected [2]. It is interesting to note that there was no statistical significant difference in mean liver enzyme levels in cases with or without hepatomegaly/hepatic tenderness in our study. Serum AP levels also showed similar

trend in our study with raise in 45% of DF, 65.3% of DHF and 72% of DSS and again the raise was statistically significant in severe groups. Elevation of AST was more compared to ALT in the present study and similar observations was made by others also [4,10,14,21]. AST rise more than ALT in dengue may be due to involvement of myocytes [10,21]. This differs from the pattern seen in viral hepatitis, in which ALT levels are usually higher than or equal to AST levels [10,21]. We found prolonged PT (INR>1.5) values in 20% of the cases and it was significantly more in DHF (31%) and DSS (13%) group. Hypoalbumenemia was observed in 66% of the cases. Hypoglobulinemia was observed more in DHF (69%) and DSS (60%) compared to DF group (17%). Wong et al reported low globulin level in 14.2% and low albumin level in 16.5%, derangements in PT and APTT in 42.5% of his adult cases [8]. However Itha S, et al noticed hypoalbumenemia in 76%, deranged PT and APTT in 7% of adult cases [7]. The reduction of serum globulin may be an important factor in fluid loss into third space which is indicative of severity of dengue infection. Jaundice has been reported in 2%-25% of cases by several authors [5,14,21]. We observed jaundice in 5 (4.5%) cases and none of them had encephalopathy. All of them recovered completely. Nimmannitya et al reported jaundice and encephalopathy in 18 cases of DHF of whom 10 died [14]. In recent studies from India and Thailand, dengue infection is the most important cause of acute hepatic failure in children contributing to 18.5% and 34.3% of the cases respectively [11,12]. In endemic areas dengue should be considered as one of the differential diagnosis in children presenting with fever and fulminant hepatic failure [3,12,13]. Mechanisms of liver injury in dengue may be due to direct effects of the virus or host immune response on liver cells, circulatory compromise, metabolic acidosis and/or hypoxia caused by hypotension or localized vascular leakage inside the liver [5,7,10,14,22]. 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 [10,23]. A study from Mexico in the mice and humans established the correlation between liver damage and dengue based on the AST activity [23]. Shivbalan et al found ALT, tender hepatomegaly and abdominal pain to

be significant predictors for bleeding in dengue children [24]. An Indian study reported correlation between mortality and severe liver dysfunction in children with dengue infection [17]. Predictive factors for liver damage have been identified as DHF, DSS, secondary infection, thrombocytopenia, elevated hematocrit, female sex and children by Wong et al [8]. Elevated transaminase levels have been suggested as a potential marker to help differentiate dengue from other viral infections during the early febrile phase by the same author [8].

Strengths of the study: Some of the previous studies are retrospective, study group included seronegative dengue cases and they have not excluded common illnesses pertinent to tropical region. Our study included only serologically confirmed children of dengue infection. In tropical countries liver can be affected in malaria, enteric fever, and viral hepatitis also. Therefore utmost care was taken to exclude these common disorders clinically and investigation wise in our study.

Limitations: On humanitarian grounds liver biopsy was not done in any children to confirm the diagnosis.

Conclusion

The spectrum of hepatic involvement in dengue varies from jaundice to elevation of liver enzymes. Hepatomegaly is a most important clinical sign. Elevation of liver enzymes can occur with or without hepatomegaly. Significant rise of liver enzymes helps in recognition of severe forms of dengue infection (DHF and DSS). Presence of fever, jaundice and hepatomegaly in endemic areas should arouse the suspicion of dengue hepatitis.

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Conflict of Interest: None

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