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STUDY ON OUTCOME OF CHILDREN WITH DENGUE INFECTION AND ITS CLINICAL CORRELATION WITH HEPATIC DYSFUNCTION

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ABSTRACT

Introduction: Dengue virus infection is a major public health problem and hepatic involvement in dengue is known with protean of manifestations ranging from hepatomegaly, elevated liver enzymes to fulminant hepatic failure. This objective of the study was to assess the spectrum of hepatic involvement in dengue infection. **Methodology**: A prospective cohort study on 110 Patients hospitalized with dengue infection admitted in Dept. of pediatrics, Navodaya Medical College, Raichur. Children aged between 2 months - 14 years were studied for their hepatic functions both clinically and biochemically. **Results:** 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 more in DHF (53.8%), DSS (56%) compared to DF(20.3%) group (P=0.001). Abnormal liver functions were significantly more in DSS and DHF group. **Conclusion:** Hepatic involvement in dengue varies from jaundice to more than 10-folds elevation of liver enzymes. Significant rise of liver enzymes signifies severe dengue. 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.

KEYWORDS: Dengue; Hepatmegaly; Jaundice; Elevated liver enzymes.

INTRODUCTION

Dengue virus infection is a Major Public Health problem with upsurge in complicated and atypical manifestations in the recent years. Dengue infection, an arthropod - borne viral hemorrhagic fever, continues to be a major challenge to public health in South-East Asia.[1] Estimates suggest that annually over 50 million cases of severe dengue occur in Asian countries with a case fatality rate of lesser than 5%. Of these, at least 90% are children younger than 15 years old.[2]

Although dengue virus is a non-hepatotropic virus, hepatomegaly is commonly seen in dengue along with a rise in serum aminotransferases. The degree of liver dysfunction varies from mild injury with elevation of aminotransferases to even fulminant hepatic failure.[3,4] Hepatic dysfunction in dengue infection may be attributed to direct viral effect on liver cells or as a consequence of dysregulated host immune responses against the virus. Jaundice in dengue infection has been associated with fulminant liver failure and by itself is a poor prognostic factor.[5]

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 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.

Objectives

To study hepatic dysfunction in children with dengue infection and to study clinical correlates like severity Clinical features, lab parameters, morbidity and mortality.

MATERIALS AND METHODS

Ethical Committee clearance was taken from the institution and informed consent was taken from the guardian of every patient who took part in this study. This prospective, hospital based study was conducted in the Department of Pediatrics, of Navodaya medical college and hospital. After taking ethical committee clearance and informed consent .All clinically suspected dengue infection as per the revised World Health Organization (WHO) guidelines 2009 in children of age between 2 months to 14 years were screened. Patients included were serologically confirmed (immunoglobulin M [IgM] positive), by dengue IgM capture enzyme-linked immunosorbent assay (ELISA), DF patients admitted to the Department of Pediatrics, all patients between 2 months to 14 yrs, patients giving informed consent for the study. Those excluded were IgM negative dengue like illness; children aged >2 months and <14 years of age, children with pre-existing liver diseases, other concomitant infections affecting the liver such as malaria, typhoid, hepatitis A and B, those patients who refused to be included in this study.

A detailed history and thorough clinical examination were performed in all cases. Data was collected in a predesigned, pretested proforma. All cases were subjected to the following investigations: Dengue IgM capture ELISA, hemoglobin (Hb), total count, differential leukocyte count, platelet count (PLC), hematocrit (HCT), peripheral blood smear, serum bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), serum albumin, serum globulin, total proteins, prothrombin time (PT), Activated partial thromboplastin time ultrasound abdomen and thorax. Other causes like malaria, viral hepatitis, enteric fever, malignancies were excluded by clinical and laboratory investigations.

Sample size of this study came to be 110 patients, As per dengue update: WHO 2009 guideline, probable dengue was defined as live in/travel to dengue endemic area with two of the following: Nausea, vomiting; rash; aches and pains; tourniquet test positive; leucopenia; any warning sign.[2] Warning signs were abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy and restlessness, liver enlargement <2 cm, laboratory: Increase in HCT with concurrent rapid decrease in PLC. Criteria for severe dengue was severe plasma leakage leading to dengue shock syndrome, fluid accumulation with respiratory distress; severe bleeding; severe organ involvement (liver: AST or ALT <1000, impaired consciousness, heart and other organs involvement).[2]

RESULTS

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. 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 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)	(24-414)	
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**

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 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
	DF	18(30.5%)	39(66.1%)	2(3.4%)	0(0%)	0	X^2=0.47
ALT	**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%)	
	DF	07(11.9%)	39(66.1%)	11(18.6%)	2(3.4%)	0	X^2=0.47
AST	**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 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 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.

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 Alkalin 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)	

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 (5 months old) with deranged

LFT, adult respiratory distress syndrome (ARDS), coagulopathy and multi organ dysfunction expired.

DISCUSSON

Liver involvement in dengue is usually manifested by hepatomegaly (clinically) or increase in liver enzymes (biochemically). Presentation with jaundice can simulate acute hepatitis. Severe dengue can manifest with fulminant hepatic failure and has been the cause of death in many children with dengue infection.[6,7]

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. In fact Petdachai and Faridi et al reported hepatomegaly in all children with DSS. 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.[15,16] 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. 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. 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] Detection of abnormally high transaminase enzymes among patients with dengue is important since the possibility of consequent hepatic encephalopathy can be expected. 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. 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 m1ore in DHF (31%) and DSS (13%) group. Hypoalbumenemia was observed in 66% of the cases. Hypoglobinemia was observed more in DHF (69%) and DSS (60%) compared to DF group (17%). However Itha S, et al noticed hypoalbumenemia in 76%, deranged PT and APTT in 7% of adult cases.[17] 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] Study 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.[9] 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. 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. 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] 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.[12] 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.

CONCLUSION

Hepatic involvement in dengue varies from jaundice to more than 10-folds elevation of liver enzymes. Hepatomegaly is a most important clinical sign, but alteration of LFT's can occur with or without hepatomegaly. Significant rise of liver enzymes signifies severe dengue. 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.

REFERENCES

1. Halstead SB. Dengue. Curr Opin Infect Dis., 2002; 15: 471–6.
2. World Health Organization. Dengue: Guideline for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization, 2009.
3. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg., 2006; 100: 608–14.

4. Lum LC, Lam SK, George R, Devi S. Fulminant hepatitis in dengue infection. Southeast Asian J Trop Med Public Health, 1993; 24: 467–71.
5. Chhina RS, Goyal O, Chhina DK, Goyal P, Kumar R, Puri S. Liver function tests in patients with dengue viral infection. Dengue Bull., 2008; 32: 110–7.
6. Wiwanitkit V. Liver dysfunction in dengue infection: An analysis of the previously published Thai cases. J Ayub Med Coll Abbottabad, 2007; 19: 10–2.
7. Kumar R, Tripathi P, Tripathi S, Kanodia A, Venkatesh V. Prevalence of dengue infection in north Indian children with acute hepatic failure. Ann Hepatol, 2008; 7: 59–62.
8. Mohan B, Patwari AK, Anand VK. Hepatic dysfunction in childhood dengue infection. J Trop Pediatr, 2000; 46: 40–3.
9. Nimmannitya S, Thisyakorn U, Hemsrichart V. Dengue haemorrhagic fever with unusual manifestations. Southeast Asian J Trop Med Public Health, 1987; 18: 398–406.
10. Petdachai W. Hepatic dysfunction in children with dengue shock syndrome. Dengue Bull, 2005; 29: 112–7.
11. Wahid SF, Sanusi S, Zawawi MM, Ali RA. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian J Trop Med Public Health, 2000; 31: 259–63.
12. Wong M, Shen E. The utility of liver function tests in dengue. Ann Acad Med Singapore, 2008; 37: 82–3.
13. Burke T. Dengue haemorrhagic fever: A pathological study. Trans R Soc Trop Med Hyg., 1968; 62: 682–92.
14. Kamath SR, Ranjit S. Clinical features, complications and atypical manifestations of children with severe forms of dengue hemorrhagic fever in South India. Indian J Pediatr, 2006; 73: 889–95.
15. Petdachai W. Hepatic dysfunction in children with dengue shock syndrome. Dengue Bulletin 2005; 29: 112-7.
16. Faridi CA, Setiabudi D, Ridad A, Colebunders R. Clinical manifestations of dengue haemorrhagic fever in children in Bandung, Indonesia. Ann Soc Belg Med Trop, 1995; 75: 291.
17. Itha S, Kashyap R, Krishnani N, Saraswat VA, Choudhuri G, Aggarwal R. Profile of liver involvement in dengue virus infection. Natl Med J India, 2005; 18: 127–30.
18. Chinnakali P, Gurnani N, Upadhyay RP, Parmar K, Suri TM, Yadav K. High level of awareness but poor practices regarding dengue fever control: A cross-sectional study from North India. N Am J Med Sci., 2012; 4: 278.
19. Dhooria GS, Bhat D, Bains HS. Clinical profile and outcome in children of dengue hemorrhagic fever in North India. Iran J Pediatr, 2008; 18: 222–8.
20. Souza LJ, Alves JG, Nogueira RM, et al. Aminotransferase changes and acute hepatitis in patients with dengue fever: analysis of 1,585 cases. Braz J Infect Dis., 2004; 8(2): 156-63.
21. Trung DT, Thu Thao LT, Hien TT, et al. Liver involvement associated with dengue infection in adults in Vietnam. Am J Trop Med Hyg, 2010; 83(4): 774-80.
22. Chen HC, Lai SY, Sung JM, et al. Lymphocyte activation and hepatic cellular infiltration in immunocompetent mice infected by dengue virus. J Med Virol, 2004; 73(3): 419-31.
23. Vázquez-Pichardo M, Rosales-Jiménez C, RojasEspinosa O, et al. Is liver damage dependent on the serotype of dengue virus?– A study in Mexico. Dengue Bulletin, 2006; 30: 114-9.