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Research Article

Study of Hepatic Dysfunction in Children with Dengue Fever

Amrita Banerjee[1]*, Pushpa G Kini[2], Shrikiran Hebbar[2] and Ramesh Bhat[2]

[1]Senior Resident, Department of Paediatrics, AIIMS Patna, India

[2]Professor, Department of Paediatrics, KMC Manipal, India

***Corresponding Author:** Amrita Banerjee, Senior Resident, Department of Pediatrics, AIIMS Patna, Patna, Bihar, India.

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Abstract

This study was done to find out any correlation between hepatic dysfunction and severity of Dengue fever. It was also done to study the range of hepatic involvement in children with Dengue infection. This retrospective study was done in seven hundred and seventy six children admitted in Department of Paediatrics at Kasturba Medical college, Manipal from August 2014-August 2017 with suspected Dengue fever.

A total of 737 children were included in the study, they were grouped into three categories as per WHO Dengue case classification, 388 children had Dengue without warning signs (DD), 272 children had Dengue with warning signs (DW) and 77 children had Severe Dengue (SD).

Most of the children affected were males (64.6%), with M:F being 1.8:1. Most of affected children affected were in the age group of 11 - 15 years (38.1%). Fever (100%) was the most common symptom followed by vomiting (53.8%), pain abdomen (49.5%) and rash (33.1%). Hepatic encephalopathy was seen in 19.1% children with SD.

Involvement of liver was seen as hepatomegaly in 46%, elevation of AST (aspartate transaminase) in 32% and ALT (alanine transaminase) in 10%, raised serum bilirubin levels in 1.2%, hypoalbuminemia in 19.1%, prolonged PT (partial thromboplastin time) in 3.9% and prolonged APTT (activated partial thromboplastin time) in 47%. There was a more than 10 fold rise of AST in 19% of SD, 4.7% of DW and only 1.7% of DD group. More than 10 fold rise in ALT in of 10.2% SD, 1.4% of DW and none of the cases in DD group. In the current study, children with Dengue fever and hepatomegaly had higher levels of AST and ALT, as compared to those who did not have hepatomegaly.

It was observed that as the severity of dengue increased hepatic derangement increased. Children with hepatomegaly had significant elevation in liver enzymes (AST and ALT) as compared to children without hepatomegaly. Hence liver function tests should be done in any child with clinical suspicion of Dengue fever to prevent catastrophic complications and to avoid use of hepatotoxic drugs.

Keywords: *Antibodies; Children; Dengue Fever; Hepatic Dysfunction; Interleukin; Interferon; Liver Enzymes*

Introduction

Dengue fever a vector-borne disease, caused by virus belonging to family flaviviridae, is a major public health threat all over the world. It is caused by one of the four types of dengue virus, which spread by *Aedes aegypti* and *Aedes albopictus* mosquito. It causes 50 million infections annually with 2.5 billion people from 100 endemic countries susceptible to it [1]. Recovery after infection from one serotype offers lasting immunity for that serotype, however subsequent infection from other serotypes will increase the risk of developing severe Dengue [1].

Liver dysfunction due to Dengue fever is a well recognized feature and it is more common and severe in children than in adults [2]. Involvement of liver during Dengue fever can range from hepatomegaly with mild elevation of liver enzymes (AST and ALT) to acute liver failure with hepatic encephalopathy. Hepatocytes and Kupffer cells are prime targets for DENV infection. Attachment of the virus to the receptors which are present on surface of host cell is the major rate limiting step for infecting cells [2]. Entry of the virus and a conductive environment for the virus to grow inside the cell are required for the cell to be affected by a virus and this property is influenced by viral serotype, strain and cell type. It has also been postulated that binding of dengue viruses onto hepatocytes is facilitatory, one binding promotes the binding of successive particles. After binding there is endocytosis which causes cellular apoptosis or hypoxic damage due to impaired liver perfusion due to fluid leakage, oxidative stress or immune mediated injury[3]. The various pathways involved in this apoptotic process include viral cytopathy, hypoxic mitochondrial dysfunction, the immune response and accelerated endoplasmic reticular stress [3].

Severe dengue infection caused due to enhanced immune reaction is due to recurrent dengue infections. The concentrations of cytokines like interleukin (IL)-2, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ increase in the first 3 days later IL-4, IL-5 and IL-10 levels increase [4]. The exact mechanism by which the host immunity damages liver is currently not known and pathogenesis of liver injury in dengue is believed to be primarily a T cell mediated process, which involves interaction between antibodies, endothelium and a cytokines with various host factors like genetic polymorphisms [4].

Materials and Methods

The present study was conducted in Department of Paediatrics at Kasturba Medical college, Manipal, from August 2014 - August 2017. All children admitted with suspicion of Dengue fever and were positive for NS1 (non-structural protein 1) and IgM Dengue were included in the study. Scrub typhus, Wilson's disease, Leptospirosis, Malaria, Sepsis and Enteric fever were excluded by history, clinical examination and investigations. Demography data, history, physical examination findings and laboratory data which included complete blood count, liver function tests (total bilirubin, AST, ALT and serum albumin) and coagulation profile were documented in the proforma designed for the study along with data and duration of treatment received, duration hospital stay and outcome.

An approval was obtained from Ethics committee of Kasturba Medical college, Manipal.

Total of 776 children had serologically proven dengue fever, however 48 were excluded due to associated co infections. Statistical analysis was done by non parametric tests such as Kruskal Wallis ANOVA tests, one way ANOVA and Tukey post hoc tests.

Results

The study group included 737 children from age group of 1 year to 18 years serologically positive (NS1 or IgM) Dengue fever. They were divided into three categories based on severity of Dengue fever as per WHO Dengue case classification as, dengue without warning signs (DD), dengue with warning signs (DW) and severe dengue (SD).

Most of the children affected were in the age group of 11 - 15 years (38.1%), with males (64.6%) being affected more than females (35.3%) and sex ratio is 1.8:1. The mean age group involved in the study was 9.5 ± 0.63.

Of the 737 children, 388 had Dengue without warning signs (52.6%), 272 had Dengue without warning signs (36.9%) and 77 had Severe dengue (10.4%). Fever (100%) was the most common symptom followed by vomiting (53.8%), pain abdomen (49.5%) and rash (33.1%). Hepatic encephalopathy 13 (19.1%), acute respiratory distress syndrome (ARDS) 5 (7.3%), edema 32 (47%) and shock 36 (52.9%) children with SD (Refer table 1).

Hepatomegaly was present most commonly in children with SD (66.1%) as compared to those with DD (31.7%). Mucosal bleeding was seen 14 (5.1%) of children with DW and 7 (10.2%) of children with SD. Jaundice was seen in 2 (0.73%) children with DW and in 4 (5.8%) children with SD (Refer table 1).

Parameters	DD (n= 388) (%)	DW (n= 272) (%)	SD (n= 77) (%)
Fever	388 (100)	272 (100)	77 (100)
Myalgia	137 (35.3)	58 (21.3)	25 (32.4)
Vomiting	173 (44.5)	171 (62.8)	48 (62.3)
Pain abdomen	98 (25.2)	226 (83.0)	37 (48.05)
Maculopapular rash	102 (26.2)	110 (40.4)	29 (37.6)
Mucosal bleeding	0	14 (5.1)	7 (9.09)
Jaundice	0	2 (0.73)	4 (5.19)
Hepatomegaly	123 (31.7)	177 (65.0)	45 (58.44)
Hepatic encephalopathy	0	0	13 (16.8)
Shock	0	0	36 (46.7)
Acute respiratory distress syndrome (ARDS)	0	0	5 (6.4)

Table 1: *Clinical features.*

Liver function tests were deranged in all three groups with Dengue fever. There was a statistically significant rise in serum bilirubin levels in SD (8.8%) as compared to DW (1.1%). AST (aspartate aminotransferase) was elevated in 65 (16.75%) children with DD, 127 (46.69%) children with DW and 50 (73.52%) of children with SD. The rise in ALT was also seen more in children with SD (33.8%) as compared to 15.0% of children with DW and 3.6% of children with DD. Serum albumin levels were lower with increased severity of Dengue. Mean serum albumin in children with SD was 3.1 whereas those with DW were 3.5 and in children with DD it was 3.6. Prolonged PT (INR > 1.5) (international normalized ratio) was seen in children with SD (36.76%) as compared to children with DW (1.1%) and DD (0.25%). Prolonged APTT was seen in 91.1% of children with SD, 79.1% of children with DW and 18.5% of children with DD. (Refer table 2).

Parameters	DD (n = 388)	DW (n = 272)	SD (n = 77)	P-value
Total serum bilirubin >2mg/dl	0	3 (1.1%)	6 (8.8%)	P=<0.001 (significant)
Mean total serum bilirubin (mg/dl) (Range)	0.31 (0.2-1.5)	0.46 (0.2-2.2)	0.91 (0.2-3)	
Elevated AST (U/I)	65 (16.75%)	127 (46.69%)	50 (73.52%)	P=<0.001 (significant)
Mean AST (Range)	89.96 (13-687)	161.49 (29-1818)	500.56 (56-6497)	
Elevated ALT (U/I)	14 (3.6 %)	41 (15.0%)	23 (33.8%)	P=<0.001 (significant)
Mean ALT (Range)	42.11 (7-800)	84.69 (12-1731)	184.18 (30-1753)	
Hypoalbuminaemia	25 (6.4%)	67 (24.6%)	49 (63.6%)	P=<0.001 (significant)
Mean serum albumin (gm/I) (Range)	3.6 (2.3-4.35)	3.5 (2.3-4.7)	3.1 (2-4.3)	
Prolonged INR (>1.5)	1 (0.25%)	3 (1.1%)	25 (36.76%)	P=<0.001 (significant)
Abnormal APTT (> 3 seconds above control)	72 (18.5%)	216 (79.1%)	62 (91.1%)	P=<0.001 (significant)
Mean APTT in seconds	30.7	40.7	54.8	
Range	27-36	28-63	38-85	

Table 2: *Profile of liver function test in different groups of dengue infection.*

There was a more than 10 fold rise of AST in 19% of SD, 4.7% of DW and only 1.7% of DD group. More than 10 fold rise in ALT in of 10.2% SD, 1.4% of DW and none of the cases in the DD group. More than 10 fold rise in transaminases levels was observed mainly in SD and DW group than in the DD group which was statistically significant (Refer table 3).

		0-45 (U/L)	46-200 (U/L)	201-400 (U/L)	401-600 (U/L)	> 600 (U/L)	P value
ALT	DD (n = 388)	275 (70.8%)	111 (28.6%)	2 (0.5%)	0	0	P=<0.001
	DW (n = 272)	121 (44.4%)	131 (48.1%)	16 (5.8%)	4 (1.4%)	0	(significant)
	SD (n = 68)	11 (16.1%)	46 (67.6%)	4 (5.8%)	3 (4.4%)	4 (5.8%)	
AST	DD (n = 388)	87 (22.4%)	282 (72.6%)	12 (3.0%)	6 (1.5%)	1 (0.2%)	P = <0.001
	DW (n = 272)	22 (8.0%)	192 (70.5%)	45 (16.5%)	8 (2.9%)	5 (1.8%)	(significant)
	SD (n = 68)	0	34 (50%)	21 (30.8%)	4 (5.8%)	9 (13.2%)	

Table 3: *Comparison of AST/ALT values in DD, DW, and SD.*

Children with dengue fever and hepatomegaly had higher levels of AST and ALT, as compared to those who did not have hepatomegaly (Refer table 4).

Parameters	Hepatomegaly		P- value
	Present	Absent	
Mean serum bilirubin Range	0.58 0.2 - 4.7	0.50 0.2 - 1.4	P = 0.5 (not significant)
Mean AST Range	300.94 21 - 4491	224.66 13 - 567	P = <0.001 (significant)
Mean ALT Range	111.82 16 - 1753	101.00 11 - 565	P = <0.001 (significant)
Mean serum Albumin Range	3.4 1.8 - 4.08	3.5 3 - 4.8	P = 0.7 (not significant)
Mean INR Range	1.12 0.7 - 2.34	1.10 0.7 - 1.7	P = 0.6 (not significant)
Mean APTT Range	42.48 25 - 74.8	41.9 14.5 - 52.2	P = 0.7 (not significant)

Table 4: *Mean value of liver function tests with or without hepatomegaly.*

In the present study 9 children died with cause of death being pulmonary haemorrhage, multiorgan dysfunction syndrome and acute respiratory distress syndrome.

Most of the children belonged to the DD group (53.2%) followed by DW group (37.3%). The mean duration of hospital stay being 4.84 ± 1.64 in DD and 5.72 ± 2.75 in DW. Children with SD had the longest mean duration of hospital stay of 9.2 ± 3.80.

Discussion

Involvement of liver in Dengue infection is not uncommon and has been described since 1970. Varying degree of liver involvement in seen ranging from mild elevation of transaminase enzymes to acute liver failure. In the current study it was found that hepatic dysfunction

was seen in children in all three categories of Dengue fever. However, as the severity of Dengue increased, the degree of hepatic dysfunction also increased. Children with severe Dengue had the maximum risk of acute liver failure. Children with hepatomegaly also had more deranged liver enzymes than those without hepatomegaly.

In a study done by K. Jagdishkumar., *et al*. [5], raised AST was seen in 88% of children with DD, 100% children with DW and 96% of children with SD. Elevated ALT was seen in 69.4% of DD, 84.6% of DW and 92% of children with SD. These findings were similar to those in the present study; children with SD had maximum derangement in liver enzymes. In this study it was observed that elevation of AST was more than elevation of ALT. In a study done by Roy., *et al*. abnormal liver function tests were significantly more in children with DW and SD.

In the earlier studies [6], there was a more than 10 fold rise of AST in 44% of SD, 22.8% of DW and only 3.4% of DD group. More than 10 fold rise in ALT in 16% of SD, 7.7% OF DW and none of the cases in the DD group. In the present study, linear by linear association used for statistical analysis, showed a significant association between severity of Dengue fever and raised AST and ALT.

In a study done by K. Jagdishkumar., *et al*. [5], there was no significant difference in liver function tests in children with or without hepatomegaly. Similarly, in a study done by Singh., *et al*. the altered liver function was evident even in the absence of hepatomegaly [7].

In this study LFT (liver function test) was more deranged in children with hepatomegaly that those who did not have hepatomegaly (Refer table 4).

Hepatic dysfunction in liver, is a serious and grave complication and must be dealt with utmost care. This study gives an idea about the degree of liver involvement in Dengue and helps us to identify those children at risk of severe Dengue who need immediate assistance. Any child with clinical suspicion of dengue with deranged liver enzymes, should be evaluated carefully for risk of acute liver failure. Also, in children with severe derangement of enzymes, hepatotoxic drugs need to be avoided and the drug doses need to be adjusted accordingly.

Conclusion

Elevations in liver enzymes and deranged LFT are common features in Dengue fever. As the severity of the disease increases, worsening of liver function tests is seen. Hence, serial monitoring of LFT can help in predicting the outcome of the disease during the acute phase. Disease related complications can be prevented with serial monitoring of liver function tests.

Limitation of the Study

This study is focussed only on the degree of derangement of LFT in DD, DW and SD. Further studies need to be done to understand the implication of these abnormalities with respect to management and outcome.

Conflict of Interest

None of the authors have any conflict of interest.

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